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Costs of Disorders of the Brain in Europe

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Preface

The human brain is not only the site of our personality, thoughts, feelings and other human characteristics; it is also the seat of many chronic disabling diseases. These diseases have not received the attention that has been devoted to heart disease, cancer or AIDS, but in recent years there has been a growing awareness of their importance. There is also a growing awareness that basic brain research is equally relevant to neurological, neurosurgical diseases and mental disorders. For these reasons the European Brain Council (EBC) was formed in 2003 uniting neurologists, psychiatrists, psychologists, neurosurgeons, basic neuroscientists, patient organizations and industrial research in one co-affiliation. This organization has, as primary purpose, to promote brain research. For this purpose, data on the burden and cost of brain disorders are crucial. As an initial project, the EBC has analysed the WHO global burden of disease study extracting European data and bringing the brain disorders under one hat. We showed that the burden of brain disorders constitutes 35% of the total burden of all diseases in Europe. This figure is, however, calculated in terms of so-called DALYs or disability adjusted life-years and is difficult to translate into real economic terms. Whilst decision makers obviously pay attention to burden, it was considered more important for them to know the actual cost of disorders of the brain. The EBC therefore embarked upon a study called: Cost of Disorders of the Brain in Europe. We were fortunate to obtain a generous, completely unrestricted grant from the Danish drug company H. Lundbeck A/S for this purpose. The project involves 12 groups of neurologists, psychiatrists, psychologists and neurosurgeons with a particular interest in epidemiology; each group describing the epidemiology of one of the many groups of disorders of the brain in Europe. Simultaneously, via collaboration with Stockholm School of Economics, health economists did a complete review of European studies of the economic consequences of brain disorders.

The present study is the compiled publication from 'The Cost of Disorders of the Brain in Europe' project. The study presents a European estimate of the cost of brain disorders. Moreover, it includes summaries of reviews on the epidemiologic and economic evidence in brain disorders in Europe. There are a number of previous publications from the project on the health economic and epidemiologic evidence in 12 specified areas of brain disorders, which are published in the *European Journal of Health Economics*[1], the *European Journal of Neurology*[2] and *European Neuropsychopharmacology*[3].

The EBC is very pleased with the data presented here. The study reveals the magnitude of the total economic burden of brain disorders in Europe. Moreover, the study identifies gaps in our knowledge of the epidemiology and the cost of disorders of the brain, particularly in the area of new admission countries. Hence, it calls for more attention to this area in order to better understand both the epidemiological impact as well as health economic consequences of brain disorders in Europe.

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[1] *European Journal of Health Economics*, 2005.
[2] *European Journal of Neurology*, 2005.
[3] *European Neuropsychopharmacology*, 2005.

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Editors foreword

This project aims at estimating the Cost of Brain Disorders in Europe. The scope of the project is by no means self-evident. First the definition of which countries to be included should be discussed. The definition we have chosen, the European Union (EU) 25 countries plus Iceland, Norway and Switzerland is both relevant and practical. But it can be argued that a greater region, for example as defined by World Health Organization (WHO) Europe, would be more appropriate as it significantly increases the total population. However, the argument against is that data are very scarce for these additional populations. Brain disorders can also be defined and structured in many different ways. From the beginning it was clear that we should include both psychiatric and somatic diseases, but to decide which disorders to include is difficult. We settled also here for a definition based on what was relevant and practical, rather than complete. An additional issue is how patients should be allocated to different groups disorders. We can only observe costs or patients with different diseases, which means that a method has to be selected where costs for patients with more than one disease must be allocated to the different diseases. This problem is most difficult for persons of older age, as comorbidity increases with age. We are aware that this may create double counting of cost and that the cost of some disorders that are frequently comorbid, such as depression, may have been underestimated. Some attempts to adjust for this factor were performed in the study. In dementia it is also a problem to allocate cost to mental or neurological disorders. By employing appropriate method and data collection procedures, these issues can be addressed. However, in this study where we use existing data sources, and thus the final estimates also reflect availability of data.

Cost is an aggregate measure, which can be divided into relevant subgroups in several ways. As health and health policy is discussed in a social perspective, we have attempted to assess costs also in this perspective. It means that we include health care costs, such as hospital care, doctor's visits and drugs, regardless of who pays, the individual, a private insurer or the public through taxes and social insurance. But we also include costs outside the medical sector, both private and public. For example nursing home costs and assistance given through the municipality to compensate for limitations in function caused by dementia, multiple sclerosis or schizophrenia, or private costs for adapting to the disorders, in terms of services or goods. To measure these external costs for a specific disease is sometimes difficult, and data are often lacking. But for many disorders such costs are as important as the direct medical costs. We also include indirect costs; resources lost from the fact that most disorders also limit the work capability, and thus create lost production from short-term absenteeism from work as well as early retirement. The estimation of these costs poses a further problem in that they are dependent on how the economy and labour market works in different countries. It is thus tempting to exclude these costs, but they are important sources of the social cost of brain disorders in the population of working age would go unnoticed. We will present separate estimates as well as aggregates in order to account for the current limitations in data.

The methodology for cost-of-illness studies used in this study is well developed, but a number of methodological decisions have anyhow been made. The first is between an incidence based and a prevalence based study. For some disorders the first would be easier and preferable and for others the latter. We have decided to go for a prevalence based study, estimating the costs for a single year, 2004. A key feature of the methodology is a separation of the prevalence of the disease and the annual cost of a defined case of the disease. The cost is thus the product of the prevalence and the cost per case. There are several advantages to this approach. First, it gives the possibility to interpret and compare the selected contributions of cost per case and prevalence for different diseases and for different countries. Secondly, it makes it possible to separately investigate the evidence of prevalence and costs per case. For the first we have used a group of epidemiologists with in-depth knowledge of selected diseases. For the second, a similar group of health economic experts, with knowledge of different countries and different disorders worked on the economic evidence. We have thus had the best possible expertise in both areas. It was also a goal in itself to make epidemiologist and health economist work together, because future studies need to be designed by teams with competence in both fields.

We think our approach is the best available for this type of study but it is important to be aware of the possible shortcomings as well. A major issue is that prevalence estimates and cost per case estimates must have the same definition. This can only be fully achieved if an appropriate study methodology and data

collection procedure is designed up front. One of the goals of this study was to create the foundations for such a study in the future. In this project, where we work on existing data bases, epidemiological and health economic studies have been decided from different perspectives and with different objectives. To put them together is a delicate task, and despite in depth collaboration you can never be sure that the definitions match. In addition, we have discovered that data on both epidemiology and costs are lacking for most diseases in most countries, and that the available estimates can differ significantly. This is not surprising, as cost of illness estimates even for the same country vary considerably, partly because of differences in methodology, but primary because of differences in the availability of data. But it poses problems in deciding which data are most relevant for use in the model that has been constructed for this project to make the best possible estimate for Europe. A number of sensitivity analyses were thus conducted to investigate the impact of different assumptions. In addition, an attempt was made to validate the estimates against other sources, mainly national top-down estimates of how health care costs are distributed on different diseases. Such estimates, based on main diagnosis, avoid the problem of double counting, but do not necessarily constitute a better estimate.

This study presents a first estimate of the cost of brain disorders in Europe and an assessment of the gaps in available data. We hope that this will stimulate discussion as well as efforts to improve the situation in the future. It is not our role to give a comprehensive interpretation of the results. But we still want to end this foreword with some reflections on the role of such data for health care policy decisions. First, we see these estimates as a complement to other estimates on the burden of diseases, based on measures of morbidity and mortality, for example DALYs. Estimates of costs give an additional insight into the consequences of diseases and have an interest in their own right. Like the DALYs they can also be used for informing policy makers in health care. What is unique in this study is the focus on disorders of the brain and the focus on Europe. Mental illnesses usually come out on the top of the list in estimates of the burden or costs of diseases. However, other diseases of the brain are often not identified since by WHO they are included in other disease groups (e.g. stroke). Estimates of burden of disease and cost of illnesses are often used as a basis in in discussion of priorities, for example regarding decisions about access to health care and decisions about investments in research and development. It is important to state that such priorities are complicated and that other types of information are important. In our view, the present data can be used to illuminate two important policy decisions. The first is the utilization and access and availability of therapies for brain diseases in Europe. This is important because the awareness of available treatments increases and the tolerance to large unexplained or unjustified variations diminishes. Secondly, investment in research and development is the main instrument for reducing the burden and cost of brain diseases. It is important for Europe not only to use existing resources in an efficient and equitable matter, but also to contribute to the development of new knowledge to improve the situation. This is a long-term view, with significant implications not only for health care but for economic development as well. These two factors also indicate the importance of future studies to improve the measures of the cost of brain disorders, to enable better decisions and to follow and document that progress is made.

The report consists of two parts. The first part presents an overall estimate of the cost of brain disorders in Europe. The second part presents summaries of the epidemiological and economic evidence for the different groups of diseases that form the basis for the report. This evidence is published separately in different journals.

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Executive summary

Key words:
brain disorder, cost, cost of illness, economic burden, Europe, mental disorder, neurology, neurosurgery

Background: Brain disorders (psychiatric, neurological and neurosurgical diseases together) figure amongst the leading causes of disease and disability. Yet, the knowledge of the epidemiological and economic impact of brain disorders has been relatively little researched in Europe. WHO data suggest, however, that brain disorders cause 35% of the burden of all diseases in Europe.

Objectives: The present study aims at estimating the economic cost of disorders of the brain in Europe based on the published epidemiological and economic evidence. A secondary objective was to identify gaps in both epidemiological and economic evidence on brain disorders thus providing focus for future research efforts.

Methods: A model was developed to combine epidemiological and economic data on brain disorders in Europe (EU member countries, Iceland, Norway and Switzerland) and thus estimate their total cost. More specifically, it consisted of the following steps in which we: (i) transformed and converted available economic data to a defined time-period as well as currency (€2004); (ii) adjusted country specific economic data for purchasing power and relative size of economy; (iii) imputed data for countries where no data are available; (iv) combined epidemiology and economic data to estimate the total cost of a defined disease; (v) added the cost of all selected disorders to arrive at the total cost for Europe. The model was populated with data collected from extensive literature reviews in the epidemiology and economic burden of brain disorders in Europe, conducted by 12 groups of European epidemiologists and health economists. The cost data were calculated as cost per patient, and epidemiological data were primarily reported as 12-month prevalence estimates. National and international statistics for the model were retrieved from the OECD (Organization for Economic Co-operation and Development) and Eurostat databases. The aggregated annual cost estimates were presented in Euros for 2004.

Results: There are an estimated 127 million Europeans currently living with a brain disorder out of a population of 466 million. The total annual cost of brain disorders in Europe was estimated to €386 billion in 2004. Direct medical expenditures alone totalled €135 billion, comprising inpatient stays (€78 billion), outpatient visits (€45 billion) and drug costs (€13 billion). Attributable indirect costs resulting from lost workdays and productivity loss because of permanent disability caused by brain disorders and mortality were €179 billion, of which the mental disorders are the most prevalent. Direct non-medical costs (social services, informal care and other direct costs) totalled €72 billion.

Mental disorders amounted to €240 billion and hence constitute 62% of the total cost (excluding dementia), followed by neurological diseases (excluding dementia) totalling €84 billion (22%). Neurosurgical diseases made up a smaller fraction of the total cost of brain disorders in Europe, reaching a cost of €8 billion.The average cost of brain disorders in Europe was €829 per inhabitant (based on a total number of inhabitants in Europe of 466 million). However, the cost per inhabitant is different between European countries, and in general cost of brain disorders per inhabitant is higher in Western European countries compared with the EU admission countries. Because of scarcity of data, our total cost results only partially includes direct non-medical cost (e.g. community care and informal care) and indirect costs, and omits completely intangible costs. We have for example shown that the cost of dementia increase with 25% when including informal care and the cost of multiple sclerosis increases with at least 50% when including intangible costs.

Discussion: The scarcity of both epidemiologic and health economic data in several countries and for specific brain disorders have led to conservative inclusions of cost items and population age groups. Together with the restriction of the present study to the most prevalent brain disorders this leads to the conclusion, that the true economic cost of disorders of the brain is substantially higher than our estimate of 386 billion Euros, perhaps in the range 500–700 billion Euros. Brain disorders are, thus, substantially more costly than other important fields of medicine such as heart disease, cancer and diabetes. However, the burden of brain disorders is seldom taken together, but rather reported by each single diagnosis. If training efforts, research funding and health care resources could be allocated according to this new knowledge, a very considerable increase in funding of brain related activities should take place. Our cost estimations are the best possible based on the economic and epidemiological data available in Europe today. However, our study has identified major shortcomings both in the epidemiological and economic evidence on brain disorders in Europe, in particular in the EU admission countries. More research of a systematic, prospective, collaborative nature is needed in order to accurately estimate the cost of disorders of the brain in Europe.

Conclusion: Based on extensive literature reviews, the present study provides best possible estimates of the cost of disorders of the brain in Europe in 2004. In 28 countries with a population of 466 million, 127 million were affected by at least one brain disorder. The total annual cost was €386 billion (386 000 000 000). Brain research funding, health care resource allocation and teaching at medical schools are proportionately much smaller. The huge cost and burden of brain disorders calls for increased efforts in research, health care and teaching.

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Cost of disorders of the brain in Europe

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Introduction

Data on the burden of a disease have gained wide spread use in evidence based health policy (Murray and Lopez, 1996a). The World Health Organization (WHO), Harvard University and the World Bank have published several studies with estimates of the global burden of diseases (Murray and Lopez, 1996b, 1997a–c; Mathers *et al*., 2002). Those studies generally show, as is seen in Table 1, that mental illness in Europe is the disease group with the highest share of disability-adjusted life-years (DALYs). It accounts for about one quarter of all DALYs lost (Kaplan and Laing, 2004).

A number of disorders of the brain are not visible in the summary tables, because WHO lists them elsewhere (e.g. stroke under cardiovascular diseases, traumatic brain injury under trauma). However, in a separate study, based on WHO data, brain disorders were estimated to represent 35% of the total burden of all diseases in Europe (Olesen and Leonardi, 2003). Hence, this already suggests that the cost of brain disorders in Europe is very high.

Whilst burden of disease data are interesting and relevant, they do not tell us anything about the cost of different diseases and where those costs occur. Such information is needed in order to compare how health care resources are used in relation to the overall cost of illness and burden of disease. Cost of illness studies are thus complementary to burden of disease studies, and they are indispensable for policy makers.

The primary objective of this project is to provide the best possible estimate of the burden of brain disorders in Europe, based on the available literature and data. The secondary objective is to identify shortcomings in the presently available health economic and epidemiologic data base on brain disorders in Europe and to suggest future research. Furthermore, the project aims at stimulating the collaboration between health economists and epidemiologists in the research field of brain disorders in Europe in order to ensure improvements in future research.

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Europe is in this study defined as the EU 25 countries plus Iceland, Norway and Switzerland (see Fig. 1). Some countries in Eastern Europe have been excluded from this study, due to resource limitations and the fact that relevant data are missing.

Materials and methods

The study is based on epidemiologic and economic data for 12 defined disorders of the brain. We have decided to use the term disorders instead of diseases, which for some mental disorders[1] is not universally accepted. However, when it is relevant in the text, we may interchangeably use the term disease or illness. The 12 disorders were included in the study as they represent the most prevalent and expensive disorders of the brain. However, the inclusion and grouping of diseases is not self evident and may be expanded or changed in future studies, based on the experience in this study. There may be good reasons to include additional diseases, or to group them in a different way. The latter is particularly relevant for the mental disorders, where the grouping of disorders is less homogeneous than for the neurological disorders. Some groups of disorders of the brain are not included in our study due to heterogeneity or lack of data: eating disorders, somatoform disorders, neuromuscular disorders and developmental disorders.

Data were mainly collected from the literature. The following sections describe the data used in the study, as well as the methodology to estimate the total cost of a specific brain disorder in a specific country based on available data. A model was developed for imputation of costs for combinations of disorders and countries where data did not exist, based on the data available in other countries.

Economic data

The economic data on brain disorders in Europe were based on extensive reviews of available evidence in the literature. The reviews were conducted by health

[1]This document refers to mental disorders as defined by the ICD 10 and DSM-V classification; this term is used in some text portions interchangeably with the older terms of psychiatric diseases or illness.

Table 1 Global burden of disease study results

	Global			EU25			EU15			EU10		
Groups	Total	Per 1000	%	Total	Per 1000	%	Total	Per 1000	%	Total	Per 1000	%
Mental	191 660 642	30.8	12.9%	14 857 720	32.8	25.3%	12 379 282	32.7	26.3%	2478 438	33.27	21.16%
CVD	138 013 023	22.2	9.3%	10 088 093	22.2	17.1%	7637 493	20.1	16.2%	2450 599	32.90	20.92%
Cancer	77 152 633	12.4	5.2%	9839 035	21.7	16.7%	7989 864	21.1	16.9%	1849 172	24.82	15.78%
Injuries	182 590 897	29.3	12.2%	5099 011	11.2	8.7%	3644 620	9.6	7.7%	1454 392	19.52	12.41%
Respiratory	55 059 995	8.9	3.7%	3523 243	7.8	5.9%	3167 675	8.4	6.7%	355 568	4.77	3.04%
Digestive	46 300 182	7.4	3.1%	2925 351	6.5	4.9%	2205 780	5.8	4.7%	719 571	9.66	6.14%
Musculoskeletal	28 349 766	4.6	1.9%	2563 271	5.7	4.4%	1994 910	5.3	4.2%	568 362	7.63	4.85%
Infections	462 516 353	74.3	31.0%	2282 694	5.0	3.9%	1849 365	4.9	3.9%	433 329	5.82	3.70%
Nutrition/End	61 520 078	9.9	4.1%	2390 372	5.2	4.0%	2042 736	5.4	4.3%	347 636	4.67	2.97%
Sense organs	69 379 818	11.2	4.7%	2868 843	6.3	4.9%	2248 811	5.9	4.8%	620 032	8.32	5.29%
Maternal	128 884 629	20.7	8.6%	725 905	1.6	1.2%	593 440	1.6	1.2%	132 464	1.78	1.13%
Oral	7 372 021	1.2	0.5%	434 767	0.9	0.7%	343 829	0.9	0.7%	90 937	1.22	0.78%
Urinary	15 213 854	2.4	1.0%	601 238	1.3	1.0%	498 616	1.3	1.0%	102 622	1.38	0.88%
Congenital	27 402 428	4.4	1.9%	608 304	1.3	1.0%	496 447	1.3	1.0%	111 857	1.50	0.95%
Total	1 491 416 317	239.6	100%	58 807 846	129.7	100%	47 092 868	124.2	100%	11 714 978	157.26	100%

Note. EU25 refers to all EU member states, EU15 refers to the EU member states before 2004 and EU10 refers to the EU member states in the European monetary union.

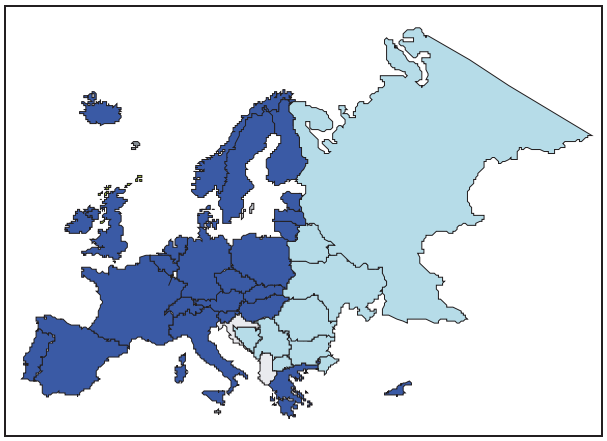

Figure 1 Countries included in study (in blue): the 25 EU member states and Iceland, Norway and Switzerland.

economists. Studies with at least an abstract in English were identified using essentially Medline and HEED (Health Economic Evaluations Database). All abstracts were screened and studies selected if they:
1 contained full or partial cost of illness information;
2 concerned any European country;
3 were not based on a clinical trial;
4 and were not limited to a specific treatment or a short treatment episode.
Economic evaluations were only included if they contained basic cost of illness information with standard care and if no other information for the country was available. Analyses using data from cost of illness studies published separately or publications relating to already published basic data were excluded, as were review studies, commentaries, and pure quality of life studies. Studies providing utility measures for defined types of patients were included to allow estimation of intangible costs. For brain disorders where little evidence was found in Medline or HEED, literature searches were also employed in other European sources such as: governmental bodies, patient organizations and research institutes. However, limitations in our literature search should be noted, as no evidence was reviewed in local languages, e.g. studies conducted in Central and Eastern European countries. Moreover, the omission of economic evolutions may have constrained the amount of evidence obtained. For a more detailed description of the methodology and results from the reviews, see previous publications by disease area (Andlin-Sobocki, 2004; Berg, 2004a,b; Ekman, 2004a,b; Ekman and Forsgren, 2004; Jönsson, 2004; Kobelt, 2004; Lindgren, 2004; Lothgren, 2004a–c)[2].

Cost data were presented in terms of average cost per patient, and stratified by age, gender and disease severity where the published evidence allowed it. The inclusion of resource use components varied between the different brain disorders according to availability of data (see Table 2).

For most mental disorders, resource use outside the health care sector is not available but it is expected to be high. The existence of data indicated in Table 2, does not mean that it was complete, or present for many countries. But there was enough data for use in the model estimating total cost. For a more detailed description of the economic input data for the present study see the section *Part II. Epidemiologic and economic evidence in specific brain disorders in Europe*.

[2]All articles are available at the official project web-page: http://www.ebc-eurobrain.net

Table 2 Resource components included in economic input data

	Healthcare costs	Direct non-medical costs	Indirect costs
Addiction			
Illicit drug dependence	X	X	X
Alcohol dependence	X	X	
Affective disorders			
Depression	X		X
Bipolar	X		X
Anxiety disorders			
Panic disorder	X		X[1]
GAD	X		X[1]
Specific phobia	X		X[1]
OCD	X		X[1]
Agoraphobia	X		X[1]
Social phobia	X		X[1]
Brain tumour	X	X	X
Dementia	X	X	
Epilepsy	X	X	X
Migraine and other headaches[2]	X		X
Multiple sclerosis	X	X	X
Parkinson's disease	X	X	X
Psychotic disorders	X	X	
Stroke	X	X	X
Trauma	X		

[1]Only including reduction in workdays due to sick-leave.
[2] Not including data on non-migrainous headaches.
GAD, generalized anxiety disorder; OCD, obsessive compulsive disorder.

National statistics

National and international statistics were collected from international data sources for the model. Population statistics and national welfare statistics (e.g. gross domestic product, healthcare expenditure) were retrieved from the Eurostat database 2004 (Eurostat, 2004a) and OECD Health database 2004 (OECD, 2003). Cost data were inflated to year 2004 with the consumer price index (Eurostat, 2004b; Bureau of Labour Statistics, 2005), and converted to Euros (€), adjusted with purchasing power parity (European Central Bank, 2004; Eurostat, 2004c). Indexes were calculated based on national welfare statistics and price level indexes retrieved from the Eurostat database 2004 (European Central Bank, 2004; Eurostat, 2004c). In Table 3 the most relevant national statistics used in the study are presented.

Epidemiology data

The epidemiology data used in this study are based on a systematic review of published epidemiology data in Europe (Wittchen and Jacobi, 2005). The extensive reviews were based on published evidence. The main source used for the reviews were electronic databases (MedLine and Web of Science) complemented with national registries and the Internet. Twelve international groups of epidemiologists worked on the project, each group with expertise in the epidemiology of one of the brain disorders covered by the project (see *Acknowledgements* for names and affiliations). All reviews resulted in articles which were published early 2005 (Berr *et al*., 2005; Campenhausen *et al*., 2005; Fehm *et al*., 2005; Forsgren *et al*., 2005; Goodwin *et al*., 2005; Lieb *et al*., 2005; Paykel *et al*., 2005; Pini *et al*., 2005; Pugliatti *et al*., 2005; Rössler *et al*., 2005; Rehm *et al*., 2005a,b; Servadei *et al*., 2005; Stovner *et al*., 2005; Truelsen *et al*., 2005; Westphal *et al*., 2005; Wittchen and Jacobi, 2005) [3]. The multinational experts included in the data collection ensured the review of all possible data including local sources as well as grey literature. Twelve months prevalence data were collected in all areas of brain disorders by country. Moreover, data were stratified on age, gender and disease severity where published evidence allowed it. In countries where no epidemiology data were available in the literature, the review group of epidemiology experts in each disease area made best estimates for the specific country or extrapolated from available data. Where multiple studies were available for one country, the most representative data were used. For a more detailed description of the epidemiologic input data used in the present study see the section *Part II. Epidemiologic and economic evidence in specific brain disorders in Europe*.

Cost-of-illness methodology

The basic principle in costing is that resources should be valued according to their 'opportunity cost' (i.e. the cost in terms of opportunities lost). This means that the best alternative use for the resources should be decided and the cost then considered in relationship to that. As it is not possible to observe this opportunity cost directly, we are in practice limited to the observation of 'accounting costs'. An important part of any cost-of-illness study is to make a judgement of how well these 'accounting costs' reflect the true opportunity cost.

The methodology used in the cost-of-illness studies is briefly discussed below and more extensively in previous publications (Hodgson and Meiners, 1982; Tolpin and Bentkover, 1983; Drummond *et al*., 1987).

Cost perspective

A cost-of-illness analysis can be conducted from several different perspectives. The perspective chosen determines which costs are included in the analysis (e.g. an individual hospital, insurance company or govern-

[3]All articles are available at the official project web-page: http://www.ebc-eurobrain.net

Table 3 National statistics included in study

	Population statistics	GDP/capita (€PPP)	Gross wage (€PPP)[1]	Healthexpenditure/ capita (€PPP)	Exchange rate (to €PPP)	Comparative price level[2]
Austria	8 053 100	26 680	27 493	2135	15.6	1.13
Belgium	10 332 785	25 620	30 143	2279	44.3	1.10
Cyprus	710 338	18 380	17 871	1489	0.6	0.99
Czech Republic	10 204 853	14 820	15 230	1096	18.6	0.58
Denmark	5 375 931	27 000	29 591	2268	11.0	1.47
Estonia	1 358 644	9 650	4 587	531	10.3	0.66
Finland	5 200 598	24 490	22 423	1714	7.9	1.33
France	59 486 121	25 240	23 883	2494	7.5	1.14
Germany	82 488 495	23 950	34 258	2587	2.3	1.15
Greece	10 538 037	16 990	18 266	1663	303.7	0.89
Hungary	10 158 608	12 830	9 575	1142	154.3	0.61
Iceland	287 523	26 250	25 514	1785	125.6	1.44
Ireland	3 931 756	30 160	27 173	1949	1.1	1.34
Italy	57 761 956	23 680	24 931	2188	2092.0	1.08
Latvia	2 338 624	8 370	4 528	703	0.4	0.58
Lithuania	3 469 070	9 570	5 225	612	2.0	0.58
Luxembourg	446 175	45 630	34 631	2738	44.9	1.11
Malta	393 028	16 530	17 489	999	0.3	0.77
Netherlands	16 148 929	26 800	31 235	2358	2.5	1.13
Norway	4 538 159	32 810	28 611	2625	12.8	1.53
Poland	38 425 492	10 010	12 728	608	2.6	0.56
Portugal	10 368 403	17 050	15 870	1568	168.5	0.84
Slovakia	5 379 056	11 340	8 703	647	21.1	0.53
Slovenia	1 994 530	16 710	7 203	1404	194.9	0.82
Spain	40 265 502	20 710	20 402	1564	150.6	0.90
Sweden	8 924 958	25 190	23 716	2191	12.0	1.31
Switzerland	7 289 542	28 130	36 907	3119	2.0	1.31
United Kingdom	59 743 113	25 840	37 171	1945	0.7	1.09
Europe	465 613 326					

[1]Gross earnings are remuneration (wages and salaries) in cash paid directly to the employee, before any deductions for income tax and social security contributions paid by the employee.
[2]Comparative price levels of final consumption by private households including indirect taxes.
Note. Purchasing power parity (PPP) is an international measure to be able to compare economic data between countries by adjusting for the relative purchasing power in the respective countries. Gross domestic product is a measure of the total national income in a country.

ment). The societal perspective implies that all costs, whether incurred by individuals, employers, or government, should be taken into account. This is preferred since the economic theory underpinning the evaluative work in the healthcare field has focused on the social welfare function, which suggests a broad societal perspective. A second reason is that brain disorders have impacts across a wide range of personal dimensions (e.g. one's health, quality of life, ability to work, social relations, income) and hence it would be falsely constraining to only look at the healthcare consequences. Thirdly, the boundaries around healthcare are different between countries so that what is called healthcare in one system is called social care in another system and consistency of estimation would require a comprehensive measure. It is also consistent with a social perspective on health and health care.

Direct healthcare costs are costs for goods and services used in the prevention, diagnosis, treatment and rehabilitation of the illness, disease or disorder in question, e.g. costs for medical visits, hospitalization and pharmaceuticals. Direct non-medical costs include all other resource use related to a disease, for example transportation, social services, adaptations of accommodations etc. Sometimes it can be difficult to decide if a specific cost item, for example informal care, should be included as healthcare cost or non-medical costs. From a societal perspective, it does not matter as long as it is included in the analysis.

Indirect costs are defined as the value of the output that is lost because people with a certain illness, disease or disorder are impaired and too ill to work, either short-term or long-term (Luce and Elixhauser, 1990). There are two main valuation methods for indirect costs: the friction method and the human capital approach. In this study the latter method was applied.

Typical cost items in this category are costs of loss of production due to short-term absence from work and from early retirement. Sometimes also reduced productivity at work due to illness, for example as a consequence

of depression, is included as well. The loss of production associated with disability is valued using gross earnings lost or some proportion of the gross earnings if an individual is unable to work at full capacity (Hodgson and Meiners, 1982; Luce and Elixhauser, 1990).

Sometimes lost production due to premature mortality is included in the analysis as well.

There are also intangible costs, which include pain, psychosocial suffering, and changes in social functioning and activities of daily living. Intangible costs are in general not included in currently available cost of illness studies due to difficulties in quantifying these costs. However, the intangible costs are probably far from insignificant for many diseases, and may often be dominating. These costs can be valued as DALYs or quality-adjusted life-years (QALYs) lost.

Top-down versus bottom-up approach

The top-down approach to cost estimation means that the total national costs for illnesses are divided between different diseases according to main diagnosis. In the bottom-up approach, data are collected directly from a sample of patients with a defined disease, and the figures from the sample are extrapolated to represent the whole population by using national prevalence figures.

The advantage of using the top-down approach is that no extrapolation is needed and that it avoids the risk of double counting. The disadvantage compared with the bottom-up approach is that diagnoses may be underreported or misreported and that important cost items are missing from the national illness registers. For example, costs for social services or unpaid home help are unaccounted for if a pure top-down approach is used as such resource use is not registered according to diagnosis. The value of informal care as a consequence of disease is also missing from a top-down approach to cost-of-illness studies. For mortality and disability pensions granted, a main diagnosis (but not other diagnoses) is registered in most cases. For short-term illness statistics are normally very deficient.

The current study is mainly based on the bottom-up approach, where the cost data are collected per patient and disease and aggregated to national levels with the help of prevalence data.

Prevalence- and incidence-based cost estimates

Cost of illness studies can be performed by using either prevalence or incidence-based methods (Hodgson and Meiners, 1982). Prevalence based studies examine costs incurred during a given time-period, usually 1 year, regardless of the date of the onset of disease. Incidence-based studies examine costs for cases of the disease that develop for the first time in that year. Future costs and production losses are then estimated for the entire lifetime of these patients and calculated in terms of present values. As incidence-based studies can be used for calculating the economic benefits of reducing the number of new cases, they are suitable for evaluating preventive measures (Henriksson *et al.*, 2001). A longitudinal analysis has the advantage of taking account of the temporal aspects of the disease, but it may be logistically difficult to follow patients over many years.

The prevalence approach has the advantage of producing cost estimates which present the annual costs for a disease in a given year and thus is comparable with the total annual costs for other, or all, diseases. If cost control is the primary concern, the prevalence approach is preferred, as the main components of current spending and lost resources (indirect costs) are identified and can be subject to savings efforts. In the present study prevalence based cost estimates were conducted as the goal was to give a broad overview of the cost of brain disorders in Europe, and to be able to compare with the cost of other disease areas as well as with national accounts.

Scope of study

The following 12 major disease areas of the brain are included in the present study: addiction (alcohol and illicit drugs), affective disorders (depression and bipolar I and II), anxiety disorders [panic disorders with and without agoraphobia, phobias (agoraphobia without panic, social phobia, specific phobias), generalized anxiety disorder (GAD) and obsessive compulsive disorder (OCD)], brain tumour, dementia, epilepsy, migraine and other headaches, multiple sclerosis, Parkinson's disease, psychotic disorders (schizophrenia), stroke and trauma (traumatic brain injury). In the presentation of results the following disease categories shall be used: neurological diseases [dementia, epilepsy, migraine and other headaches, multiple sclerosis (MS), Parkinson's disease, stroke], neurosurgical diseases (brain tumour, traumatic brain injury) and mental disorders (addiction, anxiety disorders, affective disorders, dementia and psychotic disorder). The reason for categorizing dementia into both neurological diseases and mental disorders is due to the fact that it is considered to belong to both fields in the research community. As a compromise, 50% of the specific results in dementia are referred to neurological diseases and 50% to the mental disorders. As a consequence of limiting the study to the 12 major disorders of the brain, we omit less prevalent or less homogeneous groups of brain disorders from our cost results. Hence, the total cost of all brain disorders can be expected to be much higher than the results presented in this study.

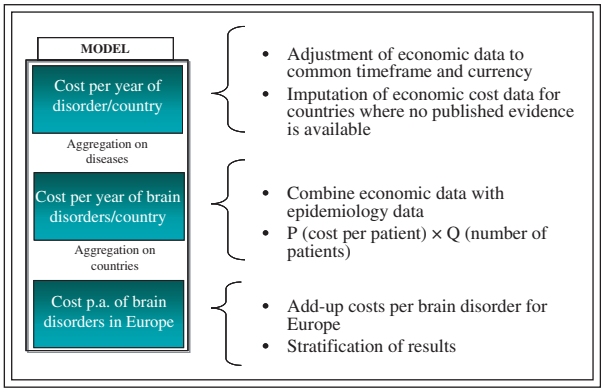

Figure 2 Health economic model.

The geographical scope is set to the 25 European member states (by 2004) plus Iceland, Norway and Switzerland.

Health economic model

The model deployed for this study aims at assessing the cost of illness for Europe with the help of three major sources of data: economic data, epidemiology data and international statistical data. The model was also used to predict results for countries where no input data were available in the literature. The economic model is depicted in Fig. 2.

As the model is based on available epidemiology and economic data from the individual brain disorders included in the study, there is an inherent problem of double counting (see *Top-down versus bottom-up approach*).

This problem stems less from the economic data, as they measure the cost for a specific brain disorder rather than the cost for a patient with the disease. In the epidemiologic data, however, which are determined by individual brain disorder, the problem of comorbidity becomes critical. Diseases are added to form an aggregated estimate for brain disorders in total (e.g. patients with dementia probably also have depression and hence are double-counted in the cost calculations). The issue of comorbidity is most apparent within the mental disorders, where multiple diagnoses are common (e.g. anxiety disorders and addiction). Hence, this problem might result in an over-estimation of the total number of patients with brain disorders in Europe and consequently may inflate the total cost estimates of brain disorders in Europe.

The health economic model described in Fig. 2 is explained in detail in the following. The model serves four major purposes:

1 Time transformation of economic data. The cost data collected from the literature are reported from different years for which they were originally costed. In order to be able to compare the price tags (cost per patient) across nations, it is necessary to transform the data to a common year. The year chosen for the study is 2004. There are several measures for inflating cost estimates. The measure chosen for the present study was the consumer price index (inflation), which is an aggregate measure of the increase in the consumer prices for a predefined basket of goods and services in the specific country. A health-specific price index could also serve as an appropriate inflator, but no international statistics were obtained covering *all* European countries selected for this study.

2 Adjustment for international comparison. The data collected for the study are reported in different currencies, and consequently influenced by the price level existing in the specific country, from where the estimate origins. In order to be able to compare the cost estimates across Europe, the collected cost data were adjusted for the differences in purchasing power. Purchasing power parity adjusted currency rates were therefore used and all results were converted to Euro (€PPP).

3 Imputation of data. For countries in Europe where no cost data were available, the model was developed to impute cost estimates based on the available input data. An average of the selected economic input data was calculated and formed the basis for imputation. The imputation used different algorithms which were based on indexes from international statistics to eliminate the price level differences across Europe. Healthcare cost data were imputed with an index on price level differences in the healthcare sector in Europe, direct non-medical cost data (e.g. transportation, adaptations due to disease, etc.) were imputed with an index on price level differences in the whole economy of European nations (national income), the drug cost data were imputed with an index on price level differences in the pharmaceutical sector and, lastly the indirect cost data were imputed with an index based on wage level differences in Europe. As a base case, the indexes applied were based on purchasing power parity statistics. Sensitivity analyses were conducted based on indexes presented in nominal values, real values and real values with purchasing power parity adjustment.

4 Assessing the cost of illness in Europe. The final step in the model is to combine the two data sets in order to estimate the cost of illness in Europe. Hence, the cost data were aggregated to national levels with the help of prevalence data for each European country and the estimates for each country were added to yield an aggregated European cost estimate.

Model validation

The health economic model was tested for its validity in two ways: sensitivity analysis on critical assumptions made in the model (internal validity) and the base case cost estimates were compared with previous cost estimates in brain disorders (external validity). Cost results were compared with previous European and American studies in the field.

Results

Total prevalence

The total number of people with any brain disorder in Europe amounted to 127 million in 2004, corresponding to 27% of the total number of inhabitants in the European countries covered by this study. The total prevalence of brain disorders is an aggregate of the prevalence estimation for each brain disorder included in the study. However, the prevalence estimates in mental disorders, migraine and epilepsy are all based on the European patient populations aged 18–65 years. The estimates in dementia and Parkinson's disease are limited to the population aged 65 years or older, and stroke on the age group 25 years or older.

Total numbers of cases with addiction in Europe totalled 9 million (including illicit drug dependence and alcohol dependence). If we were to add nicotine dependence to this estimate the total amount of cases would be 37 million. Affective disorders (depression and bipolar disorders) and anxiety disorders (panic, phobias, OCD and GAD) resulted in 21[4] and 41 million cases in Europe respectively. The most prevalent neurological brain disorder is migraine, with an estimated 41 million cases in Europe. Distribution of the total number of estimated cases with brain disorders in Europe across specific disorders are presented in Fig. 3. Amongst the less prevalent brain disorders multiple sclerosis and brain tumour have an estimated 380 000 and 135 000 cases, respectively.

As cases of specific brain disorders were added to an aggregate estimate for Europe, there is an expected overestimation. Due to comorbidity both within disorders (e.g. anxiety disorders) and between neurological and mental disorders, e.g. multiple sclerosis and depression, the number of persons with a brain disorder is smaller than the estimated prevalence. Assuming a comorbidity between neurological and mental disorder

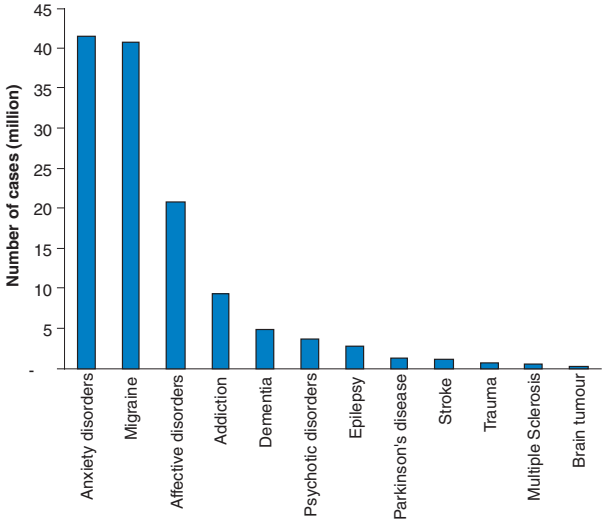

Figure 3 Total number of cases of disorders of the brain in Europe by specific disorder (million)
Note: The number of cases of stroke and trauma are based on incidence data in the lack of appropriate prevalence data in the literature. Results on addiction omit nicotine dependence and abuse.

of 31.6%[5], the total number of persons with brain disorders in Europe would be the order of 104 million.

It should be noted that the number of cases calculated for stroke and trauma were based on incidence data rather than prevalence data, and it is expected that the number of cases are underestimated relative to other disorders of the brain.

In Table 4, it should be noted that there are significant differences in the number of cases of disorders of the brain in different European countries, which mainly reflects the size of the population. The relative prevalence of any brain disorder across Europe (i.e. proportion between number of cases of brain disorders and total population) is shown graphically in Fig. 4. The frequency of brain disorders ranges from 19 to 36% (note that these numbers are not adjusted for comorbidities between brain disorders). Interestingly, some northern European countries (The Netherlands, Norway, Sweden and Germany) have the highest prevalence of brain disorders, whereas southern European countries (France, Italy and Spain) have lower prevalences. Given the considerable heterogeneity of methods, the consistency of prevalence estimates for all brain disorders is striking. It is beyond our ability to decide whether the differences between countries are true or simply results of slightly different assessment strategies and design to estimate the prevalence.

[4]This estimate refers to adults (age 18–65). Assuming the same prevalence for younger (< 18) and older (> 65) populations, the estimate would be 32 million cases in Europe.

[5]Estimate from the German Health Examination Survey (Jacobi *et al.*, 2002; Wittchen *et al.*, 2000).

Table 4 Total prevalence of disorders of the brain in Europe

	Addiction	Affective disorders[1]	Anxiety disorders[1]	Brain tumour	Dementia[2]	Epilepsy	Migraine	Multiple sclerosis	Parkinson's disease[2]	Psychotic disorders[1]	Stroke[3]	Trauma[1]	Total
Austria	194 795	479 091	847 622	2 213	79 882	48 319	537 003	7 973	16 226	136 883	18 195	12 372	2 380 572
Belgium	241 599	502 788	1 051 284	3 730	140 351	61 997	862 855	9 093	22 807	13 059	22 723	15 345	2 947 631
Cyprus	13 178	35 443	65 888	223	5 337	4 262	60 045	369	1 084	3 635	1 090	1 068	191 623
Czech Republic	34 419	366 910	1 011 929	2 657	90 640	61 229	909 655	9 082	18 411	75 723	43 231	16 177	2 640 065
Denmark	99 936	258 455	499 680	1 641	50 978	40 857	344 607	6 021	10 355	27 569	11 907	8 098	1 360 104
Estonia	25 182	67 732	125 912	330	13 651	7 201	114 747	693	2 773	6 947	5 623	2 041	372 831
Finland	147 054	193 844	421 110	1 361	50 750	32 764	441 641	7 281	10 309	26 737	12 570	7 854	1 353 275
France	462 184	2 884 026	4 510 912	17 998	629 014	356 917	4 885 941	29 743	117 093	295 798	93 508	86 891	14 370 024
Germany	1 994 420	4 905 195	8 678 421	23 112	912 145	494 931	7 122 928	68 465	260 817	1 401 484	199 900	126 673	26 188 490
Greece	209 278	562 885	1 046 389	5 536	115 393	63 228	953 606	4 110	23 439	57 732	47 507	16 959	3 106 063
Hungary	246 422	532 804	1 345 331	3 101	99 557	60 952	639 365	6 298	20 223	53 280	37 834	15 651	3 060 819
Iceland	6 602	16 236	32 294	85	2 148	1 236	23 577	342	436	4 639	450	419	88 464
Ireland	73 526	197 760	367 631	1 023	28 015	23 591	335 033	2 575	5 691	20 283	6 689	5 958	1 067 774
Italy	264 926	1 324 629	3 595 422	16 272	617 122	358 124	5 001 151	53 526	199 048	756 931	156 691	88 939	12 432 782
Latvia	43 629	117 348	218 147	486	23 470	14 032	198 804	1 169	4 767	12 036	13 622	3 535	651 046
Lithuania	63 370	170 443	316 850	847	32 364	14 917	288 755	1 249	6 574	17 481	9 994	5 135	927 979
Luxembourg	8 398	22 589	41 992	162	3 994	2 677	38 269	341	811	2 317	1 032	681	123 262
Malta	7 416	19 948	37 082	95	3 134	2 358	33 794	67	637	2 046	814	601	107 992
Netherlands	473 187	715 038	1 829 656	5 011	207 701	96 894	2 439 541	12 919	28 725	21 031	30 789	24 711	5 885 202
Norway	204 333	312 176	581 783	1 496	43 180	23 145	340 556	4 300	8 771	5 676	10 110	6 669	1 542 195
Poland	724 800	1 949 463	3 624 002	11 411	277 013	299 719	3 302 662	21 134	63 178	199 945	87 809	58 734	10 619 871
Portugal	196 353	528 122	981 766	2 626	110 211	62 210	894 712	4 873	22 387	54 166	56 485	15 911	2 929 824
Slovakia	103 606	278 663	518 028	1 242	39 560	32 274	472 094	4 106	8 036	28 581	9 115	8 396	1 503 701
Slovenia	38 978	104 839	194 892	598	18 662	11 967	177 611	1 655	3 791	10 753	6 062	3 159	572 967
Spain	192 481	1 347 368	1 457 358	10 300	506 592	165 089	3 633 574	20 650	151 019	219 979	80 102	64 619	7 849 131
Sweden	360 696	455 032	1 104 284	2 453	98 107	49 087	732 490	13 744	17 629	44 393	21 207	13 041	2 912 165
Switzerland	137 884	370 860	713 193	1 682	72 324	43 737	628 289	8 018	14 691	38 037	9 965	11 173	2 049 854
United Kingdom	2 625 589	2 137 980	6 188 889	17 559	614 957	256 895	5 363 704	79 800	119 264	150 034	133 960	88 145	17 776 776
Europe	9 194 244	20 857 669	41 407 747	135 251	4 886 252	2 690 608	40 777 009	379 599	1 158 990	3 687 173	1 128 986	708 954	127 012 482

[1]Prevalence data were based on population aged 18–65 in Europe.

[2]Prevalence data were based on population aged 65 or older.

[3]Prevalence data were based on population aged 25 or older.

Note: The total number of cases in stroke and trauma are based on incidence data and hence are expected to be underestimated relative to other disorders of the brain.

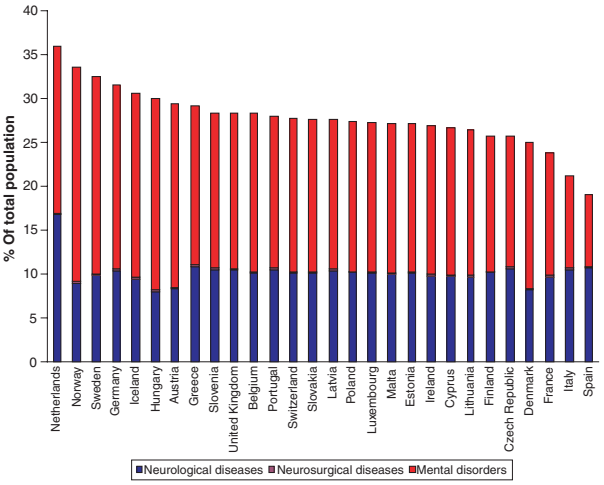

Figure 4 Prevalence of any brain disorders in European countries 2004 (%).

Cost per patient

The economic input data were calculated in terms of cost per case of each specific brain disorder. For countries where no input data were available, cost data were imputed using indexes which adjusted for price level differences across countries in Europe. The estimated cost per case is displayed by country and by brain disorder in Table 5. The cost per case differs significantly across the specific disorders of the brain, ranging from €133–1030 per case of migraine in Europe to €9000–68 000 per case of brain tumour in Europe. Our estimates show that the cost per case of brain disorder differs between countries and are highest in countries with the highest national income and healthcare expenditure per capita. This explains the estimated lower costs per case in the EU admission countries. The less prevalent disorders of the brain have a higher cost per case, e.g. brain tumour and multiple sclerosis.

Figure 5 presents the average cost per case in each brain disorder. Brain tumour has an average cost per case of €39 000 across Europe. Multiple sclerosis has a slightly lower cost per case, with an average in Europe reaching €24 000. These cost estimates are weighed averages across Europe, see Table 5. Addiction, anxiety disorder and migraine have the lowest average cost per case: €1700, 800 and 600, respectively. However, it should be emphasized that there is a considerable degree of uncertainty. Regarding the precision of such estimate – both with regard to the disorders specific total cost as well as the respective estimations for each country.

Therefore, it should be noted that direct comparison of cost results between disorders of the brain are difficult to make, due to scarce data. For instance, the cost per case of trauma is only based on cost of hospitalization, and hence omits both rehabilitation and costs due to lost workdays.

Total cost of brain disorders

The total cost of all brain disorders was estimated at €386 billion in 2004 in Europe (see Table 6). However, it should be remembered that this is a conservative estimate as: (i) not all brain disorders are included in the estimate, (ii) not all costs are included for some disorders and (iii) prevalence estimates for some disorders do not cover the whole population.

The cost of nicotine dependence was not included in the final cost estimate of brain disorders in Europe, due to the restricted scope in this study. Moreover, most cost studies on smoking concentrate on smoking in general, which is too broad a category to include under addiction. Nevertheless, the cost of nicotine dependence amounted to another €15 billion. Another specific brain disorder where a major cost component is omitted is for non-migraine headaches, as there is no economic evidence available for these in Europe. However, estimating the cost of other headaches based on American cost data would suggest an additional cost of €46 billion in addition to migraine. Including these two estimates to the total cost of disorders of the brain in Europe, it would total €447 billion. The cost of stroke is, moreover, expected to be underestimated, due to scarcity of good prevalence data and follow-up data on cost of stroke after the 1 year with stroke. In addition, several other costs are missing and shown in detail in Table 2.

As can be observed in Table 7, the total cost of disorders of the brain is unevenly distributed across European countries in absolute terms. This is due to differences both in size of the European economies as well as differences in populations. Seventy per cent of the total cost of brain disorders is attributable to the five major countries in Europe (Germany, UK, France, Spain and Italy). The same countries hold 64% of the total population in Europe. The cost of brain disorders varies substantially from one European country to another. There are two reasons for the difference: difference in the prevalence of brain disorders (which was observed earlier) and differences in the cost per case of brain disorder. Table 7 shows the distribution of the total cost. The indirect costs are almost twice as big as the direct costs. The direct healthcare costs are almost twice as big as the direct non-medical costs.

Cost of brain disorders per inhabitant

The average cost of brain disorders in Europe was €829 per inhabitant (based on a total number of inhabitants

Table 5 Cost per case of brain disorder (€PPP 2004)

	Addiction		Anxiety disorders						Affective disorders										
	Alcohol	Drug	GAD	OCD	Panic	Specific phobia	Agoraphobia	Social phobia	Depression	Bipolar	Schizophrenia	Dementia	Trauma	Tumour	Parkinson	Muiltiple sclerosis	Epilepsy	Migraine	Stroke
Austria	7649	4721	2242	443	1229	655	1202	1183	4884	7779	9487	13635	2870	49815	9291	30462	6965	768	20784
Belgium	8328	5041	2403	480	1335	710	1310	1280	5328	8512	10129	15435	3064	54338	9990	32871	7632	841	22371
Cyprus	5057	3292	1548	297	820	440	796	798	3224	5100	6615	9311	2001	32869	6409	20355	4551	500	14209
Czech Republic	4166	2424	1164	238	663	351	654	630	2710	4385	4871	7374	1474	27386	5157	16800	3958	427	11008
Denmark	8204	5016	2387	474	1317	701	1290	1265	5158	8161	12127	14690	3049	53108	9318	31938	7278	821	24360
Estonia	1431	1174	531	90	242	133	225	248	952	1492	2360	3265	714	9375	2533	6639	1329	133	4777
Finland	6221	3791	1805	359	997	531	977	957	3969	6331	7618	19480	2305	40495	7615	24912	5672	626	16763
France	7179	5516	2524	442	1202	657	1135	1213	4702	7370	11084	6084	3353	46989	11089	30634	6559	739	22765
Germany	9201	5721	2728	546	1517	806	1488	1453	7102	9603	11496	12735	3478	61610	11138	31096	8599	853	28869
Greece	5283	3679	1710	316	868	469	834	857	3377	5299	7392	10193	2236	34328	7143	21420	4712	514	15527
Hungary	3001	2526	1140	190	512	283	475	528	2037	3209	5075	7111	1535	19880	5642	13720	2868	281	10271
Iceland	6938	3948	1904	394	1100	581	1088	1041	4414	7086	7933	11694	2400	45191	7762	27305	6365	709	17889
Ireland	7432	4309	2071	424	1181	625	1166	1123	4673	7445	8660	10984	2620	48134	8088	29108	6660	752	19280
Italy	7144	4838	2260	424	1168	629	1126	1146	4664	7425	9556	13957	2941	46874	10105	24183	6733	706	20809
Latvia	1559	1556	686	104	276	156	248	297	1057	1619	3126	4144	946	10249	3356	7521	1428	136	6015
Lithuania	1634	1354	612	103	277	153	258	271	1089	1705	2721	3758	823	10721	2921	7348	1519	152	5496
Luxembourg	9697	6055	2868	562	1559	832	1522	1505	6128	9707	12166	17187	3681	62775	11554	39148	8664	965	26423
Malta	4567	2210	1103	250	707	367	714	649	2862	4636	4441	6795	1343	29663	4140	17181	4178	480	10605
Netherlands	8627	5215	2487	497	1383	735	1357	1325	5436	8622	7011	14854	3170	55925	9769	33483	7698	867	23044
Norway	8303	5805	2697	497	1364	737	1308	1348	5228	8140	11666	16363	3529	53554	10774	33603	7206	801	24317
Poland	3221	1344	695	171	490	251	503	437	2084	3465	2701	4672	817	21272	2986	12208	3164	351	7008
Portugal	4697	3468	1597	286	780	424	742	780	3084	4869	6969	9785	2108	30811	7268	19983	4348	453	14518
Slovakia	2403	1430	683	138	383	203	377	366	1596	2603	2873	4464	869	15911	3277	10167	2361	246	6504
Slovenia	2723	3106	1348	191	499	288	434	555	1826	2703	6240	7870	1888	17693	6399	13581	2344	220	11548
Spain	5661	3459	1646	327	908	483	889	872	3445	5807	5082	10107	2103	36948	6946	22703	5210	570	13383
Sweden	6892	4846	2249	413	1134	613	1087	1122	4396	6886	9738	11240	2946	44708	9073	38329	6157	667	18852
Switzerland	10463	6899	3238	617	1703	914	1650	1662	6622	10412	13862	19177	4194	67841	12996	41121	9260	1030	29541
United Kingdom	5734	4302	2184	515	1465	756	1493	1327	5088	9895	12250	13864	2615	62399	9406	25625	6435	611	16986
Europe[1]	5836	3823	1804	350	967	517	941	937	3826	6081	7688	10722	2324	38959	7577	23695	5352	579	16569

[1]Population-weighted European average cost per case by specific brain disorder.

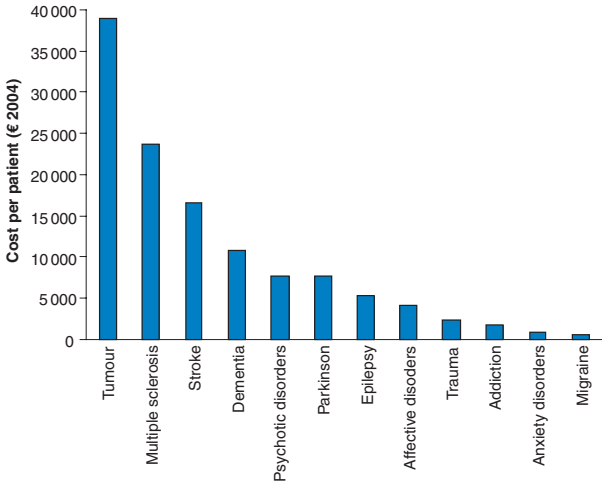

Figure 5 Cost per case of in specific brain disorders in Europe (€PPP 2004).

in Europe of 466 million). Figure 6 shows the difference in cost of brain disorders per inhabitant between European countries. The cost of brain disorders per inhabitant is higher in western European countries compared with the EU admission countries. This can be due to either higher prevalence numbers in western Europe or higher costs per case. The comparison of the cost of brain disorders per inhabitant in different European countries should be taken with caution. The economic input data are scarce in some areas of brain disorders and often depending on estimates for one single country. Furthermore differences in results are driven by the assumptions made in the cost estimation model and, thus, depend on the national statistics presented in Table 3. For instance, indirect cost estimates are imputed with the relative wage difference (adjusted for purchasing power) in European countries. The wage statistics in Table 3, explained for instance the difference in cost results obtained for Germany, UK and France. Moreover, there are substantial differences in the prevalence of certain brain disorders between countries in Europe, which heavily influences the differences in the cost per inhabitant of brain disorders.

Cost of brain disorders distributed by resource items

The distribution of the total annual cost of brain disorders in Europe on different resource items is presented in Fig. 7. Direct healthcare cost due to brain disorders in Europe (i.e. cost of hospital care, drugs and outpatient visits) amounted to €135 billion, corresponding to 35% of the total cost. The cost for hospital care is the dominating healthcare cost, reaching €78 billion in 2004 (20% of the total cost and 57% of the healthcare cost). The cost of outpatient care amounted to a total of €45 billion, making up 12% of the total cost of disorders of the brain. Drug cost totalled €13 billion (3% of the total cost). However, it should be noted that this cost estimate relies on cost data originating from the 1990s or at best beginning of 2000. The cost patterns have radically changed in many disorders of the brain (e.g. Parkinson's disease and multiple sclerosis), where new treatments have been introduced. However, it can be expected that the increased cost of treatments is offset by reduction in other healthcare resource utilization (e.g. hospital care) and these effects thus may equal out.

Direct non-medical costs (i.e. community care, transportation, adaptations and informal care) totalled €72 billion in Europe. The largest non-medical resource component was cost of social services due to brain disorders, amounting to €52 billion (13% of total cost). Informal care was only estimated for dementia and multiple sclerosis, but for these disorders it totalled €13 billion (corresponding to 3% of the total cost). The cost of adaptations and transportation (other costs) was €8 billion (2% of the total cost). However, it should be noted that direct non-medical cost was not estimated at all in several disorders of the brain (cf. Table 2). Hence the total direct non-medical cost due to brain disorders is conservatively estimated.

The bulk of the cost of disorders of the brain in Europe was due to lost workdays and production (indirect costs). The indirect cost was estimated to €179 billion, 46% of the total cost. The majority of the indirect cost of brain disorders was caused by sick leave, €124 billion (33% of the total cost). The cost of lost workdays due to early retirement and premature death each amounted to €27 billion.

An important direct non-medical cost, which was not included in our study, is cost due to criminal activity caused by brain disorders. Mental disorders such as addiction and psychotic disorder frequently cause criminal activity. We have chosen not to include these estimates in the base case results. However, we have dedicated a later section to this issue based on research conducted in addiction (see the section *Cost of crime in estimates of the cost of addiction in Europe*).

We also allowed dividing our results by the three main specialties: neurological, neurosurgical and psychiatric disorders (see Fig. 8). In the neurological diseases, the direct cost is the dominating resource, comprising 63% of the total cost. In the neurosurgical diseases (brain tumour and trauma) indirect costs are predominant, making up 42% of the total cost. A similar distribution of the cost of mental disorders can be observed, where indirect costs make up 50% of the total cost.

Table 6 Total cost of brain disorders in Europe (€PPP million, 2004)

	Addiction	Affective disorders	Anxiety disorders	Brain tumour	Dementia	Epilepsy	Migraine	Multiple sclerosis	Parkinson's disease	Psychotic disorders	Stroke	Trauma	Total
Austria	1444	2 462	856	81	1 094	316	412	213	153	1 299	395	54	8 778
Belgium	1948	2845	1148	145	2175	426	726	258	231	132	528	75	10637
Cyprus	63	122	47	5	50	18	30	7	7	24	16	3	392
Czech Republic	107	1056	561	54	672	230	388	135	97	369	498	40	4206
Denmark	765	1426	559	63	752	274	283	167	98	334	301	35	5057
Estonia	35	69	28	2	45	11	15	4	7	16	29	3	264
Finland	874	840	338	40	989	176	276	158	80	204	221	45	4242
France	3011	14448	5386	618	3865	2265	3609	805	1328	3279	2209	489	41310
Germany	17789	35917	10765	1039	11616	3808	6077	1842	2943	16111	5933	659	114498
Greece	1048	2026	794	145	1181	282	490	79	170	427	765	54	7460
Hungary	730	1156	696	47	711	184	179	79	116	270	405	44	4617
Iceland	44	75	30	3	25	7	17	8	3	37	8	2	260
Ireland	507	987	365	35	310	146	252	65	47	176	136	22	3049
Italy	1456	6492	3531	567	8648	2308	3530	1159	2040	7234	3386	436	40787
Latvia	68	132	58	4	98	23	27	8	16	38	86	6	562
Lithuania	100	198	79	7	122	25	44	8	20	48	58	8	716
Luxembourg	76	148	56	7	69	23	37	12	10	28	29	4	498
Malta	31	61	21	2	21	9	16	1	3	9	9	1	185
Netherlands	3795	4255	2105	204	3098	684	2114	376	285	147	737	110	17913
Norway	1654	1706	683	58	711	161	273	126	96	66	257	34	5825
Poland	2100	4373	1399	172	1301	811	1159	220	192	540	645	88	13001
Portugal	881	1738	679	61	1083	266	406	87	165	378	853	56	6651
Slovakia	232	477	168	15	178	75	116	37	27	82	63	14	1483
Slovenia	109	202	96	9	148	35	39	21	25	67	73	9	833
Spain	726	5226	1135	287	5145	816	2073	417	1068	1118	1142	204	19357
Sweden	2452	2111	1315	79	1115	287	489	462	161	432	418	34	9355
Switzerland	1358	2618	1091	84	1392	371	647	288	193	527	304	67	8941
United Kingdom	13873	12500	7384	755	8563	1509	3227	1727	1140	1838	2392	341	55300
Europe	57274	105666	41372	4586	55176	15546	27002	8769	10722	35229	21895	2937	386175

Note: Direct non-medical costs are missing for the following disorders: affective disorders, anxiety disorders, migraine and trauma.

Table 7 Total cost of brain disorders by country (€PPP million, 2004)

	Healthcare costs	Direct non-medical costs	Indirect costs	Total costs
Austria	3210	1463	4104	8778
Belgium	3145	2102	5390	10637
Cyprus	129	63	200	392
Czech Republic	1504	886	1816	4206
Denmark	1679	904	2473	5057
Estonia	107	56	101	264
Finland	1354	975	1913	4242
France	16823	5947	18540	41310
Germany	44481	17653	52364	114498
Greece	2607	1464	3389	7460
Hungary	1996	837	1783	4617
Iceland	92	37	132	260
Ireland	891	456	1702	3049
Italy	17129	11097	12560	40787
Latvia	259	127	176	562
Lithuania	293	143	281	716
Luxembourg	157	89	252	498
Malta	48	27	110	185
Netherlands	4652	3451	9809	17913
Norway	1739	923	3163	5825
Poland	3272	1692	8036	13001
Portugal	2523	1357	2771	6651
Slovakia	493	222	768	1483
Slovenia	403	186	244	833
Spain	5992	5563	7802	19357
Sweden	3282	1513	4560	9355
Switzerland	2922	1661	4357	8941
United Kingdom	14265	11303	29732	55300
Europe	135445	72200	178530	386175

Note: Differences in cost of brain disorders between countries in Europe are dependent on the national statistics applied in the model imputations of cost estimates to countries where no data was available (see Table 3), and variations in the prevalence of brain disorders.

Cost of brain disorders distributed by medical speciality and specific brain disorder

The total cost of brain disorders is an aggregated result of the 12 most prevalent disorders. It has already been observed that both the cost per case of specific brain disorders and the total number of cases with the different brain disorders differ substantially. Consequently, it is also expected that the aggregated cost result differs from one brain disorder to another.

Mental disorders amounted to €240 billion and hence constitute 62% of the total cost (excluding dementia), followed by neurological diseases (excluding dementia) totalling €84 billion (22%). Neurosurgical diseases made up a smaller fraction of the total cost of brain disorders in Europe, reaching a cost of €8 billion. Dementia, which is considered both a mental disorder and a neurological disease amounted to €55 billion.

Amongst the mental disorders, the cost of affective disorders (depression and bipolar disorders) was the highest, with a total of €106 billion, followed by addiction (drug and alcohol dependence), €57 billion (cf. Table 8). The cost of anxiety disorders amounted to €41 billion, whereas psychotic disorder (schizophrenia) reached a total cost of €35 billion. However, it should be noted that the cost of anxiety disorders and affective disorders did not include direct non-medical cost, and that the indirect cost due to anxiety disorders only comprised lost workdays due to sick leave. Moreover, in psychotic disorder, no cost data were included which covers indirect cost due to schizophrenia, which is expected to make up a substantial economic burden to society.

In the neurological diseases included in the study, migraine was estimated to cost European society a total of €27 billion. The second most costly neurological disease was stroke, totalling €22 billion, followed by epilepsy, Parkinson's disease and multiple sclerosis with costs of €16, 11 and €9 billion, respectively. The cost of stroke is, however, expected to be heavily underestimated, as it is based on incidence-based cost estimations (due to the lack of both appropriate cost data and prevalence data in the literature).

Two neurosurgical diseases were included: brain tumour and trauma (traumatic brain injury). The cost of brain tumour in Europe amounted to €5 billion and traumatic brain injury reached a total cost of €3 billion. The cost estimation of trauma is, however, expected to be grossly underestimated. It is only based on the hospitalization costs due to trauma, and hence omitting both rehabilitation costs and costs due to lost workdays and production. Moreover, the estimate is based on 12-month incidence data instead of prevalence data (due to lack of appropriate prevalence data in the literature). A very loose guess is that indirect costs of trauma are probably in the order of €10–20 billion.

Results on specific dimensions in brain disorders in Europe

The results presented earlier were all reported on aggregated levels without focus on specific dimensions in the costing of disorders of the brain. In the following a couple of examples will be given from specific brain disorders.

Cost of crime in estimates of the cost of addiction in Europe

The cost of crime has become an increasingly important factor for governments and other decision-makers who are concerned with the impact of crime on economy and society in general. However, there

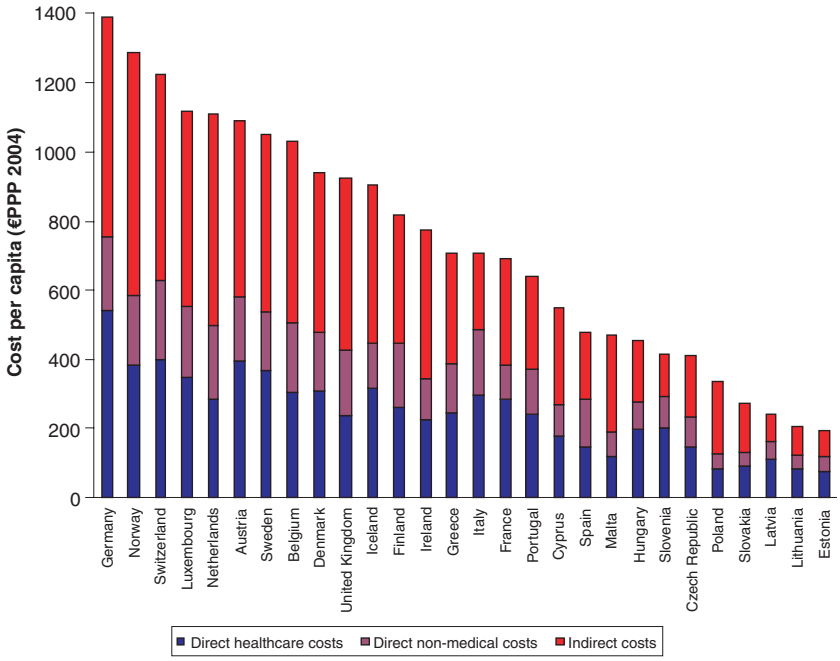

Figure 6 Total cost of brain disorders in Europe by country standardized for population size (€PPP/capita)
Note: The total annual cost of brain disorders was divided by total population in each country. Direct non-medical costs are missing for the following disorders: affective disorders, anxiety disorders, migraine and trauma.

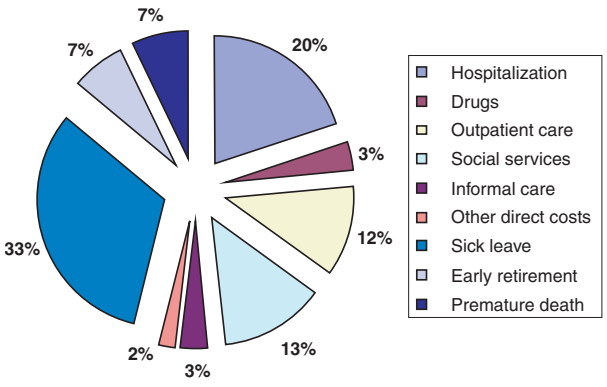

Figure 7 Distribution of total cost of brain disorders in Europe by resource use components
Note: Direct non-medical costs are missing for the following disorders: affective disorders, anxiety disorders, migraine and trauma.

are methodological challenges, not only in valuing the resources used for crime-related activities due to a disorder, but also to identify and quantify the resource use. Nevertheless, in addiction there are several studies conducted attempting to estimate the cost of alcohol and illicit drug related crime in society. This cost component was not included in the base case estimation of the cost of addiction in Europe reported earlier, as there are still too few studies to judge on the methodological appropriateness. Yet, attempting to estimate the cost of crime due to addiction in Europe, may give an impression of its impact on society.

In the estimation of the cost of crime-related activities due to alcohol dependence, the following resources were included: alcohol-related costs to the criminal justice system, costs due to alcohol-related property and victim services and lost productivity to victim, drink driving related costs (criminal justice system, lost productivity and medical resources to drink-driving casualties). In illicit drug use the crime-related resources were concentrated to the cost of victim and criminal justice system due to burglary, robbery, shoplifting and vehicle theft.

The total cost of addiction totalled €57 billion in Europe, excluding the cost of crime. When estimating the crime-related resources due to alcohol and drug dependence, an additional cost of €53 billion is estimated. Hence, the total cost of addiction would reach a total cost of €110 billion, which is almost doubling the total cost of addiction to the European society. Yet, this result is expected to be conservative when comparing with specific studies conducted for individual European countries. Still, there is little research conducted on the cost of crime related to illness and hence further research is needed to validate the appropriateness of the principles and valuation methods applied here.

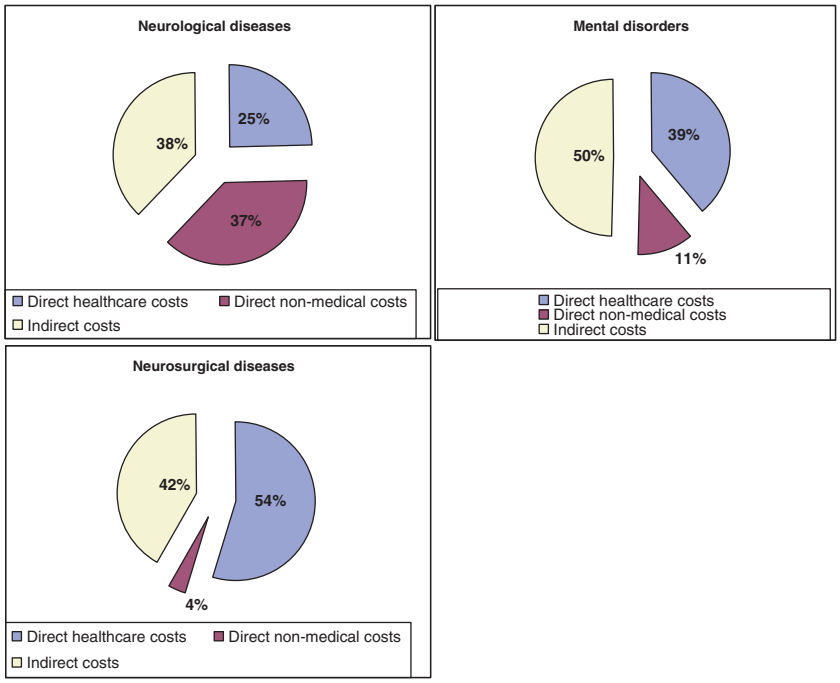

Figure 8 Distribution of total cost of brain disorders in Europe by specialty Note: Direct non-medical costs are missing for the following disorders: affective disorders, anxiety disorders, migraine and trauma.

Table 8 Cost of brain disorders in Europe by disease area (€PPP million)

€ million	Healthcare costs	Direct non-medical costs	Indirect costs	Total cost
Neurosurgical diseases	**4099**	**269**	**3155**	**7523**
Brain tumour	1162	269	3155	4586
Trauma	2937			2937
Neurological diseases	***21 286***	**20 259**	**42 389**	**83 934**
Epilepsy	2752	4240	8554	15 546
Migraine and other headaches	1495		25 507	27 002
Multiple sclerosis	2194	3977	2598	8769
Parkinson's disease	4582	6140		10 722
Stroke	10 263	5901	5730	21 895
Neurological/mental disorder	***12 840***	**42 337**		**55 176**
Dementia	12 840	42 337		55 176
Mental disorders	**97 221**	**9336**	**132 985**	**239 542**
Addiction	16 655	3962	36 657	57 274
Affective disorders	28 639		77 027	105 666
Anxiety disorders	22 072		19 301	41 373
Psychotic disorders	29 855	5374		35 229
All brain disorders	**135 445**	**72 200**	**178 530**	386 175

Informal care in dementia in Europe

Informal care is the unpaid care provided by family members, friends or voluntary workers to disabled and impaired individuals in the community. Most disabled elderly persons benefit from informal care to some degree, and many families choose informal care over formal, paid care. This is especially true for those European countries where there is a tradition of caring for the elderly at home. The majority of brain disorders have a disabling effect on the patient to the extent that care is needed. Moreover, the chronic nature of most brain disorders means that informal care is needed over a long period of time. Nevertheless, it is difficult to find appropriate cost estimates for informal care in brain disorders in the European literature. We were only able to cost informal care in multiple sclerosis and dementia.

The total annual cost of dementia was estimated at €55 billion in Europe. Twenty per cent of the total cost was attributable to informal care, corresponding to €11 billion (see Fig. 9). Hence, the total cost of informal care almost equals the total healthcare cost attributable to dementia in Europe. In these estimations the informal care costs were evaluated by measuring the time spent on care of the demented patient, valued as would care be given to a professional care-giver. This valuation principle is, however, still debated and the cost estimates vary according to the principle applied.

Multiple sclerosis – a brain disorder with comparably good data coverage in Europe

Multiple sclerosis is the brain disorder, for where we have the best availability of epidemiologic and economic evidence in Europe. In the following, we present the specific cost estimation results for multiple sclerosis in Europe. This can serve as an example of how the uncertainty in the final cost estimates

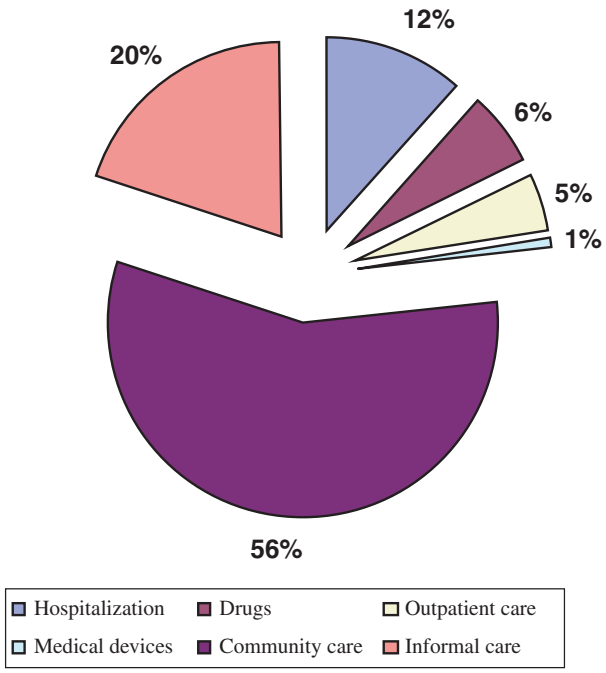

Figure 9 Distribution of the cost of dementia in Europe.

decrease with improved availability of epidemiologic and economic input data. The input data for the cost estimation for multiple sclerosis have been described in more detail in previous publications (Kobelt, 2004; Pugliatti *et al.*, 2005).

Cost per patient and prevalence in multiple sclerosis. The total cost per patient ranged from €7000 to 41 000 in 2004 across Europe, with a mean cost per patient of €23 695 (cf. Fig. 10). The total cost is fairly evenly distributed between direct healthcare, direct non-medical (including informal care) and indirect costs. The total amount of patients with multiple sclerosis was estimated at 380 000 in Europe. The point prevalence varied from 17 to 154 cases per 100 000 inhabitants across Europe.

Cost of multiple sclerosis in Europe. The total cost of multiple sclerosis was estimated at €8.8 billion in Europe in 2004 (Table 9). The total direct cost constituted 50% of the total cost and social services was the largest single cost component. Cost of informal care (e.g. family) was estimated at €1.8 billion and make up one-fifth of the total cost. The indirect costs were dominated by the cost of lost workdays due to early retirement.

The cost of drugs amounted to €462 million, and is expected to be grossly underestimated for 2004, because of new treatments that were introduced in the beginning of this decade.

The results provided so far are based on pure resource consumption and on reduced or lost working ability. However, these results exclude intangible cost due to the psychological burden and stress of the disease. As MS is a chronic disease with a relatively early onset (around 40 years on average), the intangibles are expected to be substantial. One way of measuring this is to compare the patients' self-rated quality-of-life scores at each level of severity of disease to the scores by the normal population (Raisch, 2000). The difference in quality-of-life can thus be used as a proxy to calculate the loss of QALY (Torrance, 1986,

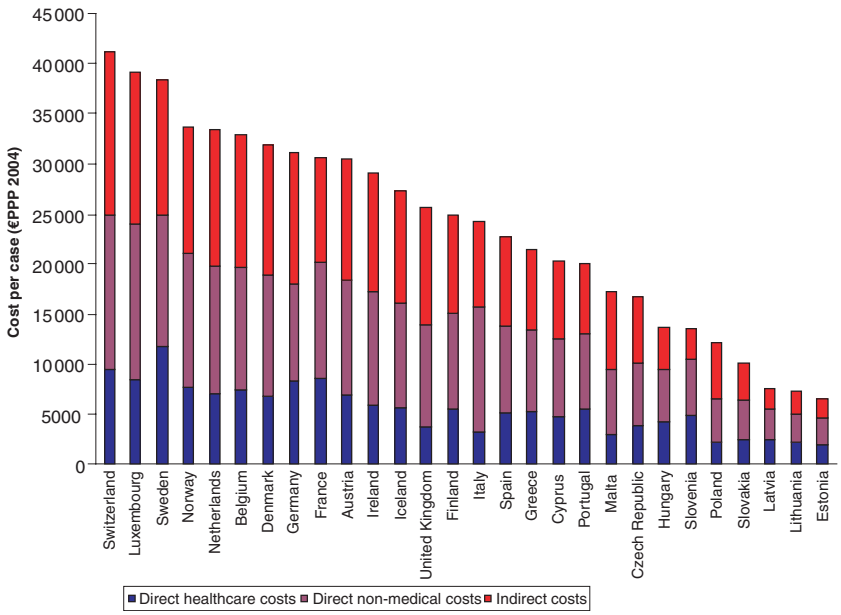

Figure 10 Cost per case of multiple sclerosis in Europe (€PPP 2004).

1998). The average reduction in quality-of-life in patients with MS is in the range of 0.30–0.5 compared with the normal population (Kobelt *et al.*, 2000, 2001). By assigning a value to (or willingness to pay for) a QALY, the intangible cost due to MS can be estimated. There is no agreed value for a QALY in Europe, and to assure a conservative, estimate the value was set to GDP/capita in Europe (Eichler *et al.*, 2004)[6]. The intangible costs due to multiple sclerosis in Europe were thus estimated to €4.2 billion. Hence, by estimating the total economic burden of multiple sclerosis in Europe, the total cost is at least €13.0 billion for 2004.

Stratification of results by gender and disability level. The prevalence of multiple sclerosis is higher in women than men. When stratifying our total cost estimate by gender, 70% of the total cost of multiple sclerosis is attributable to women with MS, corresponding to €6.1 billion.

A generally accepted way of stratifying patients according to severity of multiple sclerosis is by the Expanded Disability Status Score (EDSS) (Kurtzke, 1955, 1983). The prevalence data and cost data were stratified according to the EDSS-scale in three groups: mild (EDSS score: 0–3/3.5), moderate (EDSS scores: 3.5/4–6.0/6.5) and severe (EDSS score: 6.5+).

Figure 11 shows how the cost per patient increases with increased disease severity, being €9178 in the mild cases and €39 722 in severe cases. Consequently, the cost per patient is four times higher in severe cases of MS compared with milder forms.

Milder forms of multiple sclerosis (EDSS score: 0–3/3.5) are, however, more than double as prevalent as severe cases. Thus, at an aggregated level, the total cost of mild cases of multiple sclerosis in Europe were €4.8 billion, corresponding to 54% of the total cost, whereas the cost of moderately and severe cases of multiple sclerosis were €2.1 billion (24%) and €1.9 billion (22%), respectively.

Our findings show not only that MS has a significant impact on the national healthcare budgets in Europe, but also that it has substantial costs to social services and non-paid caregivers (informal care). As MS has a relatively early onset in life and is a highly disabling disease, there is also a high proportion of patients who stop working due to the disease. Earlier studies from individual European countries confirm the distribution of the cost of MS between care within and outside the healthcare sector (O'Brien, 1987; Holmes *et al.*, 1995; Blumhardt and Wood, 1996; Midgard *et al.*, 1996; Henriksson and Jönsson, 1998; Kobelt *et al.*, 2000; Henriksson *et al.*, 2001; Amato *et al.*, 2002). There are no previously published studies estimating the total cost of MS in Europe in the literature. However, an American study estimated the total cost of MS in the US to $8.3 billion [scaled to 2004 with the US inflation (US Census, 2005)] (Grudzinski *et al.*, 1999). Considering a higher number of MS cases in Europe and the US study being a 10 years old estimate our results can be regarded as conservative. When comparing our results with selected previous publications which were not included in the cost calculations (Midgard *et al.*, 1996; Carton *et al.*, 1998; Murphy *et al.*, 1998; Rubio-Terres *et al.*, 2003), there is a relatively good coherence in the final estimates (see Table 10).

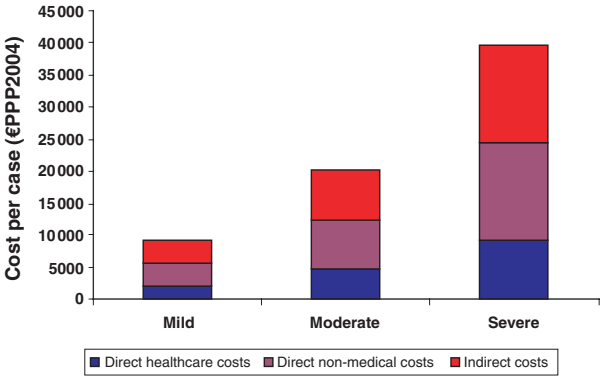

Figure 11 Cost of multiple sclerosis stratified by disease severity (cost per case, €PPP 2004).

Table 9 Total annual cost of multiple sclerosis in Europe in 2004 (€PPP million)

Cost component	Cost	%
Total direct costs	*4369*	*50%*
Hospitalization	844	10%
Drugs	462	5%
Outpatient care	662	8%
Medical devices	225	3%
Social services	1371	16%
Adaptations	673	8%
Transportation	132	2%
Informal care	*1801*	*21%*
Total indirect costs	*2598*	*30%*
Sick leave	266	3%
Early retirement	2332	27%
Premature death	n.a.	n.a.
Total costs	8769	100%

[6]There has been a suggested valuation principle for the willingness to pay for the gain of a QALY set to three times the GDP per capita (WHO, 2001). However, there are currently discussions Europe on establishing a threshold value lower than what this principle would result in.

Table 10 Comparison of results with literature findings, €PPP million, 2004

	Our results	Published evidence	Source
Belgium[1]	7449	10 475	Carton *et al.* 2000
Norway	20 352	21 385	Midgard *et al.* 1996
Spain	22 703	16 913–25 370[2]	Rubio-Terres *et al.* 2003
France[3]	8613	7766	Murphy *et al.* 1998

[1]Only comparing healthcare costs.
[2]Patients with moderate MS (EDSS 4.5–7.4).
[3]Patients with moderate MS (EDSS 4.0–6.0).

The intangible cost of all brain disorders could have been estimated similarly to that of multiple sclerosis. This was, however, not done due to lack of appropriate QALY data in many fields. Moreover, the principle of adding the intangible costs to the conventional cost estimates for an illness is still debated due to possible double-counting.

Sensitivity analysis and validation of results

Two types of sensitivity analyses are employed to test the validity of the results obtained: (i) tests of internal validity and (ii) tests of external validity. The internal validation aims at testing the sensitivity in the key input parameters used in the cost estimations. The external validity tests aim at benchmarking our results with previous study results in the literature and compare the reasonability in our results compared with European statistics. It thus validates the generalizability of our results.

Internal validity

The key input parameters that were tested for are: (i) 12-month prevalence (or incidence) data employed, (ii) estimated cost data used and (iii) the indexes used for imputation of cost data.

The prevalence and incidence data used in the cost estimations in this study were decreased and increased by 10%. The total cost of brain disorders varied between €347 and 424 billion (see Table 11). Moreover, due to the expected comorbidities between brain disorders in Europe, a sensitivity analysis was conducted by adjusting the prevalence input data. An estimated comorbidity of 31.6% between neurological and mental disorders was applied, based on a database analysis from the German GHS-MHS survey (Wittchen *et al.*, 2000; Jacobi *et al.*, 2002, 2004). The adjustment for comorbidity resulted in a total cost estimate of €309 billion.

The estimated cost data (presented as cost per patient) were varied in a similar way as the prevalence data. The results were estimated at €347 and 424 billion.

Table 11 Sensitivity analysis on model assumptions

Parameter	Change	Total cost
Prevalence		
	10% reduction in all prevalence input data	347
	Base case	**386**
	10% increase in all prevalence input data	425
	Co-morbidity adjustment[1]	309
	Base case	386
Cost data		
	10% reduction in all cost input data	347
	Base case	386
	10% increase in all cost input data	424
Prevalence & cost		
	Co-morbidity adjustment in anxiety disorder[2]	365
	Base case	386
Imputation indexes		
	PPP adjusted (base case)	386
	Nominal terms	372
	Real terms	370
	PPP adjusted in real terms	383
	Imputation based on healthcare expenditure data only	422
	Imputation based on GDP data only	397

[1]31.6% comorbidity assumed between neurological diseases and mental disorders (based on comorbidity data from the German GHS-MHS Survey (Jacobi *et al.* 2002, 2004; Wittchen *et al.* 2000)).
[2]Adjustments made for anxiety disorders, with one single aggregated prevalence estimate for all anxiety disorders (12-prevalence estimate of 12% based on the GHS-MHS Survey) and pooled resource use data for all anxiety disorders. Data was then extrapolated to all European countries.

A two-way sensitivity analysis was conducted based on the prevalence and cost data in a specific brain disorder: anxiety disorders. This was made possible as the cost data in anxiety disorders was estimated with help of primary data analysis based on the German National Interview and Examination Survey (Wittchen *et al.*, 2000; Jacobi *et al.*, 2002, 2004). An aggregated cost per patient with anxiety disorders was estimated. Similarly, an estimated 12% 12-month prevalence in anxiety disorders was employed based on findings from the same German survey (Wittchen *et al.*, 2000; Jacobi *et al.*, 2002, 2004). The sensitivity analyses resulted in an estimated cost of anxiety disorder in Europe of €20 billion (compared with the non-adjusted estimate of €41 billion). Consequently the total cost of brain disorders in Europe, when adjusted for the effect of comorbidities in anxiety disorders, reaches an estimate of €347 billion (compared with €386 billion in base case; cf. Table 11).

Cost data were imputed with indexes based on national statistics (relative national income, healthcare expenditure, drug expenditure and wages). In the base

Table 12 Comparison of proportions of results with European statistics (2004)

Cost component	European statistics	%
Healthcare costs	Total healthcare expenditure	15%
Drug costs	Total drug sales	8%
Total cost	Gross domestic income	4%

Note. The cost of different resource use components was put in relation to the total European healthcare expenditure, drug sales and gross domestic income.

case estimations the national statistics were adjusted for purchasing power differences between countries in Europe. For sensitivity analyses the following alternative adjustments in the indexes were tested for: (i) statistics based on nominal values, (ii) statistics presented in real values, and (iii) PPP adjusted statistics presented in real terms. The total cost of brain disorders varied from €370 to 383 billion, compared with the base case estimate of €386 billion. In addition, a sensitivity analysis was conducted employing the imputation based on only one national statistic: (i) purchasing power adjusted healthcare expenditure and (ii) purchasing power adjusted national income statistics. The results obtained were higher than the base case, and varied between €397 and 422.

External validity

The external validity was tested by comparing our results with European national statistics in order to verify the reliability in the results obtained. Moreover, results by country and brain disorder were compared with earlier study results from the literature. A German cost-of-illness study (Statistisches-Bundesamt, 2004) served as a benchmark. Moreover, our results were compared with previous findings in the American literature.

The total healthcare expenditure was estimated to €923 billion in Europe (Eurostat, 2004a). The total healthcare cost of disorders of the brain was estimated at €135 billion, and hence corresponding to 15% of the healthcare budgets in Europe (see Table 12).

In a similar comparison, the drug cost due to brain disorders comprises 8% of the total sales of drugs in Europe (corresponding to €290 billion in Europe). However, it should be noted that the drug cost attributable to brain disorders in Europe is based on data mainly originating from the 1990s and thus do not reflect the drug use in 2004. Finally, when relating the total cost of brain disorders in Europe to the total national incomes in Europe, a proportion of 4% is reached (total national income in Europe is estimated to be €10 382 billion).

No previous study has estimated the total cost of brain disorders in Europe. However, in order to compare our results with European data, a comparison was made with a recent German cost-of-illness study conducted by the Federal Statistics Office in Germany (Statistisches-Bundesamt, 2004). Six areas of brain disorders were possible to compare (due to a different grouping of diseases in the German study): dementia, epilepsy, migraine and other headaches, affective disorders, anxiety disorders and psychotic disorders. The estimates in neurological diseases obtained in our study overall comparable with the findings in the German study (cf. Table 13).

In psychotic disorders our result is much higher than in the German study, most probably due to differences in methodology, where the input data for our model is based on the European EPSILON study (Knapp *et al*., 2002), bottom-up cost-of-illness study with a detailed inclusion of healthcare resource use, whereas the German benchmark study is based on a top-down approach and national healthcare statistics. As was discussed in the previous section *Top-down versus bottom-up approach*, there is a possibility of under inclusion of resource utilization.

Our results were furthermore compared with previous cost-of-illness studies conducted in the US. The results of the comparison are summarized in Table 14.

In the neurological diseases, there seems to be a good coherence between our results compared with previous findings in the American literature. The only area where our results are lower is in trauma. This confirms our expectations, as our cost estimate of trauma in Europe is only based on cost data on hospital care, and hence omits other direct and indirect costs. Moreover, it is based on 12-month incidence data, which is expected to be lower than the 12-month prevalence in trauma.

Table 13 Validation of model predictions for Germany

€ million	Our results	German national study[2]	Difference
Neurological diseases			
Epilepsy	1094	1253	– 159
Migraine and other headaches	298	468	– 170
Neurological/mental disorders			
Dementia[1]	7678	5702	1976
Mental disorders			
Affective disorders	12382	8517	3865
Anxiety disorders	5298	3573	1725
Psychotic disorders	13582	2790	10792

[1]Cost of informal care and for special accomodation were excluded from the model estimation.

[2]Statistisches Bundesamt, Krankheitskosten 2002. All estimates are inflated to 2004 with the German inflation rate (*Eurostat Yearbook 2004*).

Table 14 Comparison of cost estimates for Europe with American literature

€ billion	European estimate	US estimates[1]	Ref
Neurological diseases			
Dementia	55	27–117	(Ernst & Hay 1994; Hay & Ernst 1987; Huang *et al.* 1985; Manton *et al.* 1993; 1988; Schneider & Guralnik 1990)
Epilepsy	15.5	2–12	(Begley *et al.* 1994; Begley & Beghi 2002; Halpern *et al.* 2000; Murray *et al.* 1996)
Migraine	27	8–23	(Clouse & Osterhaus 1994; Hu *et al.* 1999; Osterhaus *et al.* 1992)
Multiple sclerosis	8.8	6.6	(Whetten-Goldstein *et al.* 1998)
Neurosurgical diseases			
Trauma[2]	2.9	4.8	(Schootman *et al.* 2003)
Mental disorders			
Affective disorders	106	31–67	(Greenberg *et al.* 2003; Greenberg *et al.* 1990; Rice & Miller 1995)
Anxiety disorders	41	44–48	(DuPont *et al.* 1999; Greenberg *et al.* 1999; Rice & Miller 1998)
Psychotic disorders	35	34	(Rice 1999)
Addiction	57	160–389	(Holland & Mushinski 1992; Rice 1995; Rice *et al.* 1991)

[1]The cost estimates in the American studies were inflated to the cost basis of 2004 with the general U.S. inflation and converted to Euros (PPP).
[2]Only comparison of direct healthcare costs.

In the area of mental disorders, the American literature reports similar estimates in anxiety disorders and psychotic disorders. The cost of affective disorders was estimated lower in the US. However, the results originate from cost of illness studies conducted at the beginning of the 1990s. Hence differences can be explained by improvements in methodology over time. Moreover, addiction was estimated at a lower level in Europe than in the US. However, it should also be noted that the American cost studies are based on the full population sizes, whereas our estimates are, in part, restricted to the adult population only.

Discussion

Final results and uncertainty

The results from the present study show that brain disorders cause a substantial economic burden to healthcare systems, community, other caregivers and the wider society. The distribution of our total cost estimate of brain disorders in Europe confirms the expectations, that the majority of the costs are identified outside the formal healthcare sector. These are primarily due to reduced productivity during years of employment and to pre-mature retirement (caused by both morbidity and mortality). The indirect costs were dominant cost components, particularly in mental disorders. Furthermore, our results highlight the heavy reliance on community care as well as informal care (family and other caregivers) in brain disorders, especially in neurological diseases. The total cost of brain disorders is highly skewed to the western European countries (standardized results for population size), whereas the new EU admission countries bear a minor part of the cost, probably due to both the quantity of health services offered as well a as the price of the same. Available data does not make it possible to separate these two effects in detail. The results presented in this study are, however, attached with uncertainty. In the following the results from the sensitivity analyses shall be discussed.

External validity

The external validation of our results shows that they are in relatively strong concordance with previous research findings in the literature. Previous studies from the USA confirm the results achieved in specific brain disorders included in our study as well as the relative cost between the same (Hay and Ernst, 1987; Huang *et al.*, 1988; OTA (Office of Technology Assessment), 1988; Schneider and Guralnik, 1990; Manton *et al.*, 1993; Ernst and Hay, 1994). The comparison indicated possible underestimations in mental disorders, e.g. anxiety disorders. This is somewhat expected, as the cost input data applied in anxiety disorders are under-inclusive. Moreover, the comparison of the cost of trauma confirmed that our result substantially underestimate the true economic burden of the disease. However, there is no earlier comprehensive European cost-of-illness study in brain disorders, it was difficult to say anything about the validity of our results in relation to other studies. Studies for specific diseases, in a specific country at a specific point in time can be used to validate the estimates, but not the overall result. Thus, further research is necessary to validate the results of this study.

Internal validity

The internal validity of the cost estimation model showed little uncertainty concerning the imputation

technique employed. However, as mentioned previously, the inherent challenge of double counting becomes clear in our results. The sensitivity analyses that were conducted in order to adjust for the effect of comorbidity confirm the problem (for further discussions see the section *Methodological aspects*). In order to investigate the uncertainty around the final cost estimates, there is a need for prospective epidemiological and economic studies specifically aimed at investigating the issue of comorbidity in brain disorders in Europe.

Despite the uncertainties discussed above, the estimated cost of brain disorders in Europe of €386 billion is probably to be an underestimation due to missing data. Furthermore, the estimate is only based on the most prevalent brain disorders in Europe and excludes many important groups of diseases. Secondly, the cost coverage is far from complete in the brain disorders costed in this study. Thirdly, the cost of nicotine dependence, non-migraine headaches and crime associated to substance abuse were omitted in the base case cost estimations.

Methodological aspects

There are several methodological aspects that have been highlighted throughout our study. In this section, the most critical methodological issues are discussed further: (i) the effect of comorbidity on the cost of brain disorders in Europe and (ii) methodological issues around the epidemiologic and economic data applied.

Comorbidities

The cost-of-illness methodology was applied in the present study, using a modified bottom-up approach when estimating the cost of brain disorders: we estimated the cost per patient by specific brain disorder and country and thereafter multiplied the cost estimates with our 12-month prevalence (or incidence) and population data for each country to aggregate the results to a European level. An alternative approach would be to apply the top-down approach, estimating the proportion of the cost attributable to individual brain disorders from national statistics (e.g. health care spending). As mentioned previously (cf. under *Cost-of-illness methodology*), the bottom-up approach includes the risk of double counting, as there is mainly epidemiology and economic data on *individual* disease. There are several reasons for double counting, but the most critical one is the issue of comorbidities between disorders of the brain (see further under *Sensitivity analysis and validation of results*). The issue is most researched in the area of mental disorders, with estimated rates of comorbidity between mental diagnoses ranging from 44 to 94% (Jacobi *et al*., 2004). There are techniques to adjust for the effect of comorbidity in epidemiology surveys (Kessler *et al*., 2002). We were only able to adjust for comorbidities between the specialties in disorders of the brain, omitting the comorbidity effects between individual diagnoses. Nevertheless, our results indicated a significant reduction in the total cost of disorders of the brain when this effect was adjusted for. However, as the input data for the adjustment was based on the German National Interview and Examination Survey, the challenge remains for future research to confirm the comorbidity patterns in brain disorders all over Europe in order to better understand the full impact of comorbidities on the cost of brain disorders.

Input data

The other methodological challenge in this study concerns the economic and epidemiologic input data. The cost estimates in this study are based on a health economic model. The model predictability is, however, limited to the accuracy of the input data. The input data selected for this study were critically reviewed by groups of experts in the specific fields of disorders of the brain, in order to ensure the usage of best evidence available today. However, the lack of data, for instance in the EU admission countries, made imputations and best estimates necessary. Thus, it is difficult to verify the appropriateness of these estimates until proper field studies are conducted.

Hence, the results from our study must be interpreted in the light of these methodological limitations.

Missing data

Our cost estimates of disorders of the brain in Europe are based on the current epidemiologic and economic evidence. Our study has identified several research gaps, which have important consequences for our results.

Cost data

There was a satisfactory coverage of cost data in the major western European countries, although coverage differed substantially across the specific brain disorders and from country to country. The major gaps in terms of geographical coverage were identified in the new EU admission countries, where no single cost-of-illness study met the criteria for selection in the health economic literature review. Consequently, it is difficult to estimate the cost of brain disorders in Eastern Europe, and further studies are needed to verify the accuracy in our results.

The economic evidence in Europe was highly varying between the specific disorders of the brain. The best cost

data coverage was identified in: schizophrenia, multiple sclerosis, dementia and stroke, whereas major gaps were identified for anxiety disorders, brain tumour and brain trauma. Furthermore, there is varying amount of studies within each specific brain disorder. In migraine and other headaches, for instance, headache was omitted from the total cost estimates due to lack of data, but it was suggested to be almost twice as costly as migraine (cf. in previous section *Total cost of brain disorders*).

The available cost data selected in the reviews were of varying quality. They had different aims, designs and study populations, which makes it difficult to combine the data for the purpose of this study. Moreover, the completeness of the selected cost-of-illness studies differed between disorders. Most selected studies included complete data on direct healthcare use, but to a lesser extent resource use outside the formal healthcare sector such as community care and direct non-medical expenses (e.g. in anxiety disorders). Our results have shown that indirect costs make up the biggest part of the cost of brain disorders in Europe. However, not all cost studies selected had complete indirect cost data (e.g. anxiety disorders, addiction, stroke and epilepsy), and some did not include it at all (e.g. schizophrenia and trauma). Our results emphasise further the importance of including valuations of cost of informal care and intangible costs in studies of brain disorders. The only brain disorders where the cost of informal care has been valued properly in Europe are dementia and multiple sclerosis. Our results show that informal care comprises more than 20% of the total cost of dementia in Europe. Our specific results on multiple sclerosis also show the impact of including intangible cost to the total estimate. It added another 50% to the conventional cost estimated for multiple sclerosis. A similar result has been obtained in previous cost-of-illness studies (Henriksson *et al.*, 2001).

Thus, there is a great need for further studies based on sound cost-of-illness methodology and primary data, which picks up the full range of resources associated with the particular brain disorder at study.

Epidemiologic data

The epidemiologic evidence on brain disorders in Europe is in general more conclusive than the health economic data. However, there are still major research gaps identified particularly in the EU admission countries. The best geographical coverage of epidemiologic data was identified in multiple sclerosis, epilepsy and dementia.

The methodology in the selected epidemiology studies of brain disorders is varying between specific brain disorders and across European countries. Few studies are prospective in their design and include a broad study population.

The epidemiologic evidence in brain disorders is, moreover, scarce in the youngest and oldest population groups. In mental disorders, no studies were selected including prevalence estimates of specific diagnoses in the age groups below 18 and above 65. Thus, the omission of possible cases of brain disorders outside the age range results in an underestimation of the cost of brain disorders for the whole population in Europe.

Our cost estimations were based on 12-month prevalence data for most brain disorders, with the exception of stroke and trauma where incidence data were employed instead (due to scarce prevalence data in Europe). However, we know that incidence data serve as bad proxy for the true prevalence of stroke and trauma and hence underestimates the number of cases of these disorders significantly (see previous section *Total prevalence*). Partly this is corrected for by adjusting the cost per case estimate to the measure of the number of cases.

Comparison with cost and burden of other diseases

Cost estimates have been provided in other disease areas in previous studies. The American Diabetes Association estimated the total cost of diabetes in the USA to $132 billion in 2002 (€PPP in 2004: €104 billion; American Diabetes Association, 2003). A similar cost-of-illness study was conducted for cancer, where the American Cancer Society reached an annual cost of cancer of $172 billion in 2002 in the USA (€PPP in 2004: €135 billion; American Cancer Society, 2003). Thus, in relation to other major disease areas, brain disorders seem be most costly to society. Nevertheless, the present study strongly indicates the need for further research in brain disorders both in terms epidemiology and health economics, in order to better be able to investigate the epidemiological burden as well as economic burden of brain disorders in Europe.

Collaboration between epidemiologists and economists

The present research project initiated a close collaboration between epidemiologic experts in the disease areas included under brain disorders, as well as health economic experts in the field. The need to combine the expertise of the two research fields became very clear and leverages the quality of the final results of such a study. The hope is that this close collaboration shall be fostered further in order to be able to fill the gaps of knowledge of brain disorders in Europe. This is particularly important for addressing two methodological problems identified in this study: The need to collect epidemiological and costs data in a way that address the issue of comorbidities, and the need to make the estimates of prevalence of the disease compatible with the cost per case estimates;

i.e. to make sure that the cost per case can be multiplied with the number of cases in a consistent way to arrive at a valid estimate of the total cost of the disease.

Implications for European research policy

Previous data showing that disorders of the brain account for 35% of the burden of all diseases in Europe (Olesen and Leonardi, 2003) are now supported by economic data from the present study. It showed that costs of disorders of the brain are enormous and considerably larger than costs of diabetes or cancer. In fact, the costs of brain disorders are bigger than the costs of diabetes and cancer combined, corresponding to the WHO data on the burden of diseases. The latter studies have shown that the burden of brain diseases (and therefore also of costs of brain disorders) will increase markedly during the next two decades due to the ageing population in Europe. The only way to counteract this explosion in cost, which is a major threat to the economic welfare in Europe, is by increased research efforts. Better prevention, better treatments and better health care systems are mandatory. The time to achieve this is short which calls for immediate action. In the fifth Framework Programme (FWP) of the European Union (1998–2002), €85 million was spent on neuroscience (Sautter *et al.*, 2003). This makes up 0.01% of our estimated cost of brain disorders in Europe or €17 million per year. A draft programme for such action has been suggested by the EBC and will be developed into a full consensus programme for future brain research in Europe within the next year. This programme calls for an increase in brain research to €500 million per year or 0.13% of the annual costs of brain disorders. Compared with the Lisbon goals to spend 2% of gross national product (GNP) on research and development, this is a tiny figure even considering that research expenses at the national level are much higher than at the European level. However, relatively speaking, it would represent a huge increase as in the sixth FWP only 8% of the life science research budget was spent on brain research.

European Union spending on brain research is thus not only of a very small absolute magnitude but the proportion spent on brain research is also incommensurable with the enormous costs of these disorders, not to speak of the immense importance of a better understanding of how the brain normally works.

Implications for European health care policy

As discussed above, the WHO data on burden and the present economic data have established beyond doubt that brain disorders represent the most burdensome and costly group of diseases to society. They consume, however, only 15% of direct health care costs in Europe. There is thus a discrepancy between the impact of these disorders and direct health care spending. Part of this may be due to smaller possibilities to treat or cure these disorders compared with other fields. Whilst this may have been true in the past, a host of new drugs and other treatments have revolutionized the treatment of brain disorders in recent decades. It seems worth investigating whether the distribution of direct health care costs reflect traditional beliefs rather than present day therapeutic possibilities. It is not unusual that new treatment possibilities in health care remain under resourced for many years. Furthermore, rather than increased resources, psychiatry has witnessed a dramatic reduction in beds and resources in most western European countries which could have caused increased morbidity and crime. Such trends must be analysed in prospective studies and may provide invaluable guidance for future health investments.

It is often stated that drugs for brain diseases are overused and too costly. However, drugs for brain disorders accounted for only 8% of total drug sales contrasting the high relative and absolute costs of brain disorders. Furthermore, they represent only 3% of the total cost of these disorders. If these drugs reduce other costs of brain disorders by 3% then they have earned back what they cost. Considering that they keep large numbers of patients out of hospital, in employment and lead to less short-term absenteeism from work, the likelihood is that they save many times their own cost. Again, prospective health economic studies are necessary to prove such statements and to provide exact figures.

On balance, it seems clear already from existing figures for health expenditure that further investment in brain health will be very profitable to society.

Implications for medical school and other health educational curricula

Medical school curriculum should of course reflect the importance of the various diseases that doctors are to encounter in their professional life. However, there should not necessarily be identity between the relative burden or relative cost of a group of diseases and the per cent of curriculum devoted to the problem. The therapeutic possibilities are also important and those diseases where extensive treatment possibilities exist should receive more attention than diseases where therapeutic possibilities are significantly smaller.

We have not extensively searched and analysed the curricula in medical schools in Europe. This remains to be carried out by future studies having that focus. However, there is no doubt that teaching in basic and clinical brain related subjects is grossly smaller than the

burden and cost of brain disorders also considering the therapeutic possibilities available today. In most medical schools, the curriculum still reflects the therapeutic nihilism that characterized brain disorders 50 years ago and not modern day therapeutic possibilities.

Hopefully, the data presented here will stimulate prospective analysis of the teaching of brain sciences at medical schools and in all other health science educations in the future, so that health care professionals of tomorrow will be able to cope better with the huge burden and cost of disorders of the brain.

Conclusions and recommendations

In EU countries, Norway, Iceland and Switzerland with a population of 466 million people, an estimated 127 million Europeans currently suffer from one or more brain disorder. Brain disorders figure amongst the leading causes of death and disability. Yet, the knowledge of the epidemiological and economic impact of brain disorders has been relatively little researched in Europe. The present study estimated the total cost of brain disorders in Europe to €386 billion in 2004 prices, which corresponds to a cost of €829 per European inhabitant. Direct medical expenditures alone totalled $135 billion, comprised of inpatient stays (€78 billion), outpatient visits (€45 billion) and drug cost (€13 billion). Attributable indirect costs resulting from lost workdays and productivity loss due to permanent disability and mortality amounted to €179 billion. Direct non-medical costs (social services, informal care and other direct costs) totalled €72 billion. Our estimate only includes the most prevalent brain disorders. Due to scarcity of data, our total cost results only partially include direct non-medical cost (e.g. community care and informal care) and indirect costs, and omits completely intangible costs. We have by example shown that the cost of dementia increase with 25% when including informal care and the cost of multiple sclerosis increases with at least 50% when including intangible costs. The cost of brain disorders varied considerably from country to country, mostly explained by national variation in income.

Brain disorders receive only 15% of direct healthcare spending and 8% of total drug sales, the latter constituting 3% of the cost of brain disorders.

The current project bases its estimates on published data, and such data were largely missing in the new admission countries and also for many diseases from the old EU countries. Furthermore, data sources were often difficult to compare and cost categories were often missing.

Our study probably underestimates the full economic burden of brain disorder in Europe. Our study has exclusively evaluated the published evidence. This has identified major shortcomings in the epidemiologic and economic knowledge of brain disorders in Europe. Furthermore, treatment patterns and care provided to patients change over time. In order to better understand the impact of brain disorders to European society prospective field studies are needed in all disorders of the brain. These efforts need to be done in close collaboration between epidemiologic experts and health economic experts in the field.

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ORIGINAL ARTICLE

Cost of addiction in Europe

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Introduction

Substance use disorders (SUDs), i.e. alcohol, drug or nicotine dependence and abuse (DSM-IV) or harmful use (ICD-10) of these substances, have been linked to a considerable burden of disease in Europe in recent estimations by the World Health Organization (2002, 2003). The exact amount is hard to quantify, because quite often consequences of SUDs in a risk factor framework are not distinguished from consequences of substance use *per se*. For instance, lung cancer usually is related to tobacco smoking, and not to nicotine dependence (e.g. Ezzati *et al*., 2002). But it can be estimated that at least 10% of the overall burden of disease is attributable to SUDs (Rehm *et al*., 2005a, b).

There are two major systems to categorize SUDs, ICD (currently version 10; World Health Organization, 1993); and the DSM (currently version IV; American Psychiatric Association, 2000). Whereas the definitions converge for dependence, there are some differences between the concepts (DSM-IV). As for dependence, both systems include the notion of a syndrome, i.e. a cluster or pattern of symptoms, including compulsion or strong desire to use, impaired capacity to control, tolerance, withdrawal, preoccupation with the substance, where a great deal of time is spent on obtaining, using and trying to stop taking the substance; and continuation of use despite evidence of harmful consequences (World Health Organization, 1993; American Psychiatric Association, 2000). In additions DSM-IV specified negligence of social responsibilities as one criterion (American Psychiatric Association, 2000). In both systems, not all criteria have to be fulfilled in order to qualify for a diagnosis; three out of six for ICD, and four out of seven for DSM-IV are necessary, respectively.

Harmful use and abuse of substances are conceptualized as potential precursors for dependence, with ICD stressing longstanding use despite health problems (World Health Organization, 1993), and DSM-IV stressing the recurrence of use despite alcohol-related social problems (American Psychiatric Association, 2000). However, both diagnoses – dependence and abuse – may also be assigned jointly.

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Often epidemiological studies and cost studies do use other definitions than the above, where it is not clear how they relate to the standard criteria listed above. Consequently, only studies with DSM-IV or ICD-10 are included in the epidemiological part, and for cost estimates, costs of addiction had to be separated from costs of use or abuse in wider definitions. As definitions of abuse or harmful use are not as comparable across cultures as studies on dependence (Rehm *et al*., 2005a, b), we decided to restrict ourselves to the latter.

Prevalence data on addiction in Europe

A comprehensive search of the literature (Rehm *et al*., 2005a, b) was conducted in July 2004, using the following terms in combination with the substance classes: dependence, problems, abuse, use disorders, plus the name of the relevant countries of Europe (Austria, Belgium, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden, UK). Criteria for inclusion were: indication of a sex-specific prevalence rate for SUDs; publication in English, French, Spanish or German; field work in 1990 and later; a representative general population or primary care visitors sample and assessment of SUDs with a validated instrument. As illicit drug use is an illegal activity for estimating the prevalence of these disorders, we also included estimates from other than population sources.

The computer-aided search was complemented with a key informant's survey, where at least one expert from each country was contacted for information (Rehm *et al*., 2005a, b). The search resulted in 24 included publications covering 12 countries for alcohol, and 13 publications covering 15 countries for illicit drugs. One of the latter publications was a summary publication conducted under the umbrella of the EMCDDA (Kraus *et al*., 2003). For tobacco, we indirectly estimated TUD dependence from smoking rates (sources see http://tcrc-profiles.globalink.org), using the German national study (Jacobi *et al*., 2002; Bijl and Ravelli, 2000) as source for the proportion between nicotine dependence and smoking. The resulting rates of main studies are found in Table 1. For further details of the methodology see Wittchen and Jacobi (2005).

Table 1 Selected prevalence studies in addiction (for full list see Rehm *et al*., 2005a, b)

Country	Study	Time of fieldwork	Point prevalence (%)	*N*	Age	Reference
Alcohol dependence						
Czech republic	Czech CIDI study	1998–99	0.4	1497	18 +	Dzurova *et al*., 2000
Finland	The Health 2000 Study	2000/2001	3.9	6005	> 30	Pirkola *et al*., 2005
France	ESEMeD (European Study of the Epidemiology of Mental Disorders)	2001–02	0.8	2894	18 +	Alonso *et al*., 2002, 2004
Germany	German National Health Interview and Examination Survey (GHS-MHS)	1998–99	3.4	4181	18–65	Jacobi *et al*., 2002, 2004
Italy	ESEMeD (European Study of the Epidemiology of Mental Disorders)	2001–02	0.1	4712	18 +	Alonso *et al*., 2002, 2004
Netherlands	Netherlands Mental Health Survey and Incidence Study (NEMESIS)	1996	3.7	7076	18–64	Bijl & Ravelli, 2000; Bijl *et al*., 1998
Norway	Norwegian psychiatric epidemiological study OsLof study	1994–97	6.6	2066	18–65	Kringlen *et al*., 2001
Spain	ESEMeD (European Study of the Epidemiology of Mental Disorders)	2001–02	0.1	5473	18 +	Alonso *et al*., 2002, 2004
Sweden	PART-study	1998–2001	6.2	10 441	20–64	Hällström *et al*., 2003
UK	OPCS UK Houshold survey	1993–94	4.8	10 108	16–64	Meltzer & Maes, 1995
European estimate†			*3.7*			
Illicit drug dependence						
Germany	Transitions in Alcohol Consumption and Smoking (TACOS)	1996–97	0.1	4075	18–64	Meyer *et al*., 2000
Germany	German National Health Interview and Examination Survey (GHS-MHS)	1998–99	0.3	4181	18–65	Jacobi *et al*., 2002, 2004
Netherlands	Netherlands Mental Health Survey and Incidence Study (NEMESIS)	1996	0.8	7076	18–64	Bijl & Ravelli, 2000; Bijl *et al*., 1998
Norway	Norwegian psychiatric epidemiological study OsLof study	1994–97	0.6	2066	18–65	Kringlen *et al*., 2001
UK	Population study in the District of Derry	1993–94	0.3	923	18–64	McConnell *et al*., 2002
UK	OPCS UK Houshold survey	1993–94	2.2	10 108	16–64	Meltzer & Maes, 1995
European estimate†			0.6			
Nicotine dependence						
Austria*			7.3			
Belgium*			8.5			
Cyprus*			6.8			
Czech Republic*			5.9			
Denmark*			8.9			
Estonia*			10.1			
Finland*			7.0			
France*			9.8			
Germany	German National Health Interview and Examination Survey (GHS-MHS)	1998–99	11.0	4181	18–65	Pirkola *et al*., 2005
Greece*			11.1			
Hungary*			10.5			
Iceland*			8.2			
Ireland*			9.4			
Italy*			7.1			
Latvia*			10.3			
Lithuania*			7.2			
Luxembourg*			9.9			
Malta*			7.1			
Netherlands*			10.0			
Norway*			9.9			
Poland*			8.6			
Portugal*			5.5			
Slovakia*			12.7			
Slovenia*			7.5			
Spain*			10.0			
Sweden*			5.9			

Table 1 Continued

Country	Study	Time of fieldwork	Point prevalence (%)	*N*	Age	Reference
Switzerland*			9.8			
UK*			8.5			

For countries where multiple studies were identified the values in bold were selected.
† The European estimate is a median-value of the identified prevalence study estimates. The point estimate served as best estimate for countries where no prevalence estimates were found in the literature. The median values here correspond to the median of (Rehm *et al*., 2005; Rehm *et al*., 2005) and slightly differ from (R R). The reasons for these differences are the use of weighting and different criteria of selection.
The country specific estimate was based on smoking prevalence. An assumed proportion of 30% was applied in order to reach prevalence in nicotine dependence.

Cost data on addiction in Europe

Substance abuse and dependence accounts for one of the major disease groups in Europe within mental health in terms of prevalence as shown in the previous section, but has earned little attention in previous health economic research (Rehm and Gmel, 2001). A systematic literature review of cost studies in the area of substance use disorders in Europe revealed only a few qualitative cost studies (Andlin-Sobocki, 2004). Out of all eligible studies selected for full review on alcohol, nicotine and illicit drug dependence only a few were selected to be included in the health economic estimation of cost of addiction in Europe in the current project (Table 2). The reasons for excluding of a range of studies were: (1) poor costing methodologies applied; (2) under-inclusion of resource utilization components; and (3) non-representativeness of sample selection for the whole country. For a full discussion on the reviewed cost studies in addiction, see Andlin-Sobocki (2004). The majority of the studies selected are based on a prevalence top-down approach when estimating the cost of substance use. The studies rely on a combination of national registry data sources and own assumptions. No studies were found from the Eastern European countries in substance use disorders.

Cost data selected for study

The cost studies selected for the health economic model are put in bold in Table 2. In alcohol abuse two studies are selected: a UK study by the Cabinet Office (2003) and a German study by Bergmann and Horch (2002). Both studies are based on national surveys with the attributional fraction method being applied for estimating the cost of healthcare. Moreover, both studies cover a broad range of cost components. The estimated total cost per patient is €11 984 and €10 667, respectively, and both studies take cost of crime-related outcomes into account. In the field of drug dependence, the study by Healey *et al*. (1998) is selected for the modelling of the costs in Europe. The study is a bottom-up study based on a cohort of 1075 patients, and it takes both opioid and cannabinoid dependence into account. The study includes direct healthcare costs and cost of crime-related outcomes. The estimated cost per patient for 2004 is estimated to €18 064. In nicotine dependence a Danish study by Rasmussen and Sogaard (2000) and a German study by Ruff *et al*. (2000) were selected for the model estimations. Both studies are prevalence top-down studies based on the attributional fraction method for estimating the healthcare costs associated with nicotine dependence. The estimated costs per patient of €835 and €856, respectively, were obtained.

Prevalence data selected for study

Based on the literature review, we used the following epidemiological information in the model:

- For alcohol and illegal drugs, country-specific estimates were used whenever available. In Germany, where there were several estimates, the more comprehensive German National Health Interview and Examination Survey (Bijl and Ravelli, 2000; Jacobi *et al*., 2002) was used. For countries with no prevalence studies, the European median (Table 1) was used. When the sex-age distribution was lacking, the distribution of the aforementioned German study was use.
- For tobacco, there were data on prevalence of smoking and subsequently derived estimates of nicotine dependence for all countries.

Discussion

SUDs are widespread in Europe. Especially given their public health importance (World Health Organization, 2002, 2003; Ezzati *et al*., 2002; Rehm *et al*., 2005a, b), overall there is not sufficient information on the prevalence of these disorders, and existing studies are plagued with methodological differences. With respect to the available information, the biggest gap exists for the EU admission countries, where almost no information was available. Otherwise, information was scarcer for Southern Europe. Filling this gap with

Table 2 European health economic studies for substance use disorders

Source	Country	Year of estimate	Sample size/ prevalence	Time frame/ follow-up	Costs included	Cost per patient (€2003)	Direct healthcare cost	Non-medical direct costs/ Indirect costs	Cost of criminal outcomes	Total cost
Alcohol dependence										
Fenoglio *et al.* (2003)	France	1997	National prevalence: 4.4 million	1 years	Medical direct costs and indirect costs	698	n/a	948	890	2536
Reynaud *et al.* (2001)	France	1996	National prevalence: 7.3 million	1 years	Medical direct costs	335	n/a	n/a	n/a	335
Brecht *et al.* (1996)	Germany	1990	National prevalence: 4.4 million	1 years	Medical direct costs and indirect costs	247	n/a	703	n/a	950
Bergmann *et al.* (2002)	Germany	1995	National prevalence of 1.6 million	1 years	Total direct costs and indirect costs	2563	53	7593	1774	11 984
Portella *et al.* (1998)	Spain	1996		1 years	Medical direct costs	n/a	n/a	n/a	n/a	n/a
Varney *et al.* (2002)	Scotland	2001/2002	National prevalence: 1.2 million	1 years	Medical direct costs	4194	n/a	n/a	n/a	4194
Cabinet office, UK (2003)	UK	2001/2002	Estimated national prevalence: 2.83 million	1 years	Medical direct costs and indirect costs	1120	n/a	4243	5304	10 667
McKenna *et al.* (1996)	UK	1994	$N = 586$, age: 20–82 (Edingborough)	6 months	Medical direct costs	107	95	795	n/a	997
Drug dependence										
Fenoglio *et al.* (2003)	France	1997	National prevalence: 150 000	1 years	Medical direct costs and indirect costs	1486	n/a	200	4320	4520
Garcia-Altés *et al.* (2002)	Spain	1997	Estimated prevalence: 110 000	1 years	Direct medical and non-medical cost and indirect cost	2352	n/a	1162	869	4383
Coyle *et al.* (1997)	UK	1992/1993	$N = 1542$	1 years	Direct medical cost	863	n/a	n/a	n/a	863
Healey *et al.* (1998)	UK	1995/1996	$N = 1075$	1 years	Direct medical cost, indirect costs	2453	1417	n/a	14 194	18 064
Nicotine dependence										
Rasmussen *et al.* (2000)	Denmark	1995	National prevalence: 1.78 million	1 years	Direct healthcare costs and indirect costs	405	n/a	430	n/a	835
Fenoglio *et al.* (2003)	France	1997	National prevalence: 13.5 million	1 years	Direct healthcare costs and indirect costs	345	n/a	300	n/a	645
Ruff *et al.* (2000)	Germany	1996	National prevalence: 21.3 million	1 years	Direct healthcare costs and indirect costs	438	n/a	418	n/a	856
Sanner (1991)	Norway	1988	National prevalence: 1.53 million	1 years	Direct healthcare costs and indirect costs	184	n/a	901	n/a	1085
Cohen *et al.* (1998)	UK	1992/1993	not reported	1 years	Direct costs and indirect costs	n/a	n/a	n/a	n/a	n/a

comparative studies on the prevalence of substance use disorders seems to be the largest epidemiological challenge in the field.

With respect to methodological differences, it became evident that even studies using the same instrument in the same country came to divergent conclusions – not in the decimals of prevalence rates, but producing manifold rates. The main reason for these differences seems to be methodological differences in transforming answers into SUDs diagnoses. Of course, such divergences could not possibly reflect reality, and thus one conclusion has to be better standardization in the detailed methodology of the studies including standardized reporting of different techniques.

The methodological problems render substantive conclusions as tentative. But there seem to be stoning similarities with respect to prevalence of illicit drug disorders in European countries, whereas tobacco and alcohol use disorder prevalence rates were more varied. Alcohol use disorder rates are especially puzzling, as they do not follow the per capita consumption figures (Rehm *et al*., 2005a). In other words, there seem to be differences in the pattern of consumption between different European countries, which affect the rates of manifest disorders.

The overall coverage of cost studies in the field of substance use disorders in Europe provides strong recommendations for increased numbers of studies in future. There are several challenges ahead to get a full understanding of the size and distribution of costs across Europe, and the identified studies show the total lack of cost studies in Eastern Europe and in major parts of Western and Central Europe. Methodology-wise, the studies reviewed were conducted with varying quality, especially in terms of estimating the indirect costs due to substance use. Moreover, many of the studies identified cover a broader definition of substance use (alcohol use/abuse and smoking) instead of the clinical definitions. The cost drivers identified in substance use disorder are clearly indirect costs, and in particular cost due to premature mortality and cost of crime-related outcomes (alcohol and illicit drug use disorders). Hence, it is very important to find appropriate methods of estimating the cost to society due to these causes. Here, there is a clear need for developing a more thorough approach to combining different data sources and ways to identify, quantify and valuate the cost of, for example, resources related to crime-related outcomes as well as for law enforcement.

Conclusions

Prevalence of addiction in Europe is high and affects more than 10% of the population, with nicotine dependence being the most prevalent, and illicit drug dependence the least prevalent of SUDs. However, data on alcohol and drug dependence are scarce in several European nations, especially in the new admission countries. As SUDs constitute a major public health problem, for healthcare planning as well as for health policy it is indispensable to be able to quantify the problem.

Although a fair amount of cost studies exist in addiction in Europe, there is a strong need for further studies in the field. Most studies identified are from the early 1990s and are based on methodology of varying quality. Moreover, most studies are top-down studies incorporating assumptions about the resource use in people suffering from addiction. Moreover, all studies identified were conducted in the major European countries or the Nordic countries, and thus no studies were found from the Central and Eastern European countries.

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ORIGINAL ARTICLE

Cost of affective disorders in Europe

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Introduction

Affective (also labelled mood) disorders comprise a group of disorders characterized by clinically significant mood disturbances. Modern classificatory systems (ICD-10, DSM-IV; and APP) define these disorders with only few and minor differences by the presence of a specific number of symptoms and by specifying explicit duration, severity, distress, disability and diagnostic exclusion criteria. Convergently, both classification systems define three major groups of disorders with various subtypes, namely major depression, bipolar disorder, and cyclothymic and dysthymic disorders. The majority of epidemiological and clinical studies refer to DSM-IV and respective assessment instruments; therefore this paper focuses primarily on the DSM-IV terminology for this review. It should be noted that the term major depression with its criteria replaces by and large the older and unreliable terminology of so-called endogenous, neurotic and reactive depression, whereas bipolar disorder replaces in a more reliable way the past concept of manic depression.

The epidemiology of affective disorder and particular depression has been addressed in a fairly large number of community studies and depression is probably the most frequently studied condition across all epidemiological surveys in the EU (Wittchen and Jacobi, 2005). Despite some variation, largely due to methodological factors, the crude epidemiological measures for current and 1-year prevalence are well established. However, as for most other mental disorders, data on patterns of incidence as well as on course, disability and treatment and are largely lacking (Pini and Wittchen, 2005; Paykel *et al*., 2005).

Diagnostic classification, clinical and epidemiological features

Major depression

Major depression is defined as a period of at least 2 weeks duration in which the person suffers from at least five of a total of nine explicitly defined core depressive symptoms. In addition numerous other criteria must be met such as impairment, suffering and persistence, it must be excluded that other medical or substance-related factors are responsible for these symptoms as well as other mental disorders that might mimic such symptoms. In particular the history of manic or hypomanic episodes as well as overlap with psychotic disorders must be excluded. Major depression is subtyped by severity (mild, moderate, severe), course (single vs. recurrent) as well as the presence of specific diagnostic features (i.e. with and without somatic symptoms or melancholic features).

Every year 5–8% of the adult population is suffering from a depressive episode; the lifetime risk of major depression has been estimated to be even higher (12–16%) (Wittchen *et al*., 1994, 2001). Epidemiological data on depression may be quite variable due to differences in sampling, age group composition, diagnostic criteria and time frames (2 weeks vs. 4 weeks vs. 12 month criteria) and thus should be interpreted with caution.

Females reveal rates that are twice as high as those for males. Age of first onset of major depression can be any time after childhood. The prevalence of depression is in the range of 1–2% in preadolescent children and 5–6% during adolescence. There are indications suggesting that there are increasing rates among adolescents and that the first onset of major depression has shifted into earlier ages. The ratio of girls to boys is 1:1 in childhood and increases to 2:1 in adolescence. The epidemiological data on severity of episodes, recurrence risk and length of episode are less well studied. It is estimated that that the average length of depressive episodes is about 12 weeks and that over 70% of depressive disorders ultimately run a recurrent course. Although the short-term outcome of acute episodes has been described as being fairly good, 20–30% of patients either develop an unremitting chronic course or only partial remission with residual symptoms. Available epidemiological data from some European countries (ESEMeD/MHEDEA, 2000; Bijl *et al*., 2003) suggest that about 50% of all patients with depression have received some intervention during the past year. In the majority of cases treatment is delivered in primary care.

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It is estimated that only every second patient with depression is being cared for in the specialist mental health sector by mostly psychiatric or psychotherapeutic outpatient services, less frequently in inpatient care (Wittchen *et al.*, 2001). Treatment given is mostly antidepressant medication of various types, and less frequently psychological treatments. As most effective treatments antidepressants and CBT are regarded as effective first line treatments. There is some limited evidence for other psychotherapeutic approaches, such as psychodynamic and interpersonal therapy. In the acute phase depression is associated with a considerable degree of disability; about 2–10% of all patients are so disabled as to require inpatient care (Wittchen *et al.*, 2001). Depression is frequently associated with suicidal ideation and behaviour and also reveals increased mortality rates, of which completed suicide is assumed to be the major cause.

Bipolar disorder

The term bipolar disorder describes an usually episodic and clinically sometimes extremely severe and dramatic presentation. Bipolar disorder encompasses several phenotypes. Cross-sectionally, bipolar patients may present with either depressive, or manic or hypomanic episodes; additionally a wide spectrum of other psychopathological features may be present. This considerable cross-sectional phenotypic heterogeneity continues to be the source of some controversy and the exact clinical characteristics of bipolar disorder are subject to debate. The core diagnostic criterion of bipolar disorder is the presence of a 'manic' syndrome, defined as a period in which the person suffers from unusually and clinically significant extreme good mood or irritability and experiences a number of explicitly defined associated symptoms (i.e. decreased need to sleep, hyperactivity and impaired control). Whenever such a period does or did occur in the patient's life, the diagnosis of bipolar disorder is assigned. The separation between bipolar I (mania) and II (hypomania) is exclusively related to the illness severity. If the person can still function relatively well without the need for immediate clinical intervention or hospitalization the diagnosis of bipolar II is assigned. In contrast, if severe impairment is present bipolar I is assigned. It should be noted that this diagnosis is assigned on the basis of the lifetime course, meaning that even subjects with a severe depressive episode do receive this diagnosis, whenever a manic or hypomanic episode has been present in the past.

The epidemiology of bipolar disorder has been addressed in several studies in Europe (Wittchen & Jacobi, 2005; Pini and Wittchen, 2005). The prevalence estimates for any bipolar disorders range from less than 1% to over 5%. This variation seems to be largely dependent on the type of study, the diagnostic coverage and the type of assessment instrument used. Prospective-longitudinal studies tend to report higher rates, possibly because they are more sensitive in catching the lifetime history. The 12-month prevalence of bipolar I disorder is usually estimated to be around 1%, and on average similarly high for hypomania (bipolar II, 1.2%). Bipolar II prevalence findings show much more variation with estimates up to 6%, especially if cyclothymia – a trait-like variant – and other bipolar-spectrum like conditions are considered. Focusing on bipolar I disorder the disorder usually takes a recurrent and severe course with an increasing number of manic, depressive and missed episodes of variable severity and duration over the patient's lifetime. The majority of patients with bipolar I will frequently receive drug treatment over their lifetime to prevent further episodes. Over 60% of all patients affected will require hospitalization during the course of their disorder. The therapeutic management of bipolar disorder may be extremely complex, because of the episodic course, the usually severe disability associated with the acute manic and depressive phases, and the considerable degree of comorbidity that is typical for both bipolar I and II cases. Bipolar patients have elevated risks for almost all other types of mental disorders, including psychotic and substance use disorders, and they also have increased risks for suicide.

Cost data in affective disorders in Europe

As a result of high prevalence, frequent early onset in adolescence and early adulthood and a lifelong recurrent or even chronic course associated with disability, affective disorders are well known to constitute a substantial burden to people afflicted, as well as society. Depression was ranked as the fourth leading cause of disease burden, accounting for almost 12% of all total years lived with disability worldwide (Ustun *et al.*, 2004) and is expected to become the second most disabling disorder by 2010. A recent study estimated the total annual cost of depressive disorders in American society to be $83.1 billion in 2000 prices (Greenberg *et al.*, 2003). Additionally and as compared with other mental disorders, there seems to be at first sight a significantly larger amount of health economic research conducted in the area of affective disorders in depression in particular.

However, as will be discussed below many of these studies are part of health economic appraisals in relation to licensing studies and other evaluations of new medicines for depression, and thus might be difficult to generalize.

An extensive search of the literature for cost studies conducted in Europe on affective disorders resulted in a total of 11 studies (Lothgren, 2004). A complementary search added two further relevant studies. Four studies were found for bipolar/mania: two studies from France, one from the UK and one from The Netherlands. In depression nine relevant cost studies were found: five were from the UK, two from Sweden, one from Spain and one from Germany. No studies were identified on dysthymia. Table 1 presents the available cost data on affective disorders in Europe, inflated and converted to cost levels expressed in Euros in the cost base level of year 2004 (Eurostat, 2004; European Central Bank, 2004).

Bipolar/mania

There are four cost studies available in the literature on bipolar disorders. As can be observed in Table 1, the direct medical cost ranges from €700 to €24 000 per patient (Olie and Levy, 2002; Das Gupta and Guest, 2002; de Zelicourt *et al*., 2003; Hakkaart-van Roijen *et al*., 2004). Two studies have included indirect costs, and here the estimates range from €3000 to €10 000 per patient (Das Gupta and Guest, 2002; Hakkaart-van Roijen *et al*., 2004). However, the differences that appear in the cost literature on bipolar disorder are rather due to study designs and study populations than differences in treatment patterns or healthcare systems.

The French study by Olie and Levy (2002) estimated the direct healthcare cost as €24 100 per patient, whereas the study by de Zelicourt *et al*. (2003) reached €3600. Both studies are focused on estimating costs of manic episodes, and the respective study populations were included upon hospitalization, which explains the relatively high direct medical costs. The main reason for the substantial difference in results between the two studies stems from the study design, where the former is a bottom-up study, analyzing case record data from more severely ill patients, and the latter is a top-down prevalence-based study with its primary data in registries and literature data.

The UK study and the study from The Netherlands were focused on bipolar disorder rather than on manic episodes. In the UK study by Das Gupta and Guest (2002), the total cost estimate was €9900, of which 90%

Table 1 Cost studies on affective disorder in Europe, cost per patient (€PPP2004) (Lothgren, 2004)

Source	Country	Year of estimate	Sample size/ prevalence	Time frame/ follow-up	Costs included	Cost per patient (€PPP2004)	Direct healthcare cost	Non-medical direct costs	Total cost
Bipolar disorders									
Olie & Levy, 2002	France	1999	$N = 137$	3 months	Direct	24129	n/a	n/a	24129
de Zelicourt *et al*., 2003	France	1999	0.82% [~390000]	1 years	Inpatient care	3630	n/a	n/a	3630
Hakkaart-van Roijen *et al*., 2004	Holland	2002	$N = 40$	1 years	Direct medical, indirect	667	n/a	2699	3366
Das Gupta & Guest, 2002	UK	1999/ 2000	0.5% [~297000]	1 years	Direct medical	975	4	8917	9896
Depressive disorders									
Salize *et al*., 2004[a]	Germany	2001	$N = 270$	1 years	Direct medical	2025	n/a	n/a	2025
Chisholm *et al*., 2003[a]	Spain	2000	$N = 472$	3 months	Total direct	608	n/a	989	1598
Henriksson & Jönsson, 2004	Sweden	1996	Based on estimate of prevalence: 4.5%	1 years	Total direct	432	n/a	n/a	432
Norinder *et al*., 2000	Sweden	1996	Based on estimate of prevalence: 4.5%	1 years	Direct, indirect	446	n/a	1466	1912
Creed *et al*., 2002	UK	n/a	$n = 53$ cases, $n = 77$ subthreshold cases and $n = 66$ controls	5 months	Total direct	14499	696	n/a	15195
Jonsson & Bebbington, 1994	UK	1990	n/a	1 years	Total direct	n/a	n/a	n/a	n/a
Thomas & Morris, 2003[a]	UK	2000	Based on estimate of 2.8 million	1 years	Direct, indirect	208	n/a	4880	5088
Kind & Sorensen, 1993	UK	1990	Based on estimate of 1.5 million	1 years	Direct, indirect	512	80	4223	4815
West, 1990	UK	1990	Based on estimate of 1.5 million	1 years	Total direct	473	n/a	n/a	473

[a]Studies selected with input data for the cost model in the project.

was indirect costs. The study is based on NHS registry data and complementary data on lost work days. The Dutch study reached a total cost of €3400, of which 81% corresponded to indirect costs. The study is based on the epidemiological study NEMESIS, and resource-use data were picked up through interviews with 40 patients with lifetime diagnosis of bipolar disorder. The UK study estimate for indirect costs is substantially higher than in the Dutch study, since it includes expenses from morbidity as well as mortality.

As the manic phase of bipolar disorder is generally expected to be more demanding on healthcare resources, this further explains the difference in direct medical cost estimates between the French and the UK and Dutch studies. For the purpose of estimating the total cost of bipolar disorder in Europe, the UK study provides the most appropriate input data for the model.

Depression

Five out of the nine studies on depression were conducted in the UK (West, 1990; Kind and Sorensen, 1993; Jonsson and Bebbington, 1994; Norinder *et al*., 2000; Creed *et al*., 2002; Thomas and Morris, 2003; Chisholm *et al*., 2003; Salize *et al*., 2004; Henriksson and Jönsson, 2004). The direct medical cost estimates range from €200 to €14 500. All but the study by Creed *et al*. are top-down prevalence-based studies. In the studies by Kind and Sorensen and Thomas and Morris there are estimates of the indirect costs due to depression from €4200 to €4900 per patient (Kind and Sorensen, 1993; Thomas and Morris, 2003). However, the estimates only included cost of sick leave due to depression. The reason for the significantly higher direct medical costs in the study by Creed *et al*. was due to its study design (bottom-up study), which includes a more severe patient population with comorbidities who are acutely hospitalized due to their symptoms. Moreover, the cost results from the study by Creed *et al*. were annualized from the published 5-months costs, which may give a further over-estimation. The study by Jonsson *et al*. did not report any cost estimates per patient.

Both Swedish studies are prevalence-based top-down studies estimating the total cost of depression in Sweden, and reach a similar direct medical cost of depression of around €400 per patient (Norinder *et al*., 2000; Henriksson and Jönsson, 2004). The older study from Sweden by Norinder *et al*. (2000) estimated a total cost per patient of €1900. The Spanish study by Chisholm *et al*. (2003) and the German study by Salize *et al*. (2004) are both based on patient cohorts selected at primary care sites, and quantified resource use through interviews.

For the purpose of the study, the most appropriate study to be the basis for the cost model on depressive disorder in Europe is the study by Thomas and Morris (2003). The study applies a solid costing methodology and includes both direct as well as indirect costs (indirect costs due to morbidity and mortality). Due to the relatively underestimated cost of healthcare resources reported in the study by Thomas and Morris, data on healthcare resource use were complemented with the study estimates by Salize *et al*. (2004) and Chisholm *et al*. (2003). Hence, the healthcare cost components were imputed for the rest of Europe based on an average of the cost estimates from the three studies, and the indirect cost components were imputed based on only the UK study by Thomas and Morris.

Discussion

Except for dysthymia and cyclothymia the basic prevalence information on depression and bipolar disorders are in place, and have reached a remarkable degree of convergence, the epidemiological evidence and specifically data for patterns of onset, incidence and course, disability and treatment are largely lacking. Thus, although the prevalence numbers for affective disorders in the community are trustworthy, it is not known how many of all depressed episodes are recognized and treated in the primary care and the mental health specialty sector. Further data on type of treatment, treatment duration and hospitalization are required. Thus, a limitation to the cost calculations is that the true costs of affective disorders are likely to be underestimated. This underestimation is the result of not including dysthymia and cyclothymic disorders, known to be chronic conditions, and the incomplete coverage of costs, especially in primary care.

The economic evidence in affective disorders is remarkably poor. This is especially true for the Central and Eastern European countries. In terms of study design and methodology, most cost studies published to date are based on the prevalence top-down approach, often only including public registries and literature sources for data analyses. The resource use in patients with affective disorders by stage and age group and by country, respectively, by healthcare provider system is not known. However, these data only represent a fraction of the total cost of depression. It is well known from all studies in this domain that lost workdays due to sick-leave, reduced working capacity or death are the most critical and major sources of the cost of affective disorders (Lothgren, 2004). In each of these indicators depression reveals the greatest burden, because of the high prevalence and the high disability associated with acute phases (Wittchen *et al*., 2001). Hence, in order to

get a better understanding of the total economic burden of depression on society there is a need for more studies based on primary data collection in representative population and patient samples recruited from various types of services involved in the management of these patients, to pick up the full range of cost implications. Furthermore, more studies are required comparing proportions treated, care pathways, adequacy of recognition and adequacy treatment delivery among the different healthcare systems in different European countries.

Conclusion

The epidemiological evidence for affective disorders in Europe is incomplete and only a few population-based studies are available that provide at least some type of data needed for a sound methodological estimation of costs. Hence, there is a need for a pan-European epidemiological study to collect more complete data. The economic evidence for affective disorders is similarly deficient in Europe. Most studies are prevalence-based top-down designed depending on assumptions in terms of resource use. Moreover, these kinds of studies often do not pick up all resources utilized by patients with affective disorders. Hence, there is a great need for future health economic field studies in the area to better assess the cost of affective disorders in Europe.

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ORIGINAL ARTICLE

Cost of anxiety disorders in Europe

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Introduction

Anxiety disorders, as defined by current diagnostic classification systems (DSM-IV, APA and ICD-10), comprise a wide range of phenotypically quite different conditions. The spectrum of anxiety disorders ranges from panic disorder and generalized anxiety disorders (GAD) to various types of phobic disorders (social phobia, agoraphobia, specific phobia subtypes, etc.) and might even include conditions like obsessive-compulsive disorder (OCD) and post-traumatic stress disorder (PTSD). Because of the lack of cost data, the latter two conditions are not considered here in this overview. For historical reasons it should be noted that panic disorder and GAD closely resemble what has been labelled in the past 'anxiety neurosis', whereas phobias were lumped together in the past under the term 'phobic neuroses'.

Despite the seemingly striking differences in symptomatology and impairment, their natural course and severity, anxiety disorders all share the same core diagnostic features: namely the core role of anxiety reactions and avoidance behaviour in the development and/or the expression of the illness. With the exception of panic disorder and GAD, they also share with a few notable exceptions an early onset – mostly before age of 16 – and a considerable degree of persistence over the patient's lifetime (Wittchen *et al*., 2001). Family genetic studies also demonstrate that anxiety disorders 'run in families', although the mechanisms of this familiar aggregation remain poorly understood. According to most more recent epidemiological studies, anxiety disorders overall were almost always confirmed to be among the most prevalent mental disorders, with a lifetime cumulative incidence risk of 11% to over 20%, depending on the range of anxiety disorders covered, with females revealing approximately twice the prevalence of males (Wittchen *et al*., 2001).

The incidence for anxiety disorders in general is characterized by steep increases between ages 6 to about 16. After this age considerable incidence rates are noteworthy for panic disorder, agoraphobia and particularly for GAD. Epidemiological studies have also demonstrated some sequential and simultaneous comorbidity between various anxiety disorders and a substantial degree of continuity of childhood expression of anxiety disorders (such as separation anxiety disorder, or overanxious disorders) to various forms of adolescent and adult anxiety and affective disorders. In fact there is growing recognition for the suggestion that anxiety disorders are also a potent risk constellation for depressive disorders (Bittner *et al*., 2004). The latter two issues of comorbidity and continuity are essential for understanding the considerable degree of lasting impairments and disabilities associated with these disorders that persist from childhood to late adulthood in the majority of cases.

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Diagnostic classification, criteria and essential epidemiological features

For anxiety disorders several epidemiological studies are available that – after adjusting for technical and design issues – provide a fairly convergent picture at least with regard to the lifetime and 12-month prevalence in adulthood and adolescence (Table 1). The epidemiological data situation in old age is largely deficient and in children is hampered by numerous problems regarding diagnostic assessment instruments. Other deficits include the lack of any prevalence data from eastern EU countries, lack of detailed disability and service utilization data, and a lack of coordination in analyses and reporting (Wittchen and Jacobi, 2005).

Panic disorder

The core feature of panic disorder is the occurrence of spontaneous panic attacks (extreme paroxysmal anxiety reaction), associated with a subsequent enduring anxious predisposition and the fearful expectation of subsequent attacks. The lifetime prevalence of panic disorder is estimated to be 3–5%, the 12-month prevalence 2% (Faravelli *et al*., 2005). Onset is typically in the twenties, although the disorder may also start in early adolescence, and spontaneous remissions are rare. As a result of the panic attacks, most panic patients also develop agoraphobia. Agoraphobia denotes a complex behavioural syndrome of persistent and enduring excessive fear reactions and avoidance in relation to all outside home situations (leaving the house alone, using public transportation, shops and open places). Almost all panic disorder patients also suffer from agoraphobia, and frequently are completely unable to leave the

Table 1 Twelve-month prevalence of anxiety disorders by age and sex in the community (age 18–65) [GHS-MHS data], along with the median of all available studies conducted in EU countries, Iceland, Norway and Switzerland (Wittchen and Jacobi, 2005)

Diagnosis (DSM-IV)	Women				Men					Median[b] %
	Total (%)[a]	18–34 (%)	35–49 (%)	50–65 (%)	Total (%)	18–34 (%)	35–49 (%)	50–65 (%)	Total	
Any anxiety disorder	16.3 14.8–18.0	17.0 14.4–20.0	15.9 13.4–18.6	16.2 13.6–19.1	7.8 6.6–9.1	7.0 5.2–9.2	8.0 6.2–10.4	8.4 6.4–10.8	12.0 11.1–13.0	–
Panic disorder	3.0 0.2–3.8	3.4 2.3–5.0	3.4 2.3–4.9	2.4 1.5–3.6	1.7 1.2–2.4	1.0 0.5–2.0	2.0 1.1–3.7	2.1 1.3–3.5	2.3 1.9–3.8	1.8 0.7–2.2
Agoraphobia	3.1 2.4–3.9	2.0 1.2–3.4	2.9 1.9–4.3	4.4 3.1–6.0	1.0 0.6–1.5	0.9 0.4–1.9	1.1 0.6–2.2	0.9 0.5–1.9	2.0 1.7–2.5	1.3 0.7–2.0
Social phobia	2.7 2.1–3.4	3.1 2.0–4.6	2.7 1.8–4.2	2.2 1.3–3.6	1.3 0.9–2.0	1.9 1.0–3.4	0.7 0.3–1.8	1.4 0.7–2.7	2.0 1.6–2.5	2.3 1.1–4.8
GAD	2.1 1.5–2.8	1.1 0.6–2.3	2.9 1.9–4.3	2.2 1.2–3.8	1.0 0.6–1.5	0.5 0.2–1.2	0.9 0.4–1.9	1.8 0.9–3.2	1.5 1.2–1.9	1.7 0.8–2.0
Specific phobias	10.8 9.5–12.2	11.9 9.7–14.6	9.7 7.8–12.1	10.7 8.6–13.3	4.5 3.7–5.6	4.2 2.9–6.0	4.7 3.3–6.8	4.6 3.2–6.6	7.6 6.9–8.5	6.4 3.4–7.6
Obsessive compulsive disorder	0.9 0.6–1.4	1.0 0.5–1.9	0.9 0.4–2.0	0.8 0.4–1.6	0.6 0.3–1.0	0.4 0.1–1.2	1.0 0.5–2.0	0.3 0.00–1.0	0.7 0.5–1.0	0.7 0.5–1.1

[a]12-month-prevalences with 95%-confidence intervals.
[b]Medians of all available European data with interquartile ranges; no median could be calculated for aggregated diagnoses ('anxiety disorder').

house alone or to participate further in daily life. Agoraphobia might also occur without panic disorder and has a lifetime prevalence of approximately 4%, or 2%, respectively, in the past 12 months. Both conditions typically reveal the most severe disabilities and impairments of all anxiety disorders and carry additionally a high risk of secondary complications. In particular there is an increased risk of developing major depression and substance use dependence (sedating drugs and alcohol). Some indications have been reported for increased premature mortality rates. Typically panic patients show extensive healthcare use (consultation and diagnostic testing) and they are described as expensive high utilizers of diagnostic, general inpatient and outpatient resources. Nevertheless panic patients with and without agoraphobia usually go unrecognized and undiagnosed for many years and sometimes decades. Despite the existence of highly effective drugs (modern antidepressants) and particularly cognitive-behavioural (CBT) treatments, studies estimate that only about 10% of all sufferers receive adequate treatment (Faravelli *et al.*, 2005).

GAD

The core features of GAD are chronic (persisting for 6 months or more) anxious worrying associated with a syndrome consisting of symptoms of hypervigilance, hyperarousal and tension. Despite changes of diagnostic concepts prevalence estimates of GAD remained fairly consistent. GAD is undoubtedly a severe, disabling and chronic disorder in adulthood, with a 12-month prevalence of 2–3% and a lifetime prevalence of 5% of the adult population (Ballenger *et al.*, 2001; Lieb *et al.*, 2005). Unlike all other anxiety disorders, DSM-IV GAD incidence is highest in the thirties and fourties, severe and stable GAD in adolescence is rare. Prevalence rates are highest in females over the age of 45 (8–10%). Furthermore, there are indications that GAD is the most frequent anxiety disorder in old age (> 65). Although the severity, the disabling nature and the chronic course of GAD has been well described along with high comorbidity rates, GAD remains poorly recognized and treated according to almost all studies (Wittchen *et al.*, 2002). For GAD various effective psychological (CBT) treatments as well as drug treatments are established, yet only 10–15% of patients seem to get treated according to these modern guidelines. Similar to panic, GAD has also been described as a high-utilizer group of all types of resources, including inpatient care.

Social phobia and specific phobias

Irrespective of many etiological and clinical differences that exist between phobia subtypes, the core features of phobic disorders are intensive fear reactions that consistently occur in anticipation of or when confronted by the respective fear stimuli. Phobias can be grouped by the predominant nature of the fear stimuli, such as into social phobia, if the fear reaction occurs in response to social situations where a person might be negatively evaluated by others, or into animal phobia, if it is due to any type of animal, or into blood-injury phobia, if the syndrome is associated with thinking about or confrontation with blood, injury or medical devices.

In addition the following diagnostic criteria must be met to justify a diagnosis: (a) the occurrence of a prototypical anxiety reaction with defined cognitive, affective, physiological and behavioural symptoms that might take the form of a panic attack; (b) the person must recognize that fear and avoidance are unreasonable, excessive or exaggerated; (c) the situation must be avoided or only endured with intensive distress/anxiety; and (d) the symptoms must be associated with impairment, disability and distress.

The modern classification systems (i.e. DSM-IV) usually differentiate agoraphobia (see above) from social phobia and specific phobias; the latter being further subtyped into animal, environmental, situational or blood-injury. Specific phobias are by far the most frequent and the earliest onset conditions of all anxiety disorders before the age of 20; however, relatively few recent data about their public health impact are available. In contrast social phobia is the condition that has received the most intensive research attention (Wittchen and Fehm, 2003). In childhood and adolescence specific and social phobias tend to wax and wane, sometimes involving shifts in the type of syndrome. Once present through adolescence, anxiety disorders tend to persist over the decades, with complete remissions being rare, and with psychopathological complications such as secondary depression and substance use disorders being the rule rather than the exception. The degree of disability associated with specific phobias is extremely variable and depends on the number of phobias, comorbid conditions and environmental factors.

Social phobia is usually described as the most severe phobic condition in adulthood, although not necessarily in childhood and adolescence as the peak period of first onset (Fehm *et al*., 2005). The degree of disability and impairments, and the degree of complications (depression and substance abuse) as well as suicidal behaviours exceed that of other phobias. The treatment of choice of all phobias is behaviour therapy, respectively, CBT; for social phobia treatment with SSRIs and other antidepressant drugs have been licensed as well. Because behavioural treatments are not easily available in many healthcare systems, patients with phobias are rarely specifically treated (less than 8%) unless a depressive episode is present.

Cost data for anxiety disorders in Europe

Anxiety disorders have been found to be associated with significant costs to society. Apart from the high healthcare costs that these patients carry, the bulk of the economic burden of anxiety disorders occurs due to costs associated with reduced working capacity or premature pension (Rice and Miller, 1998). There are a couple of American studies estimating the total cost of anxiety disorders to the American society as $42–47 billion in 1990 prices (DuPont *et al*., 1996, 1999; Rice and Miller, 1998; Greenberg *et al*., 1999).

In sharp contrast to the American situation and to the importance to public health, there are only very few and diagnostically quite restrictive data sources available that do provide useful, reliable and comprehensive information about the direct and indirect and other costs of anxiety disorders in the EU.

Table 2 summarizes the results from the literature review in cost studies on anxiety disorders in Europe. The methodology and search strategy of the review is further described in Lothgren (2004).

As can be seen, and using the restrictive criteria for inclusion, there is almost no published scientific evidence for anxiety disorders in general or respective subgroups. The only two diagnoses for which some evidence is available are for GAD and panic. The following section summarizes the main findings from the detailed review of the identified GAD and panic disorder studies.

Literature review results

In the following, the main findings from the reviewed anxiety studies are discussed and the detailed data extracted from the reviewed studies are presented in a set of tables. Table 3 summarizes the selected cost studies from the literature review. All costs are converted with purchasing-power-parity weighted exchange rates into Euros and were inflated to the cost

Table 2 Literature search and screening results overview

	GAD	Panic	OCD	Social phobia	Agoraphobia	Specific phobias
No. identified studies in initial literature search	83	3	3	5	2	0
No. studies eligible for inclusion in final review	2	1	0	0	0	0
No. studies by country						
France	1					
Hungary	1					
Spain		1				

Table 3 European economic studies on anxiety disorders (cost per patient, €PPP2004) (Lothgren, 2004)

Source	Country	Year of estimate	Sample size/ prevalence	Time frame/ follow-up	Costs included	Cost per patient (€2003)			
						Direct healthcare cost	Non-medical direct costs	Indirect costs	Total cost
Generalized anxiety disorders									
Souetre *et al*., 1994	France	2003	$N = 395$ w/o comorbidity	3 months	Direct healthcare costs and indirect costs	2927	1958	n/a	969
Souetre *et al*., 1994	France	2003	$N = 604$ with comorbidity		Direct healthcare costs and indirect costs	4853	3194	n/a	1659
Zambori *et al*., 2002	Hungary	2002	$N = 51$ treatment group, $N = 75$ control group	1 year pre- and 1 year post treatment	Direct medical cost	n/a	35	n/a	15
Panic disorders									
Salvador-Carulla *et al*., 1995	Spain	1992	$N = 61$	1 year pre- and 1 year post treatment	Direct medical	1303[1]	634[1]	n/a	669[1]

[1]Calculated means based on the 1 year pre- and post treatment.

base level of year 2004 with the national consumer price index (Eurostat, 2004a,b; European Central Bank, 2004).

The French GAD study by Souetre *et al*. (1994) is a cross-sectional 3-months retrospective assessment of the resource use and costs for patients with GAD ($n = 604$ with and $n = 395$ without comorbid disorders). The Hungarian GAD study by Zambori *et al*. (2002) is a case–control combined retrospective/prospective pre-post study of treatment vs. usual care after diagnosis; the diagnosis not clearly being specified as GAD, but rather 'current anxiety' and/or mood disorder at inclusion. This study, however, does only report cost data for the drug costs. For inpatient care and indirect costs only the average number of hospital stay days and the average number of days absent from work on sick leave are reported. No costing has been done in this review for the Hungarian study data. The French study by Souetre *et al*. (1994) provides estimates of the total costs for GAD ranging from €2927 to €4853 per patient per year, without and with comorbidities, respectively. The existence of comorbidities does thus increase the costs by approximately 65% for GAD (in France). The increase in costs for GAD with vs. without comorbidities is about the same for the cost components of direct medical costs and indirect costs (short-term absence from work). The total direct medical costs are €1958 vs. €3194 without and with comorbidities, respectively, and the indirect costs are €969 vs. €1659.

The only cost study selected in panic disorder is a Spanish study with a 2-year combined retrospective/prospective design of $n = 61$ patients in Spain, and conducted by Salvador-Carulla *et al*. (1995). The results indicate that the total costs for panic disorder were €1593 1 year prior to diagnosis and treatment and €1012 the year after diagnosis and treatment. The diagnosis and treatment thus reduced the total costs for panic disorder for the patient sample in Spain. As expected, the direct medical costs increase after diagnosis/treatment whereas the indirect costs decrease. The average total direct cost was €489 during the year prior to diagnosis and treatment and €778 the year after, whereas the average indirect cost due to short-term absence from work was €1104 vs. €234. This study hence provides support for the offset of the total costs in diagnosing and treating patients with panic disorder.

A comparison between GAD and panic disorder indicates a difference in the resource use/cost structure between the disorders in that the use of tests and procedures is quite pronounced in panic disorder, where the tests and procedures account for around 30% of the total direct medical costs during the year prior to diagnosis and around 10% in the year after diagnosis and treatment. For GAD this cost component is

Table 4 GHS–MHS cost results, cost per patient (€PPP2004) (Jacobi *et al*., 2002)

Diagnosis	Total costs	Direct healthcare costs	Total non-medical costs	Total indirect costs
GAD	1628	1230	n/a	399
Social phobia	1453	750	n/a	703
Specific phobias	806	355	n/a	451
OCD	546	231	n/a	315
Panic disorder	1517	541	n/a	976
Agoraphobia	1488	366	n/a	1123

not even measured. As the French GAD study is a retrospective study it should have included any relevant resource use/costs occurring in the sample of charts reviewed.

Cost-of-illness data for model

The review of available cost studies in the field of anxiety disorders provides data that are less appropriate to use in the estimation of the cost of anxiety disorders on a European level, both due to the narrow patient populations in the studies as well as to non-conclusiveness in resource use data. In order to be able to estimate the cost of anxiety disorders in Europe, an own cost-of-illness analysis was made based on the German National Health Interview and Examination Survey, and more specifically its mental health supplement (GHS–MHS) (Jacobi *et al*., 2002). The survey was carried out in 1998/99 and included a community sample of $n = 4181$ (age: 18–65). Resource utilization data (including hospitalization, outpatient visits and productivity loss due to diagnosis) was extracted from the survey on the patients with the prespecified anxiety diagnoses. Mean costs[1] were calculated as excess costs (i.e. compared with subjects without the diagnosis of an anxiety disorder). The results are provided in Table 4.

[1]Unit cost data were collected from several sources: (1) wage statistics: Statistisches Bundesamt, 2004 [http://www.destatis.de/basis/e/logh/loghtab7.htm]; Statistisches Bundesamt 2004: Lohnkosten, Arbeitsproduktivität, Verdienst und Lohnstückkosten im Inland 2003. Table 1.12 aus Fachserie 18, Reihe 3 and BMA, Statistisches Taschenbuch. Durchschnittliche tarifliche Wochenarbeitszeit 2002; (2) inpatient costs: Institut für das Entgeltsystem im Krankenhaus GmbH (INEK). Fallpauschalen Katalog, G-DRG Version 2005 [http://www.g-drg.de]; (3) outpatient costs: Einheitlicher Bewertungsmaßstab (EBM) Stand 01.10.2001 [German tarif list for outpatient services]. Deutscher Ärzte-Verlag Köln, Zentralinstitut für die kassenärztliche Versorgung (ZI). ZI – ADT – Panel, Sonderauswertung Oktober 2004 and Kassenärztliche Vereinigung Nordrhein. Leitfaden für Psychologische Psychotherapeuten sowie Kinder- und Jugendlichenpsychotherapeuten zur Abrechnung mit der kassenärztlichen Vereinigung Nordrhein [Stand: 01.07.2000]).

The results from the GHS-MHS survey show that the excess costs associated with anxiety disorders range from €500 to €1600 per case in 2004. In agoraphobia, panic disorder and specific phobias the indirect costs exceed the direct healthcare costs. However, it should be noted that only the cost of sick leave is included in the cost component for indirect costs and that functional disability of subjects outside the workforce (student, homemaker, retired and unemployed) was not included in the present analyses.

Discussion

There is little doubt that anxiety disorders rank as the most frequent mental disorders in Europe, with a 1-year prevalence of 12% of the EU adult population. There is also convergence in studies that anxiety disorders account for a substantial amount (at least 35%) of all disability and sick leave days due to mental disorders and that they are rarely treated and even less frequently specifically cared for. Thus, given the high prevalence, the high persistence and chronic nature and the increasing number of complications, anxiety disorders should be expected to have very high indirect costs and substantial burden of illness measures. In contrast, direct treatment costs should be low, due to poor recognition and rare treatment. Unfortunately the epidemiological database does not yet allow for describing this complex picture in sufficient detail. There are no data describing the type and degree of overutilization of general healthcare resources in anxiety patients. For example for social phobia with and without depression, there is no evidence of how and where and for most studies even how many cases receive adequate treatment. Beyond this and the fairly crude prevalence estimates there is a profound lack of data informing us about EU-specific regional variation. Further noteworthy limitations are that the epidemiological data situation in old age is largely deficient and in children is hampered by numerous problems regarding diagnostic assessment instruments. Other deficits include the lack of any prevalence data from eastern EU countries, the lack of detailed disability and service utilization data, and the lack of coordination in analyses and reporting.

With these many limitations in mind, the core outcome of the inquiry is primarily that we need more and better studies to allow for substantive cost analyses in the future. There is only a handful of cost-of-illness studies conducted in the area to date and they are all based on small selected patient populations. Nevertheless, the cost estimates seem to be in the same range as the figures provided by Greenberg *et al*. (1999), who estimated the overall cost per patient for anxiety disorders at $1542. However, in the areas of social phobia,

obsessive-compulsive disorder, agoraphobia and specific phobias there were no cost studies found. Moreover, the few cost studies identified in the field were all conducted in the late 1980s and the beginning of the 1990s, and hence the methodology applied in the studies stem from the same period. As a consequence of the rather weak cost data available in the literature, a basic cost-of-illness calculation was estimated based on one comprehensive study in order to provide somewhat consistent cost estimates across the different anxiety disorders at least for some domains.

However, it shall be kept in mind that these crude estimates are under-inclusive in terms of resource use. Consequently, it is expected that our current cost estimates of anxiety disorders in Europe are quite conservative. This is particular the case because one complex and severe type of anxiety disorders was not included at all, namely post-traumatic stress disorder. Besides better identification, quantification and the costing of resource utilization in anxiety disorders in Europe, the main challenge for the future lies in the improvement of access to the healthcare system both on the side of patients and on that of caregivers, e.g. through optimizing the detection rates of anxiety disorders. As a first step, data on pathways of individuals with anxiety disorders to mental health services are urgently needed to provide starting points for effective structural interventions.

Conclusion

Currently large gaps in the available epidemiological data base and in particular in the associated literature regarding the costs of anxiety disorders in Europe prohibit detailed and stable analyses. Very few studies reporting cost estimates were found in the European literature. Only two studies in total were found for GAD (one from France and one from Hungary) and only one Spanish study was found for panic disorder. No studies were found that covered other anxiety disorders. In order to be able to estimate the total cost of anxiety disorders in Europe, an own cost-of-illness analysis was conducted based on the German National Health Interview and Examination Survey, serving as the basis for the model estimations.

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ORIGINAL ARTICLE

Cost of brain tumour in Europe

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Introduction

Incidence and classification of brain tumours

Brain tumours are classified into primary and secondary tumours, where the former originate in the brain itself, and the latter are metastases originating in another part of the body. Secondary brain tumours are always malignant, while primary brain tumours occur in both benign and malignant forms. Intracranial tumours can be further subdivided into extracerebral and intracerebral tumours. Extracerebral tumors are mainly meningiomas. Intracerebral tumours can be intrinsic, arising from the matrix of the brain, called gliomas, or extrinsic of which the most common are metastasis or lymphoma.

Brain tumours represent about 1–2% of all newly diagnosed tumours, and account for about 2% of all cancer-related deaths (Swedish National Board of Health and Welfare, 2002; Wrensch *et al*., 2002). In Europe, the incidence of malignant primary brain tumours was 7.9/100 000 for men and 5.4/100 000 for women in 1995. The age-standardized incidence rate among European countries ranged from 3.5/100 000 person-years for women in Latvia to 14.3/100 000 person-years for men in Greece. The average age-standardized mortality rates were 5.9/100 000 for men and 3.9/100 000 for women (Bray *et al*., 2002).

Meningiomas

Meningiomas are more frequent in females and in elderly patients (Wrensch *et al*., 2002). They are responsible for 15% of intracranial tumours in men and 30% in women. At autopsy, 2.7% of males and 6.2% of females over the age of 80 have a meningioma. The incidence in the literature is between 1.6 and 5.5/100 000/year. Meningiomas can be treated by radical resection in most locations or by subradical resection at the skull base with additional radiosurgery. They are usually well controlled with long survival. Only 2% at maximum are anaplastic with survival of 2 years or less.

Gliomas

Gliomas are subdivided into astrocytomas, oligodendrogliomas, mixed tumours and ependymomas. Astrocytomes are again subdivided into pilocytic astrocytomas (WHO grade I), low-grade gliomas (grade II) and high-grade gliomas (grades III and IV). Oligodendrogliomas and mixed tumours are subdivided into differentiated tumours (grade II) and anaplastic tumours (grade III) and so are ependymomas.

Pilocytic astrocytomas mainly affect children and are common in the optic system, the brainstem and the cerebellum. When well circumscribed they can be radically excised but when they are diffusely infiltrative, they can only be temporarily controlled.

Low-grade or diffuse astrocytomas occur in the young adults and make up less than 10% of all gliomas. They are the first in a line of successive dedifferentiation to grade III and IV. They can be treated with surgery or interstitial radiation and control can be for up to 10 years. Usually progression occurs before 5 years.

Anaplastic gliomas develop later in life or after progression from low-grade tumours. They are treated by surgery, radiation and chemotherapy and have a median survival of 2.5 years. Astrocytoma grade IV is the most aggressive tumour and occurs mostly in older adults, frequently with a short history and without prior low-grade stages. They comprise 50% of the gliomas and have a life expectancy of about 10–12 months despite surgery, radiation and chemotherapy. They are seen in the whole central nervous system but mainly in the hemispheres.

Oligodendrogliomas are genetically distinct from astrocytomas and occur in younger (grade II) or older (grade III) adults and progression from grade II to grade III is the rule. They have a much better prognosis with resection and chemotherapy and also radiation. Even the anaplastic variants can be controlled for more than 10 years according to the latest studies.

Ependymomas

They occur more frequently in children, mostly in the infratentorial compartment but can grow throughout the ventricular system. They are subdivided into grade II and III with progression from II to III and are treated with resection, radiation and chemotherapy. They tend to recur and like all the other gliomas are eventually fatal.

Lymphomas

This kind of tumour can originate in the brain and is then called PCNSL (primary CNS lymphomas). Its

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incidence is rising because of more widespread immunosuppression due to transplantation and HIV infection (now 40/100 000/year in retrovirally treated HIV patients). Unrelated lymphomas are also increasing because of yet undefined causes (0.5/100.000/year in the USA). The disease is controlled by chemotherapy with or without radiation but eventually the disease recurs and patients survive in different protocols for about 4 years with much delayed neurotoxicity.

Metastases

Metastatic spread to the brain is a major complication of cancer and is 10 times more frequent in incidence than all other tumours. The major reason is the increasing efficacy of systemic therapies. Treatment is costly and combines surgery, radiosurgery, whole brain radiation or any combination. Survival is determined usually by the systemic disease and is most often in the range of 12 months but varies with different tumour entities.

Epidemiological data in brain tumours in Europe

There seems to be few reviews available that comprehensively describe the epidemiology of brain tumours in Europe (Westphal *et al*., 2005). However, the Unit of Descriptive Epidemiology of the International Agency for Research on Cancer (IARC), which is part of the World Health Organization (WHO), has set up an online database that presents estimates of the incidence, prevalence and mortality of 27 different cancer types for almost all countries in the world in 2002 (available at: http://www-dep.iarc.fr/), including malignant brain tumours (ICD-10: C70, C71, C72). All disease rates are not from the year 2002, but from the most recent data available from each country.

The incidence and mortality data in IARC's GLOBOCAN 2002 database have been taken from national or regional cancer registries in IARC membership countries. The epidemiological data that were not directly available were estimated by the epidemiology unit of IARC. Often the incidence data were estimated from the cancer mortality by using a model, e.g. in Central Europe (Hungary, Czech Republic, Poland, Slovakia). For northern Europe, the incidence rates were directly available from the national registers, or from NORDCAN, the Association of Nordic Cancer Registries. Among the Baltic countries the incidence rate was directly available for Estonia, but the incidence had to be estimated from the mortality for Latvia and Lithuania. Also for southern Europe the incidence data were often estimated from the cancer mortality by using a model (e.g. Greece, Italy, Portugal and Spain). In Western Europe, only the Netherlands had the incidence rate directly available, while the incidence rates in, for example, Germany, France, and Belgium were estimated from the mortality. Mortality rates were generally obtained from the WHO Mortality Databank, and incidence rates from EUROCIM, the European Network of Cancer Registries, or the publication *Cancer Incidence in Five Continents*. Most of the incidence and mortality data were from the period 1997–2001. The prevalence data in the GLOBOCAN 2002 database have generally been estimated indirectly by using data on incidence and mortality. More details on methodology and data can be found in the publications by Bray *et al*. (2002), Parkin *et al*. (1999) and Pisani *et al*. (2002), or on the GLOBOCAN 2002 homepage: http://www-depdb.iarc.fr/globocan/GLOBOframe.htm.

The prevalence in terms of cases of brain tumours was available from IARC, but not the prevalence rate per 100 000 person-years. Also, the 1-year prevalence data presented by IARC seemed rather low, and were judged not to be reliable, especially since they were much lower than the corresponding US data. The prevalence per 100 000 was therefore calculated by combining the national incidence data for each European country with US survival data for the period 1973–1999 (CBTRUS, 2002; Pisani *et al*., 2002 for methodology).

As regards the diagnoses included in the GLOBOCAN 2002 database, only ICD-10 codes C70–72 were included, i.e. malignant brain tumours, while benign brain tumours (D32, D33) and brain tumours of unknown origin (D42, D43) were not included.

Strengths and limitations of the available epidemiological data

A strength of the data from the GLOBOCAN 2002 database is that it covers incidence, prevalence and mortality in almost all European countries. A limitation is that it is difficult to estimate the epidemiological quality of the register data from individual countries. National and regional registers may be more or less complete in different countries based on how well the systems for reporting diagnoses work. Another limitation is that only malignant brain tumours are included in the database. In the USA, the incidence was 5.7/100 000 for benign tumours and 7.7/100 000 for malignant tumours (CBTRUS, 2002). If these figures are representative for European countries, benign brain tumours constitute 43% of all new cases, and the total incidence for each country in Tables 1 and 2 should be around 74% higher (5.7/7.7 = 0.74).

Table 1 Incidence and prevalence per 100 000 of malignant brain tumours in men

Country/region[a]	Incidence			Prevalence,[d] 1-year
	Cases	Crude rate[b]	ASR(W)[c]	
Austria	309	7.9	6.1	29.8
Belgium	544	10.8	8.2	40.7
Cyprus[e]	n/a	9.3	7.0	35.1
Czech Republic	347	7.0	5.3	26.4
Denmark	228	8.6	6.7	32.4
Estonia	46	7.3	6.2	27.5
Finland	187	7.4	5.7	27.9
France	2722	9.4	7.3	35.5
Germany	3345	8.4	6.2	31.7
Greece	836	16.0	10.5	60.4
Hungary	427	9.1	7.1	34.2
Iceland	12	8.5	6.7	32.0
Ireland	153	8.0	7.1	30.2
Italy	2414	8.7	6.2	32.8
Latvia	67	6.1	5.3	23.0
Lithuania	122	7.1	6.2	26.8
Luxembourg	23	10.5	8.1	39.6
Malta	15	7.7	6.7	29.0
Norway	225	10.1	8.1	38.1
Poland	1812	9.7	8.2	36.6
Portugal	422	8.8	6.7	33.2
Slovakia	202	7.7	6.8	29.0
Slovenia	68	7.1	5.4	26.8
Spain	1643	8.4	6.4	31.7
Sweden	335	7.7	6.2	29.0
Switzerland	314	8.9	6.6	33.6
The Netherlands	597	7.6	6.1	28.7
UK	2616	8.9	6.7	33.6

Source: http://www.iarc.fr

[a]European countries include the 25 EU member states and three EFTA members (Iceland, Norway, Switzerland).

[b]Crude rate: calculated by dividing the number of new cancers observed during a given time period by the corresponding number of people in the population at risk.

[c]ASR(W): an age-standardized rate (ASR) is a summary measure of a rate that a population would have if it had a standard age structure. Standardization is necessary when comparing several populations that differ with respect to age because of the strong age-dependence of the cancer risk. The most frequently used standard population is the World standard population (W). The calculated incidence rate is then called the World Standardized incidence.

[d]Estimated from national incidence data and US survival data for malignant brain tumours (CBTRUS, 2002), since survival data for each individual country were not available.

[e]The incidence rate for Cyprus was not available (n/a). The average incidence rate for Southern Europe was used as an estimate.

Table 2 Incidence and prevalence per 100 000 of malignant brain tumours in women

Country/region	Incidence			Prevalence, 1-year
	Cases	Crude rate	ASR(W)	
Austria	277	6.7	4.6	25.3
Belgium	437	8.4	5.5	31.7
Cyprus	n/a	7.4	5.1	27.9
Czech Republic	358	6.8	4.8	25.7
Denmark	204	7.6	5.4	28.7
Estonia	41	5.7	4.5	21.5
Finland	171	6.5	5.0	24.5
France	2049	6.7	4.8	25.3
Germany	2711	6.5	4.2	24.5
Greece	639	11.9	7.3	44.9
Hungary	373	7.2	4.8	27.2
Iceland	10	7.1	5.8	26.8
Ireland	113	5.8	4.4	21.9
Italy	1873	6.3	4.2	23.8
Latvia	64	5.0	4.1	18.9
Lithuania	114	5.9	4.5	22.3
Luxembourg	20	8.8	5.9	33.2
Malta	10	5.1	3.6	19.2
Norway	146	6.4	5.0	24.1
Poland	1546	7.8	5.9	29.4
Portugal	362	7.0	5.0	26.4
Slovakia	161	5.8	4.7	21.9
Slovenia	53	5.2	3.6	19.6
Spain	1529	7.5	5.0	28.3
Sweden	264	5.9	4.6	22.3
Switzerland	205	5.7	4.0	21.5
The Netherlands	381	4.7	3.7	17.7
UK	2033	6.7	4.8	25.3

Source: http://www.iarc.fr

See Table 1 for notes and definitions.

The difference between the total prevalence and the prevalence of malignant tumours is even larger. In the USA, the prevalence rate for all primary brain tumours was 130.8 per 100 000 (CBTRUS, 2002), while the prevalence for primary malignant tumours was 29.5, or only 23% of the total prevalence.

Leaving out benign tumours leads to serious underestimation of the total burden of illness. However, comprehensive statistics about benign tumours do not seem to be available at the European level.

Cost data on brain tumours in Europe

Only one comprehensive cost of illness study was available for brain tumours. Many cost studies were based either on small case series, or were part of a comparative clinical investigation of particular treatments with little relevance for the population of brain tumour patients as a whole. The Swedish study by Blomqvist *et al.* (2000) estimated both direct and indirect costs of brain tumours in Sweden in 1996 (Blomqvist *et al.*, 2000). They also came to the conclusion that studies on health care utilization and costs for brain tumours have only been performed for selected subgroups of patients, mainly in conjunction with new treatments. Many studies have been based on a single case series from a local hospital.

Blomqvist *et al.* (2000) used a prevalence and top-down approach, which means that as far as possible national annual data for a specific year (1996) were used

for the cost estimations (Blomqvist *et al*., 2000). They included direct costs for hospitalizations, long-term care, outpatient visits and pharmaceuticals, and indirect costs for sick leave, early retirement and premature mortality. The results showed that indirect costs represented 75% of the total cost. Costs for early mortality constituted a majority of these costs. Hospital care was the largest cost item of the direct costs. Taking the prevalence of brain tumours into account, the cost per patient amounted to €35 450 (in PPP-adjusted 2003 prices). Among tumour subtypes, astrocytomas III–IV accounted for 42% of the direct costs and meningiomas accounted for 30%.

In a British study, Latif *et al*. (1998) studied the direct hospital costs of treating patients with biopsy proven malignant glioma (glioblastoma and anaplastic astrocytoma) (Latif *et al*., 1998). The mean total costs were €26 052 (in PPP-adjusted 2003 prices) per patient, of which 56% represented radiotherapy, 15% neurosurgical bed days and 13% neurosurgery. No indirect costs or costs for community-based care were included in the study.

A Swiss study by Wellis *et al*. (2003) analyzed the direct costs of microsurgical treatment of brain tumours and other brain pathologies in 1998 and 1999 (Wellis *et al*., 2003). The treatment costs of 127 patients with arteriovenous malformation, acoustic neuroma, meningioma or brain metastasis were studied. The mean total direct cost per patient amounted to €12 562 (in PPP-adjusted 2004 prices) (Eurostat, 2004a, b; European Central Bank, 2004). Indirect costs were not included in the analysis.

Strengths and limitations of the available economic data

The most obvious limitation of the economic data is that there is so little of it. However, the only comprehensive cost study, i.e. the one by Blomqvist *et al*. (2000), is quite complete and seems to be methodologically sound.

Data for the estimation model of the total cost of brain disorders in Europe

The major problem of estimating the total cost of brain tumours in Europe is that there is so little evidence on the costs side. The study by Blomqvist *et al*. (2000) was primarily a prevalence study, even though the indirect costs for production losses due to premature mortality were calculated by a mix of an incidence and prevalence approach (Ekman, 2004). A problem with the epidemiological data is that the IARC database only covers primary malignant tumours, while the cost of illness study by Blomqvist includes both malignant and benign tumours. A possible way of adjusting the European prevalence data would be to multiply the rates with the US ratio between the prevalence for all primary tumours and the prevalence for malignant primary tumours, i.e. $130.8/29.5 = 4.43$. However, it is hard to know to what extent this ratio is valid for European countries.

Discussion

The International Agency for Research on Cancer (IARC) has compiled incidence and prevalence data for most malignant tumour types in most of the countries of the world. For Europe as a whole, the IARC seems to be the best available source for basic epidemiological data on brain tumours. However, the IARC data only concern primary malignant tumours, while benign primary and metastatic (secondary) tumours are left out. Brain metastases are the most common brain tumours, but it is questionable whether they qualify as a disease of the brain, since the origin is elsewhere in the body.

The prevalence per 100 000 was calculated by combining the national incidence data for each European country with US survival data. If survival for brain tumour patients in the USA differs from that for European patients this will of course lead to some error, but for most countries the approximation is probably quite good.

Only one comprehensive cost study was available for brain tumours. Although other cost studies were available, they did not include all relevant diagnoses and cost items needed for assessing the total cost of illness. However, brain cancer is the most common cause of cancer mortality among those under 35 years of age, which makes the costs for premature mortality high. Since so few studies on the cost of brain cancer in Europe are available, further research in this area is much needed. Since the indirect costs are by far the largest, the potential gains of more effective treatments may be substantial even if the treatment costs as such would increase as a result of the introduction of new treatments.

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ORIGINAL ARTICLE

Cost of dementia in Europe

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Definition and diagnosis

According to the *Diagnostic and Statistical Manual of Mental Disorders*, revised 3rd edn (DSM-III-R) (American Psychiatric Association, 1987), the criteria for dementia include demonstrable evidence of impairment in memory and either (a) impairment in one other intellectual function (abstract thinking, judgment or higher cortical functions) or (b) a personality change. These disturbances must be sufficient to interfere with work, usual social activities or relationships with others. Compared with DSM-III-R, ICD-10 criteria for dementia appear to be more restrictive, requiring a decline in memory and other cognitive abilities sufficient to impair normal everyday personal activities. Another popular definition proposes that 'dementia is the decline of memory and other cognitive functions in comparison with the patient's previous level of function as determined by a history of decline in performance and by abnormalities noted from clinical examination and neuropsychological tests' (Mckhann *et al*., 1984).

In 2004, for ongoing studies the DSMIV criteria are used but, for dementia, there are only a few differences from the DSM III or the DSMIII-R.

Prevalence data

Criteria for inclusion of prevalence results in this work were (1) indication of prevalence rate for dementia with raw data on number of cases and sample size (global, age and/or sex-specific); (2) publication in English, German or French; (3) field work on a representative general population of a European country (Medline research for Austria, Belgium, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, The Netherlands, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden, United Kingdom); and (4) assessment of dementia referring to a validated classification system. When more than one large epidemiological study was published in one country, we restricted our choice to the most recent one, generally using the most recently revised criteria (e.g. DSM III-R instead of DSMIII) and to population-based studies. Crude prevalence rates for dementia after 65 years of age in Europe varied between 5.9 and 9.4/100/year with a strong increase by age and a predominance in women (for a separate report on epidemiology of dementia see Berr, 2005). As dementia is leading to impairment of physical functions and ultimately to complete dependency, care requirements and cost for formal and informal care are substantial.

For several countries, cost-of-illness studies have been carried out producing data on costs of care in relation to dementia severity. We have age-specific prevalence in most studies but very few data on severity. In order to integrate the difference in cost according to severity, we need to consider the link between disease severity and age. As this relationship is determined by the natural course of the disease and not, at least not to a large extent, influenced by the health care system, we expect no large variations between countries.

Cost data

Cost-of-illness studies in dementia have been undertaken in several countries based on data collected from individual patients and caregivers (bottom-up methodology) (Souetre *et al*., 1995; Kronborg Andersen, 1999; O'Shea and O'Reilly, 2000; Scuvee-Moreau *et al*., 2002; Jönsson, 2005). Most have been retrospective with respect to resource utilization data collection (Souetre *et al*., 1995; Kronborg Andersen, 1999; O'Shea and O'Reilly, 2000) while a few have followed patients prospectively (Scuvee-Moreau *et al*., 2002; Jönsson, 2005). The range of resource items included in cost calculations has varied between studies, which limits comparability. All studies have considered formal care costs (medical care, community care) while only a subset of studies have included costs of informal care. Informal care costs are difficult to assess as there are methodological problems associated with the measurement as well as the valuation of informal care activities; these issues have been reviewed elsewhere (McDaid, 2001). The resulting cost estimates vary considerably depending on the chosen methodology.

Costing studies based on primary data from a sample of patients have the potential risk of selection bias; typically there is an under-sampling of patients in the most severe disease stages. This problem can be reduced by dividing patients into strata and estimating average

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costs of care within each stratum. The most commonly applied stratification is to divide patients into categories by the degree of dementia severity (Jönsson, 2003). This can be done according to, for example, the Clinical Dementia Rating (CDR) scale, or a simple instrument such as the Mini Mental State Examination (MMSE). Again, comparability between studies is limited by the use of different severity scales and different cut-off levels for dividing patients into strata. A universal finding, however, is that the cost of care is highly dependent on the stage of dementia, assessed by cognitive and/or physical functioning.

Institutionalization represents an important milestone in the clinical history of dementia. It usually marks a dramatic change in resource utilization, with a shift from informal to formal care and normally a considerable increase in care costs. Some cost-of-illness studies have only included community-living patients, which explains some of the differences in cost estimates.

Results

Table 1 below shows the final cost estimates, presented in Euros (2004). Cost estimates range from about €6000 to about €19 000 annually, with most estimates in the range of €9000–16 000/year. Table 2 presents the prevalence per 100 in countries with available data.

Discussion

Including all resource utilization for demented elderly in cost-of-illness estimates may lead to over-estimation of the costs for dementia, as it does not take into account the fact that also non-demented elderly have a certain level of resource use. It is not possible to directly observe the costs due to dementia, as it is only the total resource use in demented subjects that can be measured. Any estimate of the 'net' cost of dementia will be a theoretical construct. We have therefore chosen to present total care costs for demented subjects.

Table 1 Annual cost of care for patients with dementia (€PPP 2004)[g]

	Belgium[a]	Denmark[b]	Finland[c]	France[d]	Germany[e]	Ireland[f]	Norway[c]	Sweden[c]
Hospitalization	2460	3113	4342	894	738	755	1096	944
Drugs	1055		887	451	423		834	1007
Outpatient care	907	173	659	696	627		388	501
Total medical care*	4705	3286	5888	2042	1788	755	2318	2451
Devices and procedures	283		0		152		0	0
Social services	9402	7258	6625	1736	10 795	4212	11 444	4522
Adaptations	31	66		73	0			
Transportation			13		0		105	125
Informal care	1297		6932	2130	0	4889	2549	4222
Total non-medical care*	10 730	7324	13 570	3940	10 795	9101	14 098	8870
Total cost*	15 435	10 610	19 458	5981	12 583	9856	16 415	11 321

[a]Scuvee-Moreau *et al.* (2002); [b]Kronborg Andersen *et al.* (1999); [c]Jönsson (2005); [d]Souetre *et al.* (1995); [e]Schulenberg *et al.* (1998); [f]O'Shea and O'Reilly (2000); [g]The cost data were inflated to 2004 with inflation and converted to Euro adjusted for purchasing power (European Central Bank, 2004; Eurostat, 2004a, b).

*Sums of cost items.

Table 2 Prevalence (per 100, with 95% confidence interval) in selected European studies, by age

Country	65–74	75–84	≥ 85
Belgium (Kurz *et al.*, 2001)[a]	4.4 [3.2–5.9]	11.1 [9.1–13]	11.5 [9.1–14]
Denmark (Andersen *et al.*, 1997)[b]	4.7 [3.8–5.6]	11.4 [9.7–13]	–
Finland (Rahkonen *et al.*, 2003)	–	18.3 [15–22]	39.4 [31–48]
France (Letenneur *et al.*, 1993)[a]	2.9 [2.1–3.8]	7.1 [5.6–8.5]	21.6 [18–25]
Germany (Riedel-Heller *et al.*, 2001)[b]	–	9.4 [7.7–11]	34.8 [30–40]
Italy (Ravaglia *et al.*, 2002)[a]	1.2 [0.6–2.5]	4.5 [2.7–7.3]	32.2 [24–41]
Netherlands (Ott *et al.*, 1995)[a]	1.4 [1–1.9]	10.9 [9.4–12]	34.8 [31–38]
Spain (Lobo *et al.*, 1992)[a]	3.2 [1.8–4.7]	8.3 [5.9–11]	20 [12–28]
Spain (Manubens *et al.*, 1995)	–	13.9 [11–17]	27.1 [23–32]
Sweden (Von Strauss *et al.*, 1999)[b]	–	13.5 [11–16]	33.4 [30–37]
UK (Saunders *et al.*, 1993)[a]	1.4 [1.0–2.0]	6.4 [5.4–7.6]	19.9 [18–22]
European average	2.1	6.9	

[a]Data used in the model.

[b]Studies based on subpopulations, not used on the model.

Non-demented controls have been included in some studies allowing estimation of the additional costs due to dementia by comparing demented patients with controls. Studies that have included non-demented controls have found that these subjects have much lower resource use compared with demented patients, even when comparing with patients with mild dementia.

Disease estimation and cost estimation is focused on mild to severe dementia. Few data exist on the costs of very mild dementia, which is very difficult to distinguish from mild cognitive impairment. In the few studies presenting costs data for very mild dementia, costs are very low compared with mild dementia, and in the same magnitude as age-matched controls. Also, few studies have explicitly studied costs in very severe or terminal dementia and the number of such patients included in cost-of-illness studies is usually small.

No studies have been found that specifically look at the cost of care for patients with other underlying causes of dementia than Alzheimer's disease (AD); the included studies have either included only patients with AD or they have included patients with any-cause dementia without differentiating between different subtypes. It can be expected that patients with vascular dementia, the second-most common type, would have somewhat higher costs for cardiovascular comorbidity than AD patients. Patients with Parkinson's dementia and Lewy-body dementia could be expected to vary in dependency and resource use depending on the degree of motor impairment, however, no data have been presented to our knowledge.

Topics for further research include:

1 estimating prevalence stratified not only on age and gender but also on disease severity, to allow better linking of epidemiological data and cost-of-illness data;
2 establishing appropriate methods for measuring and valuing informal care;
3 conducting cost-of-illness studies in areas where data are currently not available, e.g. southern and eastern Europe.

Conclusions

There is consistent evidence that costs of care for patients with dementia are very high across European countries. Equally consistent is the finding that costs of care increase with the successive loss of cognitive and physical function in progressing dementia. Estimates of costs of care vary between countries depending on differences in the structure of dementia care as well as differences in methodology between studies.

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ORIGINAL ARTICLE

Cost of epilepsy in Europe

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Introduction

Epilepsy is a symptom-complex characterized by repeated unprovoked seizures (Commission on Epidemiology and Prognosis, International League Against Epilepsy, 1993). An unprovoked seizure is a seizure occurring in the absence of precipitating factors. By contrast, a provoked (acute symptomatic) seizure is a seizure occurring in close temporal relationship with an acute systemic, toxic or metabolic insult, which is expected to be the underlying cause. Unprovoked seizures include events occurring in the absence of a recognized etiological or risk factor (idiopathic and cryptogenic seizures) and events occurring in patients with antecedent stable (non-progressing) central nervous system (CNS) insults (remote symptomatic seizures). The worldwide annual incidence of epilepsy ranges from 24–53/100 000 and the incidence of single seizures is 33–44/100 000 (Hauser, 1997). In the USA, the incidence of acute symptomatic seizures is 40/100 000 (Annegers *et al*., 1995). Epilepsy is a fairly common clinical condition affecting all ages and with a fairly similar distribution across Europe. The prevalence of the disease is slightly higher in males than in females, although most studies show shifting rates between sexes in different age groups (Forsgren *et al*., 2005). As with prevalence, the incidence of epilepsy is slightly higher in males than in females, although similar rates between genders or a female predominance have been occasionally found. The prevalence of epilepsy is slightly different in children and adolescents (4.5–5/1000), adults (6/1000), and in the elderly (7/1000). By contrast, the mean annual incidence of the disease tends to vary significantly according to age, being about 70/100 000 in children and adolescents, 30/100 000 in adults, and 100/100 000 in the elderly.

In population-based incidence studies, the etiology of epilepsy can be documented in about one-third to one-half of the cases, the commonest causes being cerebrovascular disorders (14–21%), head trauma (2–16%), tumours (6–10%), developmental disorders (4–7%), degenerative disorders (1–5%) and infections (0–2%) (Forsgren *et al*., 2005). Modest differences can be found in the etiology of epilepsy between Europe and developing countries, which may reflect a different distribution of environmental factors and different genetic backgrounds (Beghi, 2004).

Epilepsy is a treatable clinical condition. About 50% of cases achieve seizure remission soon after onset of treatment; seizures can be controlled after one or more treatment changes in about 25–35% of cases, leaving 15–25% of patients with drug-resistant epilepsy (Jallon, 2003). Seizure control may be obtained in a variable proportion of these cases by surgical resection of the epileptogenic lesion.

The disease severity varies considerably from patient to patient, but the societal costs for epilepsy are high, mainly due to severe epilepsy in a substantial part of the epilepsy population. This makes it important to assess the costs for patients with epilepsy, not least since several new antiepileptic drugs have been introduced in recent years.

Availability of European prevalence and incidence data for epilepsy

Population-based epidemiological studies on epilepsy are available mainly from the UK and the Nordic, Baltic and western Mediterranean countries. In a recent review on the epidemiology of epilepsy in Europe no studies were identified from large areas of Europe, especially from Eastern Europe (except the Baltic countries) and the eastern Mediterranean countries (Forsgren *et al*., 2005).

Most descriptive epidemiological studies of epilepsy are prevalence studies. Twenty of the 33 studies presented in Table 1 only provide prevalence rates for active epilepsy. Among the remaining studies 10 provide data only on incidence rates and three studies present data for both prevalence and incidence. Thus, prevalence rates are available from 23 studies altogether, and incidence rates from 13 studies.

All ages in the study population have been included in 12 studies (seven prevalence studies, four incidence studies and one combined prevalence and incidence study) and an additional study included all above age 10 years. In these studies, the size of the population differs widely and the numerator part of the rates of active epilepsy varies from 33 to 428 cases. The corresponding numbers in the incidence studies are similar and vary from 31 to 494 cases.

Studies limited to specific ages are mostly focused on children. In 14 studies on children the rates in the 10

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Table 1 Prevalence of active epilepsy (per 1000), and annual incidence (per 100 000), in Europe

Author (year)	Country	Prevalence	Incidence	Age	No. of cases
Zielinski (1974)	Poland	7.8	–	All ages	33
Granieri *et al.* (1983)	Italy	6.2	–	All ages	278
Maremmani *et al.* (1991)	Italy	5.1	–	All ages	51
Beghi *et al.* (1991)	Italy	3.9	–	All ages	199
Giuliani *et al.* (1992)	Italy	5.2	–	All ages	235
Rocca *et al.* (2001)	Italy	3.3	–	All ages	81
Joensen (1986)	Faroes, Denmark	7.6	43	All ages	333/118
Olafsson and Hauser (1999, 1996)	Iceland	4.8	47	All ages	428/42
Loiseau *et al.* (1990)[a]	France	–	44	All ages	/494
Jallon *et al.* (1997)[a]	Switzerland[b]	–	46	All ages	/176
MacDonald *et al.* (2000)	UK[c]	–	46	All ages	/31
Keranen *et al.* (1989)	Finland	6.3	24	Adults > 15 years	1233/230
Forsgren (1992), Forsgren *et al.* (1996)[a]	Sweden	5.5	56	Adults > 16 years	713/160
Õun *et al.* (2003a, b)	Estonia	5.3	35	Adults > 19 years	396/81
de la Court *et al.* (1996)	Netherlands	7.7	–	Adults 55–94 years	43
Luengo *et al.* (2001)	Spain	4.1	–	Children > 10 and adults	405
Brorson (1970), Brorson and Wranne (1987)	Sweden	3.5	50	Children 0–19 years	195/68
Sidenvall *et al.* (1996, 1993)[a]	Sweden	4.2	73	Children 0–16 years	155/61
Blom *et al.* (1978)	Sweden	–	82	Children 0–15 years	/43
Waaler *et al.* (2000)	Norway	5.1	–	Children 6–12 years	198
Sillanpaa (1973)	Finland	3.2	25	Children 0–15 years	348/397
Eriksson and Koivikko (1997)	Finland	3.9	–	Children 0–15 years	329
Endziniene *et al.* (1997)	Lithuania	4.3	–	Children 0–15 years	378
Beilmann *et al.* (1999b)	Estonia	3.6	45	Children 0–19 years	560/216
Cavazzuti (1980)	Italy	4.5	–	Children 5–14 years	178
Sangrador and Luaces (1991)	Spain	3.7	–	Children 6–14 years	62
Tidman *et al.* (2003)	England	4.3	–	Children 4–10 years	69

[a]Single seizures included.
[b]Rate calculated only on unprovoked seizures.
[c]Incidence 57 with single seizures included.

prevalence studies are based on 62–560 cases, and on 43–397 cases in the incidence studies. Most studies included children between ages 1 month up to 15–19 years. Four prevalence studies were focused on school children.

Studies confined to adults include all adult age groups (two prevalence, two incidence and one combined prevalence and incidence study) or only the elderly (one prevalence study). The number of cases in the prevalence studies including all adult ages is large, 396–1233 cases. In the incidence studies, rates were based on 81–230 cases.

Many of the studies in Table 1 provide rates by age, gender and seizure type. Characterization of epilepsy populations by seizure frequency and comorbidities is missing from almost all studies.

Strengths and weaknesses of the epidemiological studies and suggestions for future research

Based on the available epidemiological studies, the incidence and the prevalence of epilepsy in Europe are fairly similar, the differences being mostly interpreted as a reflection of the age structure of the target population, the inclusion criteria, the different sample size and the intensity of case ascertainment. One may thus assume that similar incidence and prevalence rates are expected in European countries where such rates are as yet unavailable. The epidemiological features of the disease that may be of interest for the purposes of disease management and costs are patient's age, putative etiology and extent of seizure control. In this context, the syndromic classification of the epilepsies and the expected response to the available treatments are the variables to be considered. However, data on the incidence and prognosis of the main epileptic syndromes in most European countries are virtually non-existent.

With reference to population-based data, a model has been developed by Begley *et al.* (1999) to define the clinical course and outcome of epilepsy in a well-defined population. In this model, 67.4% of patients achieve permanent remission (18.0% as patients < 15 years vs. 49.4% as patients 15+ years), 9.5% tend to relapse after treatment withdrawal (1.9% vs. 7.6%), 7.8% present delayed remission (1.7% vs. 6.1%), 6.6% have rare seizures (1.3% vs. 5.3%), 8.7% have frequent seizures (1.1% vs. 7.6%), and 0.1% are institutionalized (0.1% vs. 0.0%). These prognostic categories, which

Table 2 Summary of selected cost-of-illness studies of epilepsy

Source	Country	Cost categories	Population size; [P]revalence/[I]ncidence	Cost per patient in PPP adjusted EUR (2004)[a]
Studies to be included in the model:				
Van Hout *et al.* (1997)	France, Germany, and the UK	Direct medical and non-medical costs; indirect costs	300 adults (18–65) [P]	Seizure free:€674, Daily seizures:€1876 (based on 3-month costs)
Tetto *et al.* (2002)	Italy	Direct medical costs	525, all ages [P]	SR:€412, OS:€578, NDR:€1626, DR:€2198, SC: €4085 (1 year)[b]
Persson *et al.* (2003)	Sweden	Pharmaceutical costs	~60000, all ages [P]	€463 per year
Cockerell *et al.* (1994)	UK	Direct medical and non-medical costs; indirect costs	1628, all ages [P]	Medical:€691, Non-medical:€1772, Indirect: €5760, Total:€8224
Some additional studies:				
De Zélicourt *et al.* (2000)	France	Direct medical costs	1942, all ages [I]	€2973 for 1st year, €783 for 2nd year
Beghi *et al.* (2004)	Italy	Direct medical costs	641 randomly selected patients > 18 years of age [P]	SR:€519, OS:€768, ND:€903 NDR:€1386, DR: €2027, SC:€3349, Tot:€1205 (1 year)[b]
Berto *et al.* (2000)	Italy	Direct medical and indirect costs	3236, all ages [P]	€1293 for 1 years, children €1,722, adults €1,120
Guerrini *et al.* (2001)	Italy	Direct medical costs	189 children, adolescents, and young adults [P]	€1635 per year
Kotsopoulos *et al.* (2003)	Netherlands	Direct and indirect costs	116 adults from three clinical settings [P]	GP:€686, UH:€3,732, EC:€4721 (per year)[c]
Jacoby *et al.* (1998)	UK	Direct medical costs	785, all ages [P]	€281 inactive,€2042 active (€1434 < 1 seizure/month, 2650 ≥ 1 seizure/month)
Cockerell *et al.* (1994)	UK	Direct medical and non-medical costs; indirect costs	602, all ages [I]	From €1194 the 1st year to €330 the 8th year

[a]Prices were inflated to 2004 with consumer price index (Eurostat, 2004b), and converted to Euros with adjustment for purchasing power (European Central Bank, 2004; Eurostat, 2004a).
[b]SR, seizure remission; OS, occasional seizures; ND, newly diagnosed; NDR, frequent seizures, non-drug resistant; DR, frequent seizures, drug resistant; SC, surgical candidates.
[c]GP, general practices; UH, university hospital; EC, epilepsy centre (cost per month transformed into cost per year).

might be used in cost studies from European countries where optimal drug treatment is available, may not be applicable in countries with suboptimal management of epilepsy. Prospective studies on the outcome of epilepsy with reference to the response to treatment are thus awaited in these countries. Studies on the prognosis of epilepsy by age and etiology in well-defined European populations are also awaited.

Availability of European cost data for epilepsy

Data on the cost of illness of epilepsy in Europe was available from five countries in Western Europe. However, as was established in a recent literature review on cost studies in epilepsy, there are no cost studies conducted in central and Eastern Europe (Ekman and Forsgren, 2004). Incidence-based cost studies were available from France and the UK, and prevalence-based studies were available from France, Germany, Italy, The Netherlands, Sweden and the UK. For most European countries no cost studies were available. In terms of methodology, most studies were bottom-up (i.e. based on patient records and questionnaires), prevalence-based, and longitudinal with 1- or 2-year follow-up (Hodgson and Meiners, 1982). Some previous reviews of cost-of-illness studies are also available, e.g. Begley *et al.* (1999), Kotsopoulos *et al.* (2001) and Begley and Beghi (2002).

In Table 2, the total annual costs per patient are displayed for a selected sample of European countries. The studies that were chosen as input in the model for estimating the cost of brain disorders in Europe are listed first, followed by some additional studies.

Strengths and weaknesses of cost data and suggestions for future research

Many studies have a bottom-up design, which makes it possible to get a fairly detailed view of the resource consumption of epilepsy patients. An additional strength is that the studies are generally well described, which makes it possible to explain differences in costs based on factors such as the seizure frequency, temporal stage of disease and healthcare setting. However, many bottom-up studies are limited to patient recruitment from one single or a few hospitals. This makes it questionable whether it is possible to generalize the findings to a national level. Another weakness is that it is often difficult to distinguish the epilepsy-specific costs from costs for comorbidities, i.e. the data may tend to show the average costs of patients with epilepsy rather than the epilepsy-specific costs.

Several incidence studies only cover the first-year costs, which are generally higher than the costs for subsequent years. A more thorough incidence estimate of the costs would require a few years of follow-up. For example, the incidence studies by De Zelicourt *et al*. (2000) and Cockerell *et al*. (1994) showed that the costs are the largest during the first year after the onset of epilepsy and tend to decrease substantially the second year.

A further problem is that not all studies include costs for production losses (indirect costs). Since epilepsy is a condition that affects all age groups including people of working age, the indirect costs are substantial. Finally, cost data from many parts of Europe, in particular east and southeast Europe, are lacking. More cost-of-illness studies on epilepsy are clearly needed, especially in east European countries.

Choice of studies to include in the model

Since epidemiological data were not available for all 28 EU and EFTA-3 (Switzerland, Norway, Iceland) countries, some assumptions have to be made concerning the prevalence of epilepsy in countries where no data were available. For this purpose the average prevalence rates were used, i.e. 4.5 for children and adolescents and 6.0 for adults. As mentioned earlier, similar prevalence rates would be expected in European countries where data are as yet unavailable. The cost studies that were included into the model were chosen based primarily on how complete, representative and recent they were. Only prevalence-based studies were included, since this seems to be the most suitable perspective for the cost estimation model.

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ORIGINAL ARTICLE

Cost of migraine and other headaches in Europe

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Introduction

With better but more expensive treatment options becoming available during the last 10–15 years, migraine and other headache disorders have become the subject of considerable interest from the health economic and public health perspective. In a WHO report from 2000 grading the severity of different disorders, a patient with a severe migraine attack was considered to be as disabled as one with active psychosis, dementia or tetraplegia. With regard to the number of years lived with disability (YLDs) caused by various disorders worldwide, migraine came out as number 19 (number 9 among women) (Mathers *et al*., 2002).

Migraine is a relatively severe form of headache occurring in attacks usually lasting between 4 hours and 3 days, and with disabling accompanying phenomena such as nausea or vomiting, severe intolerance to light, sound, odours and body movement. Tension-type headache (TTH) is usually less disabling than migraine, and with few accompanying phenomena. This headache type was not considered in the WHO report cited above, but because it is by far the most prevalent headache type, and also has a tendency to become chronic in a substantial proportion of patients, the individual and societal consequences of TTH may be as significant as those of migraine. Other relatively rare forms, like cluster headache, may be even more disabling than migraine during attacks.

Irrespective of the diagnosis, the consequence for most headache sufferers is that normal function is interrupted by headache episodes at irregular and unpredictable intervals, and this may impose severe limitations on their daily lives, at school, at work and during leisure time. This, and the fact that these disorders seem to be extremely prevalent all over the world, make them important from an economic perspective. The fact that headache predominates in women and that headache sufferers have a normal life expectancy may explain why headache patients have received less attention and resources than they deserve. The present overview is an attempt to calculate the costs of headache disorders in Europe based on health economic and epidemiological studies.

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Methodology

The search for relevant epidemiological studies has been described previously in a review of headache epidemiological studies in Europe (Stovner *et al*., 2005). Epidemiological studies on headache and migraine are available for many countries in Western Europe, but there are very few studies for Eastern Europe and on TTH. Only population-based studies with epidemiological data on headache in general, migraine and TTH were included in the overview. Virtually no studies had data on headache incidence, and almost all studies presented prevalence rates (3-months, 1-year or lifetime prevalence). Most studies used 1-year prevalence rates, a parameter that indicates the proportion of the population with an active disease, which is most relevant for calculating economic consequences. With regard to migraine and TTH, only studies appearing after the advent of the diagnostic criteria published in 1988 by the International Headache Society (IHS) were considered. The data extracted from these studies were overall prevalence and the distribution among the sexes and different age groups, and, whenever available, data on the prevalence of 'chronic headache' (defined as headache occurring more than 15 days per month, or 'daily'), frequency of headache (number of days per month or year) and absenteeism from work.

The review methodology and results of relevant health economic studies have also been described in detail previously (Berg, 2004). Based on the literature search for studies containing cost data for migraine and other headaches, 11 European studies evaluating the direct or indirect costs of migraine were identified. Three of these studies were excluded from the review, since they did not use a societal perspective. No studies analysing the cost of TTH or other non-migraineous headaches were found. In summary, cost estimates for migraine were available for France (Michel *et al*., 1993, 1999), Germany (Neubauer and Ujlaky, 2002), the Netherlands (van Roijen *et al*., 1995), Spain (Lainez, 2003), Sweden (Björk and Roos, 1991) and the UK (Blau and Drummond, 1991; Cull *et al*., 1992).

Overall, most studies were conducted before 1995, meaning that the impact of the triptan class on both direct and indirect costs is not captured in these studies. While these drugs are likely to have increased the direct medical costs, this could be offset by savings in terms of improved productivity. However, no population-based

cost-of-illness studies have been conducted to date that assess potential changes in the cost distribution resulting from new treatment patterns.

All identified cost estimates were prevalence-based, but were otherwise derived through a mixture of methodologies. Direct costs were mostly calculated using a top-down approach, while indirect costs were mainly derived through a bottom-up method. In the case of migraine, outpatient visits and pharmacological treatment tend to account for the majority of direct medical costs. The population-based studies analysing indirect costs generally used retrospective questionnaires to estimate the impact of migraine on work absence and productivity. No studies were identified that stratified costs by age or disease severity. Cost data were inflated to the year 2004 with consumer price index, and converted to Euros adjusted for purchasing power (Eurostat, 2004a, b; European Central Bank, 2004).

Results

Considering the epidemiological data, large variations in the prevalence of both headache and migraine were found among different European countries (Table 1). Both headache and migraine were most prevalent in the age groups from 20 to 50 years in both sexes, and there was a clear female preponderance in all age groups except among children. By selecting articles that covered age groups from at least 25–60 years, we found the average 1-year prevalence of headache to be 51% (61% women and 44% men), of migraine 14% (17% in women and 8% in men), and of 'chronic headache' 4% (6% in women and 2% in men). As there was only one study giving the 1-year prevalence of TTH in adults, no average could be calculated for this headache type. Data on headache frequency were difficult to compare between studies, but it seems that both migraine and TTH patients have headache 30 days per year on average. Relatively recent and population-based studies indicate that 14–15% of the adult population were absent from work due to headache in Denmark (Rasmussen *et al*., 1992) and England (Boardman *et al*., 2003), and the number of days missed from work ranged from around 1100 to 1300 days per 1000 employed persons per year in these studies. The number of days with reduced efficacy at work was estimated to be four times higher (Boardman *et al*., 2003) and thus result in an even greater loss of work time than the days missed.

If one considers the studies that deal specifically with the economic consequences of headache, it is found that annual cost estimates for migraine vary substantially across the six European countries where data were available, ranging from around €100 per patient in Sweden to nearly €900 in Germany (Table 2). The major reasons for these variations lie in different methodologies and years of reference. The vast majority of total costs, between 72% and 98%, are due to lost productivity, in the form of either work absence or reduced efficiency levels when working with migraine. The impact of migraine on patients' work performance is substantial, with an average of 2.5 workdays per year lost due to work absence, and an average efficiency level of 65% when working with migraine leading to the loss of further 4.1 days per patient. Stratifying costs by gender, women tend to lose more work days than men, but indirect costs are similar due to lower salaries and labour force participation amongst women.

Discussion

The main shortcomings of the epidemiological data are that there is a lack of studies in large parts of Europe (particularly the Eastern part) and that very little data exist on TTH, which is the most frequent headache

Table 1 One-year prevalence (%) of headache and migraine in adults from different European studies

				Headache			Migraine		
Country	Year	Respondents (n)	Age range (years)	Male	Female	Overall	Male	Female	Overall
Austria	2003	997	≥ 15	43.6	54.6	49.4	6.1	13.8	10.2
Croatia	2001	3794	15–65				13	20.2	16.7
Denmark	1991	740	25–64				6	15	10
Finland	1981	200	> 15	69	83	77			
Greece	1996	3501	15–75	19.0	40.0	29			
Hungary	2000	813	15–80				2.7	6.9	9.6
Italy	1988	1154	> 7	35.3	46.2	46			
Netherlands	1999	6491	20–65				7.5	25	23.2
Norway	2000	51 383	≥ 20	29.1	46.8		7.4	16.1	12.0
Sweden	2000	728	40–74					18	
Sweden	2001	1668	18–74	50	76	63	9.5	16.7	13.2
UK	1975	1718	> 21	63.5	78.4				
UK	2003	4007	16–65				7.6	18.3	14.3

Table 2 Total, direct and indirect cost of migraine per patient and year for six European countries, scaled to 2004 prices (€PPP)[a]

Country	Total cost	Direct medical costs	Indirect costs	Short-term absence from work	Reduced productivity at work
France[b]	405	66	n/a	338	n/a
Germany	879	29	850	493	358
The Netherlands	340	68	273	133	140
Spain[c]	532	33	499	n/a	n/a
Sweden	111	31	80	29	51
UK	543	12	520	156	375
Values used for European estimation[d]:					
France	698	66	632	338	293
Germany	538	29	509	295	214
UK	532	12	520	156	375
Average[e]	590	36	554	263	294

[a]Costs were inflated with consumer price index, and converted to Euros adjusted for purchasing power (Eurostat, 2004a, b; European Central Bank, 2004).
[b]Total estimate for France does not include costs of reduced productivity at work.
[c]Cost estimate for Spain refers to working population.
[d]Using average wage for German indirect costs and average between UK and adjusted German estimates for reduced productivity at work in France.
[e]Average is used for overall European cost calculations.

type. The latter is in part compensated for by the good data on headache in general, as it can reasonably be assumed that the difference between the prevalence of headache and migraine to a large degree (≥ 80%) consists of TTH patients.

Analyzing the variations in headache prevalence between different studies and countries, it seems that much, if not all, of this variation may be due to differences in methodology. Important methodological factors seem to be the age and sex composition of the population, the type of period prevalence (1-year vs. life-time prevalence), and the way IHS criteria are implemented in the study. The exact phrasing of the screening question is very important, as prevalence rates of headache in general were much higher in studies using a neutral question ('have you had headache?') than in studies with a question referring to headache degree or frequency ('have you suffered from headache?', 'have you had more than three headaches during the last…?', etc.). Since it is not possible to correct for these methodological differences in a systematic way, one cannot with any certainty conclude that there are real variations in headache prevalence across the continent. Hence, for calculating the costs of headache based on purely epidemiological data for any particular country, it is probably most correct to use the summary data on prevalence given in the Results section.

A main weakness of the cost data available in Europe and the USA is that they only refer to migraine. To our knowledge, no study has assessed the costs of TTH or other non-migraineous headaches to date. This constitutes a major gap in current research, since TTH affects a much larger proportion of the population than migraine, and thus a major component of headache costs cannot be accurately accounted for. Furthermore, the cost-of-illness studies for migraine identified during this review were mainly based on data gathered up to 1995, meaning that most cost estimates do not capture recent changes in patient management strategies, including the use of triptan drugs. Overall, it is likely that the available cost data for migraine in Europe is an underestimation of actual costs. On the one hand, the top-down approach generally used for direct costs carries the risk of underestimating or leaving out relevant cost items, while indirect costs are highly sensitive to the calculation method used, which varies across studies. Thus, the conservative estimates taken from relevant studies constitute a minimum cost threshold. Finally, most cost studies have not included children and adolescents in their evaluations, meaning that costs incurred by this patient segment are not accounted for.

Given the limited availability of up-to-date and comprehensive cost-of-illness studies for most European countries, any estimate of the total burden of migraine and other headaches in Europe should be interpreted as a best guess, based on available evidence and reasonable assumptions. While the absolute and relative price differences between countries can be adjusted for, the way in which healthcare is funded and provided is more difficult to factor in. The most straightforward way to extrapolate from existing data is to use an average of the most representative cost estimates as a basis. For migraine, the relevant cost estimates are for the UK, Germany (adjusted by using wage rates instead of gross domestic income for indirect costs) and France (adjusted by using the average between UK and adjusted German costs for reduced productivity at work). The Dutch study is not included due to its use of the friction cost method. Thus, an average annual cost of €590 per migraine patient can be assumed for these Western European countries. Since there are 14% migraineurs among adults, the total annual cost of this disorder in a given country can be estimated to be: number of adults in the population × 0.14 × €590.

A more speculative estimate for the cost of headache, rather than migraine alone, can be derived by using the results of the Danish (Rasmussen *et al.*, 1992) and British (Boardman *et al.*, 2003) population-based studies, which both demonstrated that around 1100–1300 days per 1000 workers were missed due to headache each year. The British study also suggested that the number of days with reduced efficacy ($n = 5213$) was around four times higher than the number of days

missed ($n = 1327$). If one assumes that work efficacy was reduced by one-third during these days (see the Results section), this will result in an additional 1700 workdays lost, i.e. a total of 3000 days per 1000 workers are likely to be lost due to headache each year. The productivity loss due to headache can then be calculated on the basis of 3 days lost per year for all employed individuals, which, for example, in Germany would result in total indirect costs of €18bn per year due to headache. Assuming that, as for the adjusted migraine estimates, direct costs constitute about 8% of indirect costs, the total cost per headache patient (irrespective of the diagnosis) can then be approximated on the basis of a prevalence rate of 51% in the general population. Using estimates for France, Germany and the UK, the average total cost per headache patient can thus be estimated to be roughly €425 per year (of which €394 would be due to indirect costs and €32 due to direct medical costs). However, as these data are based on a speculative estimate of the cost of TTH, the total cost of headache should be the focus of future research and will not be used to estimate the cost of brain disorders in Europe at this stage.

Conclusions

In summary, migraine, with a 1-year prevalence of 14% in the adult population, seems to entail a cost of €590 per year per patient in some Western European countries. No valid cost data are found for Europe for overall headache, and hence the aggregated cost estimation concentrates on migraine. Although the cost per patient for other headaches seems to be somewhat lower than for migraine, the total societal costs due to headache are certainly much higher than what can be calculated based on the migraine data, since headache in general affects around 50% of the population every year. Both cost and prevalence figures must, however, be considered as best guesses as current data on the epidemiology and cost of migraine and other headaches suffer from similar serious shortcomings, namely:

- data are only available for selected countries;
- heterogeneous methodologies hinder cross-country comparisons;
- there is a significant lack of data for TTH, particularly with respect to cost studies.

In addition, the cost studies are not up to date, and do thus not take recent developments in headache management into account.

Consequently, there is a need for up-to-date and comprehensive population-based studies that capture all the costs resulting from migraine and other headaches. More studies are also needed from countries outside the major pharmaceutical markets in Western Europe. On a methodological level, a standardized and hopefully more reliable approach for cost-of-illness studies would facilitate future decision-making regarding the funding of headache research and management. As new severity measures for headache emerge, it would be of value to understand how costs are linked to disease severity, so that management strategies can be targeted more specifically towards each subpopulation. Moreover, further analysis of different productivity measures is needed to allow realistic evaluation of indirect costs, which constitute the key burden of headache. In this context, it would also be of interest to understand the intangible costs of the condition by conducting research on the utility scores for different severity levels and the related costs of quality adjusted life years lost due to migraine.

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ORIGINAL ARTICLE

Cost of multiple sclerosis in Europe

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Introduction

Multiple sclerosis (MS) is a chronic progressive potentially disabling disorder with a considerable social impact and economic consequences despite its relatively limited prevalence. It is the major cause of non-traumatic disability in young adults. Epidemiological data are somewhat conflicting, and while there is a wealth of economic data studies, they are often too specific to provide an overall picture for costs.

MS is an acquired inflammatory and neurodegenerative immuno-mediated disorder of the central nervous system, characterized by inflammation, demyelination and primary or secondary axonal degeneration. It is clinically manifested by multiple neurological dysfunctions (e.g. visual and sensory disturbances, limb weakness, gait problems and bladder and bowel symptoms) often increasingly disabling over time due to irreversible functional disability. However, more aspecific symptoms can be detected, such as fatigue which affects nearly 70% patients regardless of their disability or course status and interferes with their quality of life and productivity. The efficacy of immunoprophylactic therapies on disease course is modest overall and the disease shows heterogeneity with respect to its pathogenesis, clinical manifestations and prognosis. Etiology is unknown. MS is a complex multifactorial disorder, in which environmental factors are hypothesized to interact with genetically susceptible individuals.

Early disease stage is usually characterized by a relapsing-remitting course (RR-MS). Over time, increasing demyelination and the axonal degeneration lead to a secondary progression (SP-MS), while 10–20% of patients present with a primary progressive course from clinical onset (PP-MS).

Diagnostic criteria imply evidence of dissemination of neurologic signs/symptoms in space and time, by the use of paraclinical data, including magnetic resonance imaging and cerebrospinal fluid examination. Poser *et al.* (1983) appear to be the most widely used in MS epidemiological surveys in the past 25 years.

Economic consequences are predominantly the early loss of work capacity due to the development of physical disability and the impact of fatigue in a population of young adults, the requirement for hospitalization during severe disease exacerbations and the need for assistance in activities of daily living. More recently, the introduction of new biological treatments is thought to have led to an increase in direct costs due to the cost of these drugs themselves, but also to a more intensive management of patients. A considerable number of cost studies were performed in the 1990s, prior to the introduction of these drugs, often to provide the basic data upon which to make decisions on resource allocation. However, data on the current cost picture, incorporating the economic consequences of changes in patient management are not yet available. Estimating today's cost thus requires a number of assumptions and extrapolations.

The following is a summary of available data, both epidemiological and economic, and a description of the data used to estimate the cost of MS in Europe, based on previous findings (Kobelt, 2004; Pugliatti *et al.*, 2005).

Epidemiology of MS in Europe

Despite the wealth of data deriving from systematic epidemiological studies on MS conducted over the past five decades, the attempt at redefining the pattern of MS geographical distribution in Europe is still a hard task due to: (a) the variability of the surveyed populations in terms of size, age structure, ethnic origin, etc.; (b) the capability to detect benign and/or early cases; (c) the different degree of case ascertainment coverage based on geographical and time setting, access to medical care, number of neurologists, availability of new diagnostic procedures, public awareness about MS, etc.; and (d) the impact of different diagnostic criteria used and the inter observer variability when comparing incidence and prevalence rates between studies.

Recent reviews on European epidemiological data for MS have been carried out from population-based studies reported in the international scientific peer-reviewed literature for the time period 1980–2003 (Rosati, 2001; Pugliatti *et al.*, 2002, 2005). Evidence reported in non-English scientific literature have also been used, although with caution, when the search on international peer-reviewed literature failed to produce any result. Information on total prevalence rates has been found not to meet inclusion criteria (incomplete, biased, out of date or lacking) for only a few European countries, such as Bosnia-Herzegovina, Moldova, Slovakia and Turkey. Yet, when searching for age-specific prevalence rates, for the distribution of

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prevalent cases by disease severity and course, and for incidence rates, reliable information is lacking for nearly two-thirds of all European countries. On the contrary, a few nations, such as Italy, Norway and the UK, have provided data by means of repeated assessments over the same time intervals.

Epidemiological indices are reported for those countries whose data were suitable for the computation of disease costs.

Prevalence

The distribution of total prevalence rates for each of the countries with available reliable data is reported in Fig. 1. According to prevalence rates, European countries can be grouped as follows: Malta (0–34/100 000); Cyprus, Estonia, France, Greece, Hungary, Ireland, Latvia, Lithuania, Poland, Portugal and Spain (35–69/100 000); Austria, Belgium, Czech Republic, Germany, Italy, Norway, Slovenia, The Netherlands (70–104/100 000); Denmark, Iceland, Switzerland, UK (105–139/100 000) and Finland and Sweden (140/100 000 and over).

Mean rates are higher in northern countries possibly due to a better degree of disease ascertainment, i.e. better accuracy in survey methodology and repeated assessments over time, often based on nationwide investigations and the use of registry systems. However, a certain extent of prevalence heterogeneity has been found within countries, such as in Italy (Sardinia), the UK (Scotland) or Norway (southern regions), therefore the role of environmental factors and their interaction on the population's genetic susceptibility underlying rates differences cannot be ruled out.

A tendency for a decreasing variability in prevalence rates among and within countries is observed over time, which points to an improvement of case ascertainment and survey methodology over the same time, rather than to biological factors accounting for such variability.

European mean total MS prevalence rate is currently estimated at 79 cases per 100 000 population (95%CIs, 68–89, range 17–154), with a median of 73/100 000.

The estimation of prevalence rates by gender can be computed from data deriving from the following countries: Austria, Belgium, Cyprus, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Malta, Norway, Spain, Sweden, Switzerland, The Netherlands and the UK. Mean prevalence rates for men are 57 cases per 100 000 (95%CIs, range 44–67) and 110 for women (95%CIs, range 94–125), with a mean F:M ratio of 1.9:1. Prevalence rates are higher for women in each of the countries considered. However, lower gender ratios have been observed for Malta (1.5), Belgium and Ireland (1.4), Denmark (1.3) and Cyprus (1.1), and higher ones for the UK and France (2.4), Austria (2.5), Hungary (2.8) and Germany and Greece (2.9).

Prevalence rates by age have been computed based on data from the following countries: Belgium, Estonia, Finland, Greece, Ireland, Italy, Malta, Norway, Poland, Spain, Sweden, Switzerland and the UK. Mean estimated total prevalence rates are 2/100 000 (95%CIs 1–8; F/M: 1.5) for age group 0–17 years, 64 (95%CIs 47–87; F/M: 2.0) for age group 18–34, 161 (95%CIs 148–226;

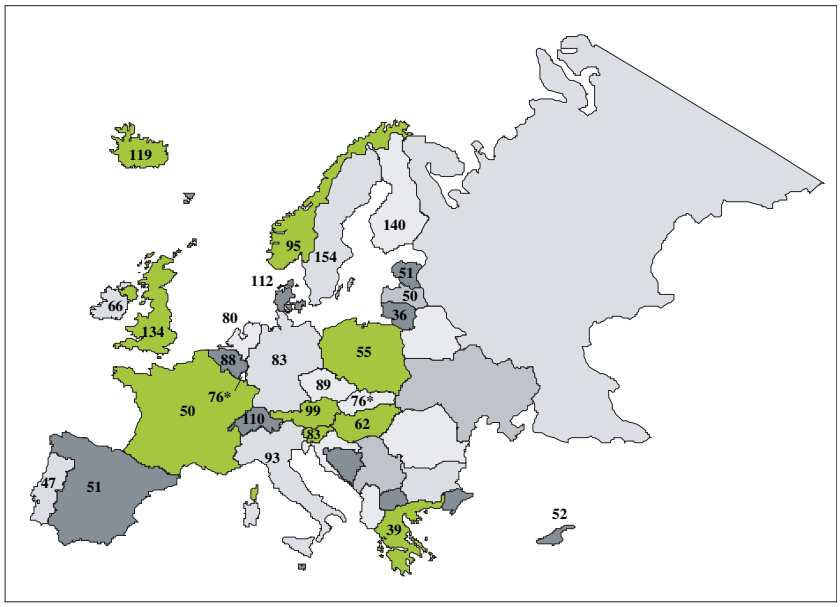

Figure 1 Prevalence of MS in Europe. *Mean European MS total prevalence rate (12-month rates).

F/M: 2.1) for age group 35–49, 142 (95%CIs 116–180; F/M: 1.7) for age group 50–64, 87 (95%CIs 63–124; F/M: 1.6) for age group 65–74, and 44 (95%CIs 23–88; F/M: 1.6) for age 75 years and above. The highest prevalence estimates have been found for age group 35–64 for both women and men and for all countries considered, with the exception of Switzerland where high total rates (220/100 000) were also found in age group 65–74.

In most studies the distribution of disease severity was expressed by using the proportion of disability according to Kurtzke's Expanded Disability Status Score (EDSS) in prevalent cases (Kurtzke, 1983). The Kurtzke EDSS is a method of quantifying disability in MS in eight functional systems (pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral, other) thus allowing neurologists to assign a score in each of these. EDSS scores of 0.5–3.5 refer to fully ambulatory patients showing mild neurological signs (mild cases); 4.0–6.5 refer to impaired deambulation (requiring constant bilateral assistance, i.e. moderate cases); 7.0–9.5 refer to patients restricted to wheelchairs, confined to bed and totally helpless. A mean distribution of 57%, 22% and 21% for mild, moderate and severe cases, respectively, was estimated by using data from Austria, Belgium, Cyprus, Hungary, Ireland, Italy, Luxembourg, Slovenia and Spain.

The distribution of prevalent cases by disease course is a hard task in that categorization in the different course forms can be especially confusing between the relapsing-progressive (RP-MS) and SP-MS courses. Furthermore, depending on the article-specific purpose, these two categories are sometimes omitted. A mean distribution of 57% for RR-MS, of 28% for combined RP-MS and SP-MS, and of 15% for PP-MS was found based on prevalence data from Austria, Bulgaria, Cyprus, Finland, Germany, Greece, Hungary, Italy, Norway, Serbia Montenegro, Spain, Sweden, the Netherlands, Turkey, Ukraine and the UK.

Incidence

European total mean MS incidence rate is estimated to be 4.2 cases per 100 000/year (95%CIs 4.0–7.5, median 4.7, range 0.7–6.9) based on data from Croatia, Denmark, Finland, France, Greece, Hungary, Iceland, Italy, Malta, Norway, Poland, Spain, Sweden, Ukraine and the UK.

Total mean incidence rates are higher (above distribution third quartile) in Finland and the UK and lower (below first quartile) in Greece, Malta, Poland and the Ukraine. For the time period considered, high peaks of total incidence rates have been registered in Seinajoki, Finland (11.6/100 000/year), southeastern Scotland (9.3/100 000/year), eastern Norway (8.7/100 000/year) and northern Sardinia, Italy (6.8/100 000/year).

Cost of MS in Europe

The review was limited to studies that contained full or partial cost-of-illness information in a European country, and studies based on a clinical trial or limited to a specific treatment episode in a specific population were excluded. For further details see the review by Kobelt (2004).

The 15 studies included differ in a number of aspects: their approach to data collection; the type of resources included; the valuation of the resources, in particular of productivity losses; the type of patients concerned; the sample process; and last but not least the quality of the analysis. Results are heavily influenced by these factors, in addition to known differences between the countries in absolute and relative prices and healthcare and social organization. It is hence inappropriate to directly compare the studies and the costs, even within the same country.

Nevertheless, the studies agree in their overall findings.

- Costs outside the healthcare system (productivity losses due to short-term sick leave and early retirement), non-medical costs (investments, transformation of the house, etc.) and informal care by family or friends, dominate the costs of MS. Studies differ, however, in the way these costs are estimated. Indirect costs are calculated using either the human capital approach or the friction cost method, which lead to different results. Informal care is calculated as a productivity loss of the caretaker and is thus considered an indirect cost, or valued as a direct cost using a replacement cost (i.e. the cost of a health or community professional providing the same care), or as a mixture of both. As a consequence, the proportion of costs represented by indirect costs varies between studies due to methodological difference, in addition to the difference caused by the selection of resources included in direct costs (e.g. inclusion of patient-borne costs or not).
- Indirect costs represent a larger proportion of costs in patients with limited permanent disability (i.e. at lower EDSS levels). Direct costs are essentially limited to short-term hospital admissions for exacerbations, with limited costs for comorbidity, while on the other hand patients are often on extended sick leave. With the new treatments, this is likely to have changed, due to fewer relapses, but considerable drug costs. No data are available yet however.

- Men have higher total costs than women, driven by higher productivity losses, as in most countries the labour force participation of men exceeds that of women, and salaries are higher.
- Healthcare costs are dominated by inpatient care (40–50%), with drugs representing a minor part. Again, this is likely to be different today, depending on the proportion of patients who receive the new drugs.
- Costs increase with increasing severity of the disease. A number of studies have shown that taken individually, age, disease duration and disease severity all are positively correlated with resource consumption and work capacity. However, there is also a clear colinearity between these variables, and in multiple regression analysis, only the level of EDSS remains significantly correlated with costs (Kobelt *et al*., 2003). The mean cost per patient with severe disease (EDSS 7.0 and above) is 4–5 times higher than the cost of a patients with mild disease (up to EDSS 3.5).
- Costs are higher overall for patients with SP-MS than for those with RR-MS. However, when controlling for EDSS this is less clear: costs appear to be driven by the level of EDSS rather than by the type of MS. Conversion from RR-MS to SP-MS is not clearly defined, and patients can convert at different EDSS levels ranging as wide as 1.0–6.0, with a mean/median at 3.0. Thus, at EDSS levels between 3.0 and 5.0 there will be patients with both disease types, and there appears to be no significant difference in costs between the two types of MS at the same level of EDSS, in the absence of a relapse (Kobelt *et al*., 2003).
- Quality of life (QoL) and/or utility decreases with increasing disease severity. While generic QoL instruments such as the SF36 have shown more limited differences, mean utility decreases from around 0.7–0.75 for patients with mild disease to 0.2–0.3 for patients with severe disability.
- As a consequence, intangible costs are considerable, but few studies have addressed the issue. There is no commonly accepted methodology to calculate intangible costs, but three studies in Sweden, Germany and the UK provide an approach and an estimate, using utility measurements obtained with the EQ-5D. Patients' utility scores at each level of disability were compared with population scores (matched for gender and age) and the difference used to calculate the loss of quality-adjusted life-years (QALYs). Assuming a hypothetical willingness to pay for a QALY of €30 000, intangible costs were estimated to range between €10 000 and €15 000 which would be much as one-quarter to one-third of total costs.

The most complete recent studies are four large cross-sectional or short-term prospective bottom-up studies including 500 or more patients, in Sweden, Germany, the UK and Italy (Kobelt *et al*., 2000, 2001; Henriksson *et al*., 2001; Amato *et al*., 2002). However, even these recent studies relate to the second half of the 1990s and hence do not include substantial effects on costs from the new treatments, other than drug costs. One could speculate that the consumption of certain resources, such as inpatient admission for example, has changed as a consequence of fewer relapses, and are therefore probably not an entirely accurate representation of current costs. The studies in Sweden, Germany and the UK included a proportion of patients treated with β-interferons, and usage in the study population was adapted to the level of national usage at the time of the studies. Although in Germany it was shown that usage of other prescription drugs was lower in patients treated with β-interferons, it is unlikely that any other cost savings would have been captured, as these will appear only after some time. Also, recent (unpublished) evidence shows that due to more intensive patient management, other drug costs have also increased. The study in Italy collected data in 1996 and none of the new drugs were available in Italy at that time.

These four studies are the only published data that can reasonably be compared, at least at the level of total costs, by inflating costs to current costs and adjusting for purchasing power parity (Eurostat 2004a, b; European Central Bank, 2004). Tables 1 and 2 show the

Table 1 Comparison of annual total cost per patient in four countries, € 2004 (PPP adjusted)

	Germany (1999)	Italy (1996)	Sweden (1998)	UK (1999)
Direct costs[a]	8333	3297	11 729	3848
Out-of-pocket costs and informal care	9635	7001	13 089[b]	10 031
Indirect costs	13 128	8418[c]	13 511	11 746
Total costs (€ 2003)	31 096	18 716	38 329	25 625

[a]Includes interferon use adjusted to national usage at the time of the study, except for Italy where interferon was excluded.
[b]Includes personal assistants provided by the social service.
[c]Includes caretaker loss of income.

Table 2 Estimated spending on MS in four countries, € 2004 (PPP adjusted)

	Germany (1999)	Italy (1996)	Sweden (1998)	UK (1999)
Estimated prevalence	120 000	70 000	11 000	88 000
Cost per MS case (€)	31 096	18 716	38 329	25 625
Total estimated costs (€, millions)	3732	1310	422	2255
Cost per inhabitant (€)	45	23	47	38

Source: adapted from Kobelt (2003).

comparison. All four studies included estimates of costs for different levels of disease severity. Combined with the mean estimates of prevalence at given levels of disease severity, this allowed estimating total costs of MS in different countries.

Discussion

The number of epidemiological and economic studies of MS is larger than for most other neurological diseases. However, this brings with it not only a large quantity of information, but also the need for interpretation and understanding of differences between studies and in the results. Studies can seldom be directly compared but must be carefully scrutinized to identify differences in the objective, set up, sample selection, data collection and analytical methods. and while it appears possible to extrapolate overall prevalence as well as the distribution into different levels of severity of the disease to countries where no estimates exist to derive an overall estimate for Europe, this is more difficult when costs are concerned. Absolute and relative prices differ and so does the way in which healthcare is provided and financed. Nevertheless, when identical or at least similar studies provide very complete and detailed data on resource consumption in a number of countries across Europe, such as is the case in MS with the four studies mentioned, it is possible to provide overall estimates of costs by combining the data with relevant epidemiological data and adjusting for the economic differences between countries.

Conclusions

More extensive epidemiological and economic research of MS in Europe is needed with special regard to the assessments of both prevalence rates and costs by gender, age, disease course and disability. Investigations should be conducted for each country possibly with a standardized approach and predefined guidelines.

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ORIGINAL ARTICLE

Cost of Parkinson's disease in Europe

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Introduction

Parkinson's disease (PD) is one of the most common chronic neurodegenerative diseases. Main symptoms of PD are bradykinesia, rigidity, rest tremor and postural instability (Oertel and Quinn, 2003). In addition to the motor symptoms mental disorders like depression or psychosis, autonomic and gastrointestinal dysfunction may occur, which considerably impair the quality of life of PD patients. Although the cerebral structures undergoing neurodegeneration in PD are well characterized, the causing mechanisms of the disease are still unknown. No cure has been found to stop the progressive course of the disease and severe disability may occur in its later stages. The aim of this study was to evaluate the epidemiology and the costs of PD in the different European countries.

Methods

The search for relevant epidemiological studies as well as cost-of-illness studies has been described previously in two independent reviews (Lindgren, 2004; Campenhausen *et al*., 2005).

Epidemiology data

A systematic literature search was performed to identify studies on the prevalence and incidence of PD in the different European countries. The search was performed on the following databases: MedLine (1966 until 2004), Premedline (1966 until September 2002), Current Contents (all editions, 1993 until July 2002), the Cochrane's database of systematic reviews (until 2004), EconLit (1969 until July 2004), Biosis, PsycLit and EMBASE (until 2004). Only published studies were included. Abstracts, reviews, meta-analyses and letters to the editor were excluded. There were no language restrictions. Data were extracted using a standardized assessment form, and evidence tables were used to systematically report and compare the data. To classify the studies we developed a short scoring instrument for the assessment of the quality of epidemiological studies in PD as we did not find quality assessment instruments suitable for our purpose. A pool of possible questions was generated and discussed by the authors considering published recommendations for the reporting of results from the synthesis of observational studies (Stroup *et al*., 2000). A reduced set of questions was selected, tested with actual publications and revised thereafter. The final version of the quality assessment form contained questions from nine domains with one or two questions per domain. Each domain scored from 0 to 2 points. Domains represented description of study question (domain 1), population and design (2 and 3), data sources (4), case definition and identification (5 and 6), and reporting of study results (7), potential bias (8) and the topic of relevance (9).

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Cost data

Two data bases were searched to find studies: MedLine (PubMed) and OHE-HEED, no restriction to when studies were published was applied but due to the delay until manuscripts are indexed in the databases no studies published later than July 2004 were included. One study that was known to be in press was also included. To be included in the review, studies had to have an abstract in English, to contain data on a European country, and to contain primary data on costs associated with PD. Five studies were found that fulfilled these criteria, representing five different European countries: Germany, Finland, France, Sweden and the UK (LePen *et al*., 1999; Hagell *et al*., 2002; Findley *et al*., 2003; Keranen *et al*., 2003; Spottke *et al*., 2005). The studies are all fairly recent, published between 1998 and 2003 (with one study currently in press). All studies were bottom-up studies that estimated the resource use in individual patients and then aggregated the patient specific cost to get an average measure.

Epidemiology of PD in Europe

Actual epidemiological studies of PD have not been published for all European countries. We identified epidemiological data for the following European countries: Austria (A), Czech Republic (CZ), France

Table 1 Epidemiological studies in the European Union

Country	Prevalence data	Incidence data
Austria	–	–
Belgium	–	–
Cyprus	–	–
Czech Republic	–	–
Denmark	+	+
Estonia	+	+
Finland	+	+
France	+	–
Germany	+	–
Greece	–	–
Hungary	–	–
Ireland	–	–
Italy	+	+
Latvia	–	–
Lithuania	–	–
Luxembourg	–	–
Malta	–	–
Netherlands	+	+
Norway	+	–
Poland	+	+
Portugal	+	+
Slovakia	–	–
Slovenia	–	–
Spain	+	+
Sweden	+	+
UK	+	+

–, no data available; +, data available. The prevalence and incidence data communicated in the different studies are depicted in Figure 1.

(F), Germany (G), Italy (I), The Netherlands (NL), Portugal (P), Spain (E), Sweden (S), and the UK (UK) (Table 1).

Estimates of crude prevalence rates varied considerably, from 65.6/100 000 in Sardinia (Rosati *et al*., 1980) to 12 500/100 000 institutionalized patients in Germany (Evers and Obladen, 1994). Not all publications reported detailed age-specific prevalence rates, and reported age ranges varied. In six studies (Sutcliffe *et al*., 1985; Granieri *et al*., 1987; de Rijk *et al*., 1995; Schrag *et al*., 2000; van de Vijver *et al*., 2001; Claveria *et al*., 2002) the crude prevalence increased with age. However, in six other studies (Rosati *et al*., 1979; D'Alessandro *et al*., 1987; Errea, 1997; Chio *et al*., 1998; Benito-Léon, 2003; Bergareche *et al*., 2004) the crude prevalence continued to decrease between 70 and 90 years of age.

In respect to disease stage (Hoehn and Yahr classification; HY) in the Italian and Spanish studies more than 55% of the patients were classified as stage HYI or HYII and fewer than 5% were classified as stage HYV, while in the English study only 27% of patients were classified as stage HYI or HYII and 10% were classified as stage HYV (Mutch *et al*., 1986; Benito-Léon, 2003).

Incidence data

We identified 13 studies reporting annual incidence rates. Crude incidence estimates varied from 5/100 000 to 346/100 000. The latter estimate is for incidence in persons aged 65–84 years, from the Italian Longitudinal Study on Ageing (ILSA).

Cost of PD in Europe

In our search for economic studies, we identified five studies from the following European countries: Germany, Finland, France, Sweden and the UK (LePen *et al*., 1999; Hagell *et al*., 2002; Findley *et al*., 2003; Keranen *et al*., 2003; Spottke *et al*., 2005). All of these were bottom-up studies estimating the resource use in individual patients and then aggregating the patient specific cost in an average measure.

All included studies found in the literature review were of good quality and were suitable to be included in the model. Table 2 shows the mean direct and indirect costs reported in the studies. The higher costs of outpatient care in France were due to the fact that many patients in the French study were recruited from specialist offices. Only the UK included costs for adaptations to the home made by the patient, which explains the higher total direct cost there.

Discussion

Epidemiology

The included studies reported prevalence and incidence rates for PD of approximately 108–257/100 000 and 11–19/100 000 per year, respectively. When only older age groups (> 60 years) were included, rates of prevalence and incidence were much higher: 1280–1500/100 000 and 346/100,000, respectively. The large observed variations in rates (65.6–12 500/100 000) may result from environmental or genetic factors. However, observed variations may also be the consequence of differences in methodology, survey design, case-finding strategies and particularly age distributions (note that the highest prevalence of 12 500/100 000 was obtained from a study of patients with Parkinsonism in nursing homes). Another potential source of variation is differences in diagnostic criteria. de Rijk *et al*. (1997) showed that a change in the diagnostic criteria may result in a decrease of up to 36% of identified cases in community-based studies. Differences in methods for case ascertainment may also influence estimated rates (Anderson, 1998), and screening procedures and validations differed considerably in the identified studies. Moreover, screening personnel had different levels of

Table 2 Mean costs per year as reported in the literature expressed in Euros

	LePen 1999	Hagell 2002	Keränen 2003	Findley 2003	Spottke 2005
Country	France	Sweden	Finland	UK	Germany
Year of monetary value	1996	2000	1998	1998	2003
HY I	2720[a]	1980[c]/4140[d]	NA	2240[e]/1280[f]/1220[g]	4640[h]/6990[i]/2050[j]
HY II	4600[a]	3530[c]/6630[d]	NA	2300[e]/1360[f]/1300[g]	3960[h]/3910[i]/1970[j]
HY III	6420[a]	13 967[c]/6080[d]	NA	4450[e]/3060[f]/2570[g]	8730[h]/11 100[i]/3540[j]
HY IV	10 360[a, b]	2980[c]/6630[d]	NA	5760[e]/6360[f]/4080[g]	15 350[h]/1310[i]/2900[j]
HY V	–	15 690[c]/4420[d]	NA	6500[e]/11 670[f]/11 100[g]	11 220[h]/9560[i]/7420[j]
Stage not known				1580[e]/3510[f]/5430[g]	
Total direct costs	4710	7920	4900	3360	8160
Drugs	1020	1420	980	–	3350
Outpatient visits	300	890	440	–	80
Inpatient care	1840	790	2350	–	2200
Formal care	540	4650	690	3270	2990
Diagnostic procedures	–	100	–	–	20
Special equipment	–	–	–	–	880
Rehabilitation	780	–	440		1470
Transportation	230	70	–	–	30
Others	–	–			140
Indirect costs	–	5810	5000	–	6590
Patient's costs	–	–	1900	2680	3240
Transfer payment	6990	–	–	–	1410

[a]Direct costs; [b]pooled data for HY IV and V; [c]direct costs; [d]indirect costs; [e]direct cost from perspective of the NHS; [f]social services; [g]private expenditures; [h]direct cost from perspective of the GKV; [i]indirect costs; [j]private expenditures.

training and clinical experience: several studies were performed with medical students or GPs. Keeping in mind that up to 24% of the diagnoses of PD are wrong, even when made by experts (Hughes *et al.*, 1992), a considerable uncertainty cannot be excluded: as a consequence of false-negative screening results, prevalence may be underestimated (Bermejo *et al.*, 2001).

Beyond the methodological problems, there are several additional inconsistencies among the studies that make a comparison of age-specific prevalence estimates difficult. For example, the age categories are not homogenous. In particular, the highest age category varies significantly by study: from 75 years (Dias *et al.*, 1994), to 80 years (Schrag *et al.*, 2000), to 90 years (Tison *et al.*, 1994; Claveria *et al.*, 2002), and to 95 years (van de Vijver *et al.*, 2001). Several surveys found an increasing tendency with age (Sutcliffe *et al.*, 1985, Granieri *et al.*, 1991; de Rijk *et al.*, 1995; Schrag *et al.*, 2000; van de Vijver *et al.*, 2001; Claveria *et al.*, 2002), while others reported a peak at the age of 70 (or 75) to 79 years (D'Alessandro *et al.*, 1987; Kis *et al.*, 2002), followed by a decreased prevalence at ages over 80 years. This decline of crude prevalence in the older age groups was reported in six studies; however, six studies reported an additional increase in the crude prevalence in the oldest age groups. When assessing the validity of estimated prevalence in the most advanced age groups, it must be taken into account that the number of patients in such age groups is very small: a few cases can distort the results (van de Vijver *et al.*, 2001; Claveria *et al.*, 2002). For instance, a German study of persons living in nursing homes reported a PD prevalence of 12 500/100 000 (Evers and Obladen, 1994). As previously suggested (Twelves *et al.*, 2003), we therefore recommend reporting age-specific or age-standardized rates; this would facilitate comparison between studies.

Only a few studies reported rates by gender (Fall *et al.*, 1996). We found conflicting evidence of an increased prevalence for men: some studies found a 1.5- to 2-fold increase, but these findings were not confirmed in other studies (Granieri *et al.*, 1991). Anderson emphasized the difficulties with estimating prevalence in elderly women (Anderson, 1998): non-response and selection biases may be related to health status, and thus are potentially significant problems in elderly PD patients.

Data on the distribution of the extent of the disease are important for healthcare planning: patients in advanced stages of PD consume higher healthcare expenditures than patients in the early stages of the disease (Findley *et al.*, 2003; Spottke *et al.*, 2005). Rates stratified by HY stage were reported in only a few studies; however, the distribution of PD severity in Europe was quite similar in most studies. Higher probabilities of participation by patients with mild symptomatology in the population-based studies may explain the high number of cases with mild disability

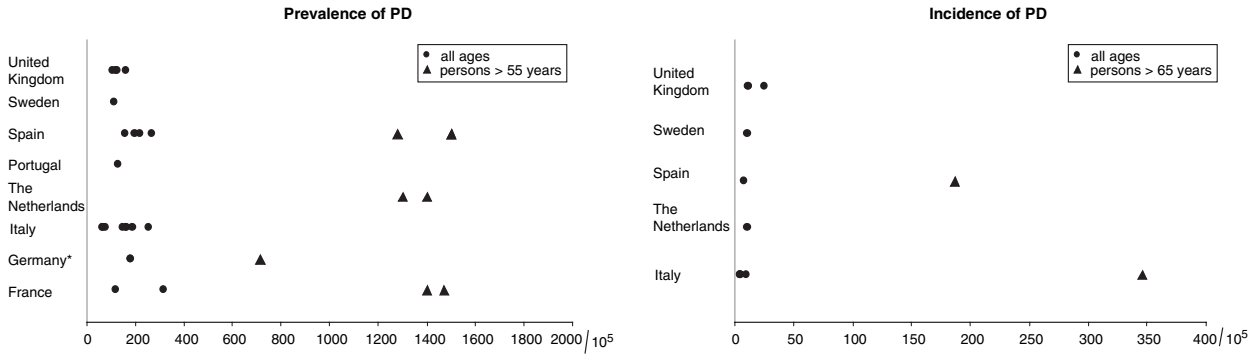

Figure 1 Results of prevalence and incidence studies in Europe.

(HYI-II). As is the case for elderly PD patients, patients with advanced disease have a lower probability of participation in a study and are more likely to be living in nursing homes. The results by Evers and Obladen (1994) and Mutch *et al.* (1986), in which 10.2% of the study population was confined to bed or a wheelchair, suggest a bias towards underestimation of advanced stages of the disease.

To classify the studies we developed a short scoring instrument for the assessment of the quality of epidemiological studies in PD as we did not find quality assessment instruments suitable for our purpose. The quality of epidemiological studies has been evaluated according to the chosen quality criteria. The mean rating was 12.5 with a range from 5 to 18.

Cost studies

All the cost studies we identified in the literature are bottom-up studies where patient level costs have been estimated based on the resource consumption of individual patients and then aggregated to estimate average costs per patient. This is generally considered a better approach than to perform top-down studies where the cost per patient is established by deriving a total cost from available registers and dividing this figure by the number of patients, as this may lead to the exclusion of cost items not included in the registers. The studies also provide a detailed description of what components have been included which makes a comparison between them easier.

One difficulty when comparing costs across studies apart from different resources being included is that the patients included in the studies have different characteristics. The higher cost of hospitalizations observed in France and Finland may be due to the fact that these studies have included more advanced patients, which are more likely to be treated in a hospital setting. The French patients were recruited from both general and specialist practices with half of the patients coming from each setting. This is another illustration that patients may be different as this distribution between the two settings are likely not a representation of the average patient.

As samples get smaller when breaking down the analysis by Hoehn and Yahr stages the uncertainty around these estimates increases. This may in part explain the variations observed between the countries at different severity levels of the disease. There is also a risk of confounding by age when looking at the stratified data. If we look at the Swedish and German indirect costs, they appear to be independent of disease severity. However, as PD progresses over time, older patients are more likely to be found in the more severe stages and many of the patients who have reached stage V are thus likely to have retired because of their age. Unfortunately, none of the published studies present their data in a way (e.g. multivariate analysis) that allows for an interpretation based on both age and Hoehn and Yahr. With the sample size of the existing studies, this is also likely to be a difficult analysis to perform.

One limitation of the available cost data is that it stems from a limited number of countries, all from Northern and Western Europe. No data from central, eastern or southern Europe has been published depending on our selection criteria, which is a limitation when trying to extrapolate the costs from the available countries to a pan-European setting.

To get a proper picture of the costs associated with PD suitable for use in the discussion about prioritizations and economic evaluations, further research is necessary. The gaps in the data are considerable with no information about the costs associated with the disease in the majority of European countries. New treatments and treatment patterns are leading to changes in resource consumption, which are not captured in the studies currently available. As can be illustrated by the studies included here, what components are included in the analyses have great impact on the estimates of total

costs. A common protocol for the data collection in cost-of-illness studies would therefore be useful for comparing different studies across populations and healthcare systems.

Conclusion

In conclusion, the results from our study emphasize the problems and obstacles in performing epidemiological studies in PD. Only a few high-quality studies are currently available that allow a comparison of European incidence and prevalence rates. Recently, a review of incidence studies in PD proposed a provisional set of minimal scientific criteria that would improve the quality and consistency of such studies (Twelves *et al.*, 2003). Furthermore, standardized criteria would allow a more accurate comparison of national and international studies. Finally, as shown in Table 1, there is still a lack of epidemiological studies in several European countries.

The published literature on the cost of PD shows that this is a costly disease that causes considerable strains on both the patients and on society as a whole. Progression of the disease leads to higher costs, and there are substantial gains to be made from hindering this progression. There is need for further research as cost studies are only available in five European countries at present, and new treatments have been introduced since these studies were undertaken, which may have influenced the cost structure.

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ORIGINAL ARTICLE

Cost of psychotic disorders in Europe

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Introduction

Schizophrenia and psychotic disorders are a heterogeneous category usually combined for practical reasons in the International Classification of Diseases. The most frequent and most important illness group is schizophrenia.

Schizophrenia is a severe mental disorder characterized by fundamental disturbances in thinking, perception and emotions. Although the clinical features of schizophrenia include a diversity of symptoms, it has proven useful to split schizophrenic symptoms into two categories, i.e. positive and negative symptoms. Positive symptoms comprise hallucinations (e.g. internal voices discussing or arguing), delusions (e.g. of being controlled or persecuted), bizarre behaviour (e.g. being aggressive or agitated) and thought disorders like incoherence. Negative symptoms include among others poverty of speech, inappropriate or flattening affect, apathy and anhedonia. Episodes with predominantly positive symptoms alternate with states of sustained negative symptoms.

The treatment of schizophrenia rests on three main pillars. Firstly, there are medications to relieve symptoms and prevent relapse. Secondly, psychosocial interventions help patients and families to cope with the illness, and aim at preventing relapses. Thirdly, rehabilitation helps to reintegrate patients into the community, and helps them to regain occupational functioning. The challenge in the care of people suffering from schizophrenia is the need to coordinate services; from early identification and treatment to regular treatment and rehabilitation. Currently, only a few patients with schizophrenia need long-term hospitalization.

The total cost of schizophrenia was estimated at $32.5 billion in the USA in 1990 prices [1], of which half of the costs were attributable to direct medical costs. The economic evidence on schizophrenia in Europe is fairly good in terms of number of studies. However, the methodology applied and quality achieved varies.

This paper aims to summarize the available evidence on psychotic disorders in epidemiology and costs for Europe, and is based on already published literature reviews in the field [2, 3]. Hence, for more detailed information on methodology and full results please consult the references. The data presented here serve as input data for the estimation of the cost of affective disorders in Europe.

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Epidemiological data on psychotic disorders in Europe

Schizophrenia is not a very frequent disease. It occurs worldwide. Out of 100 individuals, about one will experience a schizophrenic episode in his lifetime.

Schizophrenia usually starts in young adulthood. Life expectancy is reduced by approximately 10 years, mostly as a consequence of suicide. About 30% of patients diagnosed with schizophrenia attempt suicide at least once during their lifetime. But individuals with schizophrenia also show an increased morbidity due to physical illnesses, which certainly also contributes to their increased mortality.

Even if the course of the illness today is considered more favourable than when it was originally described, it is still only a minority of those affected who fully recover. But there are only a few European studies that have provided prospective and standardized data on representative samples of first-admitted patients.

It has been repeatedly demonstrated that schizophrenia follows a more severe course in industrialized countries like Europe than in developing countries. Though attempts have been made to explain this better outcome on the basis of stronger family support and fewer demands on the patients, the exact reasons for these differences are not clear.

Gender differences are well known. In fact, men seem to show their peak of onsets in their early twenties and women theirs only in their late twenties; and there is a second, smaller peak of onsets in women after age 45. Women seem to have a more favourable course and a better psychosocial 'outcome' than men. Their hospital stays were fewer and shorter, and their social adjustment and living situation better than those of men, whereas the symptom-related course seems to be similar for both genders. Women's mortality is also lower, due mainly to their significantly lower suicide rate.

The burden of schizophrenia is large and multifaceted. It does not only concern the affected individuals but also their relatives, friends, other caregivers, the

Table 1 Twelve-month prevalence of schizophrenia in Europe [3]

	Total (%)	Male (%)	Female (%)
Germany[a]	2.6	2.5	2.5
Czech Republic[b]	1.07	0.81	1.32
Italy[c]	2.0	2.0	2.0
Netherlands[df]	0.2	0.2	0.2
UK[ef]	0.4	0.4	0.4
European estimate	0.8		

[a]GHS-MHS (Jacobi *et al*., 2002; 2004).
[b]Unpublished data provided by expert (Dragomirecka).
[c]Faravelli *et al*. in press).
[d]Only schizophrenia; Bijl *et al*. (1998).
[e]Meltzer *et al*. (1995); first age group: 16–34.
[f]Predominantly focusing on the diagnosis of schizophrenia.

community and the wider society. In the World Health Report 2001, schizophrenia is listed as the eighth leading cause of disability worldwide in the age group 15–44 years.

Negative attitudes towards the mentally ill, especially towards persons with schizophrenia, are widespread. Individuals with schizophrenia are looked at frequently as being dangerous and unpredictable. Many media reports reflect this fear; even if, in reality, a potential risk is mainly directed to the closest relatives. By and large, it is only a negligible proportion of community violence that could be attributed to schizophrenia. But this and other stigmata attached to schizophrenia create a vicious cycle of discrimination leading to social isolation, unemployment, drug abuse, long-lasting institutionalization, or even homelessness – all factors that further decrease the chances of recovery and reintegration into normal life, in addition to the often-deleterious consequences of the illness itself. The prevalence data included in the cost estimation of schizophrenia in Europe are shown in Table 1.

Economic data on psychotic disorders in Europe

A literature search on cost studies conducted in the area of schizophrenia resulted in a total of 18 studies, spread over 10 European countries. There were multiple studies for Italy (two studies), the Netherlands (two studies) and the UK (six studies). Despite this fact, many gaps remain in the literature and knowledge of the costs of schizophrenia. No studies were identified for many countries in both Western and Eastern Europe.

Table 2 allows for a comparison of the available economic data retrieved in the literature. It presents the findings for total costs (and its main components) inflated and converted to cost levels expressed in Euros at the cost base level of 2004 [4, 5].

As can be observed, there are large variations between countries and also within countries (e.g. Italy and UK) in both direct costs and indirect costs. The direct medical and non-medical cost estimates per patient per year range from €2505 in Spain [2] to €21 325 in the UK [14], and thus there are substantial differences in results across the studies. One likely reason for the difference in the estimates is differences in study designs; and in particular in a study like the UK(4) study by Lang *et al*. [13], where there is a potential risk for selection-bias towards a more severely ill study population with inpatient treatment. Moreover, among the 18 studies reviewed only three reported any estimates of the indirect costs due to schizophrenia. In these four studies indirect costs comprised the majority of the total cost of schizophrenia (average of 58% of the total cost).

The best case for assessing differences between countries is to use the results from the pan-European EPSILON study reported by Knapp *et al*. [2], where a similar study design and methodology has been used in five European countries (Denmark, Italy, Netherlands, Spain and the UK). However, these studies only include direct costs and thus omit a substantial cost component in a life-long chronic disorder like schizophrenia: costs due to lost workdays.

Discussion

Although schizophrenia does not show a high incidence, due to the early age of onset and the often-chronic recurrent course, it shows a relatively high prevalence. This, and the fact that it often leads to mental and social disability, makes it one of the most burdensome and costly illnesses worldwide.

The burden of schizophrenia can be very different in men and women, and the consequences of these differences for treatment and the provision of care have only begun to impact on professionals. Over the last decades, there has been considerable progress in treatment and care, with most efforts directed towards severely ill and chronic patients. Only recently has interest also been directed to early intervention, which might offer an opportunity to make a further major step towards positive changes in psychiatric practice. Yet it has to be stated that there are still many open research questions in this area.

A decrease in costs could be achieved mainly by a reduction in incidence; moderately, given an improvement in prognosis, and relatively minor, given the economies in direct treatment costs likely to follow a transfer to community treatment. Current interventions avert some 13% of the burden, whereas 22% could be averted by optimal treatment. Improvement in

Table 2 Cost studies on schizophrenia in Europe (cost per patient, € 2004)

Source	Country	Year of estimate	Sample size/ prevalence	Time frame/ follow-up	Costs included	Cost per patient (€ 2004)	Direct healthcare cost	Non-medical direct costs	Total cost
De Hert *et al.* (1998)	Belgium	1994	$n = 108$ patient samples in the study; 2.5/1000 = 25274 patients	1 years follow -up after enrollment in study	Total direct medical and non-medical	10383	287	n/a	10670
Knapp *et al.* (2002)[a]	Denmark	1998	$n = 52$ (Denmark /Copenhagen)	3 months	direct medical and non-medical	11510	n/a	n/a	11510
Rouillon *et al.* (1997)	France	1992	$n = 356$	1 years	direct medical and non-medical	9257	n/a	n/a	9257
Salize and Rossler (1996)	Germany	1994	$n = 66$	1 years	direct medical	9237	6235	n/a	15472
Moscarelli *et al.* (1991)	Italy	1989	$n = 20$	3 years	direct medical and non-medical	2960	n/a	n/a	2960
Knapp *et al.* (2002)[a]	Italy	1998	$n = 107$ (Italy/Verona)	3 months	direct medical and non-medical	8296	n/a	n/a	8296
Amaddeo *et al.* (1997)	Italy	1993	$n = 136$	1 years	direct medical and non-medical	10488	3375	n/a	13863
Evers and Ament (1995)	Netherlands	1989	0.6% [~90600]	1 years	overall estimates of direct medical, non-medical and indirect costs	4504	n/a	416	4920
Knapp *et al.* (2002)[a]	Netherlands	1998	$n = 61$	3 months	direct medical and non-medical	4797	n/a	n/a	4797
Rund and Ruud (1999)	Norway	1994	$n = 412$	1 years		not rep.	not rep.	not rep.	not rep.
Knapp *et al.* (2002)[a]	Spain	1998	$N = 100$	3 months	direct medical and non-medical	2505	n/a	n/a	2505
Hertzman (1983)	Sweden	1975	#	1 years	direct medical costs	not rep.	not rep.	not rep.	not rep.
Davies and Drummond (1990)	UK	1987	# [~185400]	1 years	direct, indirect	4056	52	18385	22493
Davies and Drummond (1994)	UK	1990/1991	# [~185400]	1 years	direct, indirect	3960	156	17223	21338
Knapp (1997)	UK	1992/1993	# [~185400]	1 years	direct medical	6618	1181	n/a	7799
Lang *et al.* (1997)	UK	1995	$n = 193$.	6 months	direct medical and non-medical	16261	5063	n/a	21325
Guest and Cookson (1999)	UK	1997	# [$n = 7500$]	5 years	total direct medical and non-medical, and indirect	13572	4498	26449	44520
Knapp *et al.* (2002)[a]	UK	1995	$n = 84$ (London/UK)	3 months	direct medical and non-medical	9138	n/a	n/a	9138

[a]Studies selected for the cost estimation of schizophrenia in Europe.

community treatment might also be associated with a further improvement of prognosis.

In general there are a sizeable number of solid cost studies on schizophrenia in Europe. However, they differ significantly in terms of patient selection, study design and methodology, which make it difficult to interpret the differences in the costing results. There is though a clear lack of economic data from the central and Eastern European countries. In order to reduce the possible patient-selection bias, differences in study designs and costing methodologies, the studies selected for the costing model of schizophrenia are based on one pan-European study including data from five different European countries. The advantage of only using these studies is obviously the reduction in differences mentioned above, that hence gives a more valid comparison of economic data across countries. On the other hand, the costing model consequently only relies on the cost items included in the EPSILON study. One drawback with the EPSILON study is that no estimation of the indirect costs is included. As could be seen in studies where indirect cost was included, the cost component constituted more than 50% of the total cost. Hence, by applying the EPSILON study data, the model would be

likely to underestimate the economic burden of schizophrenia in Europe.

Conclusion

There are a fair amount of both epidemiological and cost studies in schizophrenia in Western Europe. However, the studies selected differ significantly in methodology and study design, which is why the results are difficult to compare across studies. For the cost model the EPSILON study was selected as it has the advantage of applying the same methodology and design in several European countries, and hence allows for more valid comparison between countries. However, there is though still a great need for more epidemiological and health economic research in the area of schizophrenia, especially in the central and Eastern European countries, where there are no data available today.

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ORIGINAL ARTICLE

Cost of stroke in Europe

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Introduction

In the European Union (EU), Iceland, Norway and Switzerland an estimated 1.1 million new stroke events occur each year and currently 6 million subjects live in these countries having survived a stroke (Truelsen, 2004). According to population projections from the United Nations the number of new stroke events will increase to 1.5 million per year in 2025 in these countries if stroke incidence rates remain stable solely due to demographic changes (Truelsen 2004). The costs for stroke treatment and rehabilitation are already considerable and the increasing number of subjects with stroke is likely to increasingly burden health systems in the future.

Data on stroke occurrence are essential for improved planning of stroke prevention and management. The purpose of the present study is to summarize the available studies on incidence/prevalence and also on costs of stroke. A secondary purpose is to identify strengths and weaknesses in presently available data sources and studies. A third purpose is to provide incidence and costs data that will be used as an input into a model estimating the total costs for stroke (and more generally for disorders of the brain) in Europe.

Epidemiology data in stroke in Europe

Availability of stroke incidence studies

Stroke incidence studies were available from 43 studies in 14 different countries (Truelsen, 2004). Two-thirds of the studies were from Sweden, the UK, Italy and Finland. Studies on stroke incidence were available from only three East-European countries: Poland, Lithuania and Estonia (Czlonkowska, 1994; Korv, 1996; Rastenyte, 1995; Vibo, 2004). There were 14 stroke incidence studies that met criteria for an 'ideal' stroke study (Feigin, 2003). In all studies, case ascertainment was predominantly restricted to urban areas although previous studies suggest that stroke occurrence is likely to differ between urban and rural populations (Correia, 2004; Powles, 2002). Rates were higher in men than in women for all stroke subtypes combined. The same pattern was found for studies on ischemic stroke and intracerebral hemorrhage, whereas incidence rates for subarachnoid hemorrhage were higher in women than in men in most populations.

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Availability of stroke prevalence studies

Stroke prevalence data were available from 12 studies (Truelsen, 2004). Of these, four were from Italy and three from the UK. There were no prevalence studies from the selected East-European countries. In all studies the prevalence increased with age. While stroke prevalence rates were higher in men in younger age groups several studies reported that women had the highest stroke prevalence rates in older age groups (Truelsen, 2004). Rates increased from approximately 5000/100 000 in subjects aged less than 75 years to 10 000 or more per 100 000 in those aged 80+.

The World Health Organization's estimates for stroke incidence and prevalence

The World Health Organization (WHO) has developed a method for estimating stroke incidence and prevalence for countries without data (Truelsen, 2004). The methodology is based on routine mortality statistics covering entire country populations, assuming that all subjects dying within the initial 28 days after stroke symptoms onset die due to stroke, and that it is possible to calculate three estimates for the 28 day case fatality that are relevant for all European countries. For the present analyses the 28 day case fatality was assumed to be 20% for all included countries, except Estonia, Hungary, Latvia, Lithuania, Slovakia and Slovenia where it was estimated to be 28%. Based on these assumptions the stroke incidence rate was estimated to be 235/100 000 equivalent to 1070 000 new stroke events per year. The stroke prevalence rate was estimated to be 1337/100 000 equivalent to 6090 000 prevalent stroke events per year. Comparisons of WHO stroke incidence estimates with those from 'ideal' studies suggest that there is a fair agreement (Truelsen, 2004). In some populations, however, reported and estimated rates differ markedly and it is emphasized that the WHO estimates only provide a rough overview of the stroke burden. When data from population-based studies were not available the WHO estimates were used in the present calculations for estimating the costs of stroke in Europe (Tables 1 and 2).

Strengths and weaknesses of epidemiological data

Many of the stroke studies are at a high scientific level and provide best possible stroke rates for the examined populations. The many studies from a few European countries indicate that collection of stroke data is possible both economically and practically, and that future investments in establishing studies would be successful in providing more and better data for improved health planning and stroke prevention.

A major problem for assessing the stroke burden in countries is that the coverage of data collection varies considerably. Even when 'ideal' epidemiological stroke data are available the source populations are unlikely to be representative for the remaining part of the country in which data were collected. Socio-economic differences including place of residence, years of education, occupation, access to medical control, and income are likely to vary among regions within a country as well as among countries. It is therefore not possible with confidence to generalize results from single studies. Furthermore, stroke occurrence studies are predominantly from Western European countries with low stroke mortality rates. Most countries in Eastern Europe have no data on stroke incidence or prevalence and this is likely to considerably hinder prevention and planning of management of stroke patients in the future in these countries.

The WHO's estimates for stroke provide rough country-level estimates for incidence and prevalence. However, with the limited amount of stroke data these estimates must be carefully interpreted. Routine mortality data form the basis for these calculations and it is well known from previous studies that such data are not ideal for epidemiological calculations (Bonita 1995; Stegmayr 1992). Case fatality may vary considerably between countries and within countries, yet the WHO estimates assume that 28 day case fatality is equal across many European countries. Where there is a lack of other data that could provide a better picture of the stroke burden these estimates may be used when no other information is available.

Cost data on stroke in Europe

Stroke cost data were available from 19 studies (Ekman 2004). One- or several-year costs were available from six different countries: Denmark, France, Germany, The Netherlands, Spain and Sweden, as was concluded in a recent study (Ekman, 2004). There was also a multicountry study that included patients from Denmark, Finland, France, Italy, Latvia, Lithuania, Poland, Portugal, Spain and the UK (Grieve, 2001). The multicountry study is valuable since it makes it possible to compare stroke costs across countries from several different European regions. However, it only included the costs in the first 3 months after stroke, which makes the results less suitable for estimating the total costs of stroke.

The majority of the available studies were incidence based, and usually covered the first year after stroke, but there were also some incidence-based studies that presented lifetime or at least long-term costs (Bergman, 1995; Kaste, 1998; Persson, 1990; Youman, 2003). Prevalence-based studied were less frequent, although there were examples of studies that partly used prevalence-based costs (Kaste, 1998; Terent, 1994). In Table 3, the total annual costs per patient are displayed for a selection of European countries.

Strengths and weaknesses of cost data on stroke

The studies are generally well presented, which makes it possible to explain differences in costs based on case mix and the type of stroke care provided (special stroke units, home care, etc.). The costs depend on type of care, age, gender and severity as measured, for example, by the Barthel index. Many studies were directly based on patient records and questionnaires (bottom-up design), which makes it possible to get a fairly detailed view of the resource consumption of stroke patients.

Most studies, however, are limited to patient recruitment from one single or a few hospitals, which makes it questionable if it is possible to generalize the results to a national level. Another problem is that most studies only cover the first-year costs, which are generally higher than the costs for subsequent years. A true incidence estimate of the costs would require a few years of follow-up. Also, several studies show the average costs of patients with stroke, but do not provide an estimate of the stroke-specific costs.

Most studies do not include costs for production losses (indirect costs). Since the average age is rather high for stroke patients (70+), however, the average indirect cost per patient is probably not very high in most countries.

Geographically, countries from north and west Europe are well represented among the studies, while data from east and southeast Europe are completely lacking.

Choice of studies to include in the model

The studies that were included in the model were chosen based primarily on how complete, representative and recent they were. As for epidemiological data, the data presented in Table 1 were included in the model estimations of stroke in Europe. In terms of cost data, only incidence-based studies were included, since a majority

Table 1 Stroke incidence estimates, The World Health Organization, men and women per 100 000 (from Truelsen, 2004)

	Austria		Belgium		Cyprus		Czech Republic		Denmark		Finland	
Age	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
25–34	13	10	19	12	10	5	17	7	30	15	23	12
35–44	26	20	37	23	20	11	33	14	60	30	46	24
45–54	153	69	139	84	83	40	271	119	194	80	201	74
55–64	324	172	312	186	229	134	678	347	351	184	384	191
65–74	877	613	812	550	672	463	1989	1449	882	580	987	653
75–84	1631	1376	1446	1237	1752	1726	3474	2918	1514	1250	1708	1391
85+	2005	1801	1754	1661	2535	2753	4056	3513	1771	1628	2009	1784

	France		Germany		Greece		Iceland		Ireland		Italy	
Age	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
25–34	19	9	14	9	21	11	11	9	14	21	14	8
35–44	37	18	28	17	42	21	23	19	28	42	27	16
45–54	131	49	131	60	215	98	107	74	126	99	124	63
55–64	253	109	316	152	533	288	212	187	315	192	295	154
65–74	630	364	899	588	1541	1216	690	647	877	672	918	585
75–84	1105	837	1696	1395	3131	3312	1381	1493	1621	1396	1946	1569
85 +	1325	1113	2096	1857	4032	4671	1697	1990	1992	1732	2521	2214

	Luxembourg		Malta		Netherlands		Norway		Portugal		Spain	
Age	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
25–34	15	18	16	10	11	12	13	8	47	20	12	8
35–44	31	36	32	20	21	25	26	17	93	39	24	15
45–54	146	103	153	81	119	93	123	69	362	149	132	57
55–64	366	231	381	203	284	175	287	148	842	390	298	143
65–74	988	721	1126	789	847	565	905	530	2299	1431	804	498
75–84	1852	1584	1870	1637	1567	1265	1796	1359	3769	3193	1413	1207
85 +	2314	2087	2098	2021	1889	1657	2234	1887	4262	4153	1682	1647

	Sweden		Switzerland		UK		Estonia		Latvia		Hungary	
Age	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
25–34	8	6	8	6	16	9	27	12	18	14	27	14
35–44	16	13	17	12	32	18	54	25	37	27	54	29
45–54	122	65	58	49	129	94	367	133	455	205	367	141
55–64	294	164	171	110	301	209	877	407	1155	587	877	332
65–74	841	535	515	329	845	652	1858	1171	2563	1645	1824	907
75–84	1579	1287	1074	822	1512	1453	2641	2473	3963	3539	2607	1680
5 +	1943	1767	1401	1158	1809	1925	2953	3284	4656	4757	2953	2070

	Lithuania		Poland		Slovakia		Slovenia	
Age	Men	Women	Men	Women	Men	Women	Men	Women
§	17	9	17	12	7	4	21	11
35–44	35	17	34	25	14	9	41	22
45–54	268	138	250	103	156	58	194	139
55–64	670	332	613	289	469	183	612	296
65–74	1404	882	1255	800	1132	631	1467	858
75–84	2029	1659	1619	1459	1568	1102	2344	1754
85+	2320	2081	1706	1792	1654	1251	2784	2244

Table 2 Stroke Prevalence Rates, Estimates from The World Health Organization, Men and Women per 100 000 (from Truelsen, 2004)

	Austria		Belgium		Cyprus		Czech Republic		Denmark		Finland	
Age	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
25–34	77	56	114	65	59	25	99	39	196	87	150	67
35–44	147	106	218	124	113	48	189	74	374	165	285	127
45–54	1163	634	1072	804	380	171	2037	1103	1607	775	1652	695
55–64	2246	1304	2185	1476	929	553	4604	2637	2658	1484	2887	1490
65–74	5359	3791	5052	3568	2354	1507	11 959	8965	5869	3820	6529	4168
75–84	8656	6807	7830	6260	4215	3112	18 711	15 171	8974	6554	10 032	7148
85+	10 619	8733	9403	8362	5998	4881	21 192	17 156	10 198	8342	11 497	8890

	France		Germany		Greece		Iceland		Ireland		Italy	
Age	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
25–34	118	50	83	46	114	55	66	52	85	132	79	42
35–44	225	95	158	87	217	104	126	99	161	252	150	80
45–54	1048	465	992	535	1481	838	788	702	950	1044	868	548
55–64	1849	857	2172	1122	3318	2037	1417	1464	2148	1708	1864	1114
65–74	4064	2324	5472	3524	8497	6996	3998	4140	5318	4777	5095	3416
75–84	6242	4218	8947	6646	14 616	14 686	7066	7537	8522	8178	9172	7038
85+	7371	5553	11 072	8759	19 308	21 217	8668	9954	10 454	9681	12 237	10 178

	Luxembourg		Malta		Netherlands		Norway		Portugal		Spain	
Age	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
25–34	95	107	99	58	62	73	72	42	282	109	68	40
35–44	180	203	188	111	119	139	138	80	538	208	130	76
45–54	1129	1022	1180	787	893	919	851	589	2770	1400	965	509
55–64	2552	1914	2666	1639	1924	1,464	1798	1060	5841	3020	1973	1061
65–74	6149	4854	6968	5167	5059	3780	4962	3049	14 151	9038	4714	3017
75–84	9872	8441	10 582	8878	8260	6752	8583	6060	21 026	16 185	7306	5698
85+	12 425	10 944	11 291	10 422	9824	8681	10 733	8534	22 701	20 578	8527	7805

	Sweden		Switzerland		UK		Estonia		Latvia		Hungary	
Age	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
25–34	43	32	48	33	93	50	106	52	72	57	95	55
35–44	81	62	91	63	177	94	222	108	150	119	198	104
45–54	827	554	415	455	952	857	1363	647	1661	984	1283	838
55–64	1800	1155	1094	847	2021	1,589	3326	2108	4320	2994	2862	2037
65–74	4550	3090	2933	2062	5016	4041	6153	4772	8326	6628	5608	6996
75–84	7428	5750	5132	3911	7918	7101	7631	6434	10 893	8994	6979	14 686
85+	9127	7953	6926	5639	9315	9288	7391	6669	11 456	9548	5942	21 217

	Lithuania		Poland		Slovakia		Slovenia	
Age	Men	Women	Men	Women	Men	Women	Men	Women
§	68	38	73	53	28	18	131	68
35–44	142	79	156	114	59	38	250	130
45–54	982	697	1228	661	710	349	1566	1418
55–64	2517	1769	2877	1523	2032	902	4432	2524
65–74	4603	3746	5569	3584	4583	2617	9714	5966
75–84	5710	4741	6492	4920	5816	3726	13 444	9760
85+	5742	4402	5296	4627	4757	3035	15 631	12 098

Table 3 Summary of selected studies

	Country	Cost categories	Population size	Costs per patients in PPP adjusted 2004 EUR (EUR Stat, 2004a; Eurostat, 2004b; European Central Bank, 2004)
Studies to include in the model:				
Carod-Artal *et al.* 1999[a]	Spain	Direct medical costs	118 patients	€5435 during the 1st year
Ghatnekar *et al.* 2004[a]	Sweden	Direct and indirect costs	4357 patients from Riks-Stroke, a nationwide register	€13 903 in direct costs during the 1st year
Grieve *et al.* 2000[a]	UK	Direct costs	328 patients from the South London Stroke Register	€7393 during the 1st year
Porsdal & Boysen 1999[a]	Denmark	Direct medical and non-medical costs	475 patients with intracerebral hemorrhage (90), cerebral infarct or unspecified stroke (385)	€9815 during the 1st year
Spieler *et al.* 2002	France	Direct medical costs	494 consecutive patients	€20 114 over 18 months (€13 409 per year)
Van Exel *et al.* 2003[a]	Netherlands	Direct medical costs and non-medical costs	598 consecutive patients	€16 048 over 6 months
Weimar *et al.* 2003[a]	Germany	Direct and indirect costs	586 patients	€20 239 over 1 years
Some additional studies:				
Andersson *et al.* 2002	Sweden	Inpatient costs and social services	121 patients	€26 557 during the 1st year
Bergman *et al.* 1995	Netherlands	Lifetime direct costs	24007 patients	€33 604 for women; €28 716 for men
Claesson *et al.* 2000	Sweden	Direct medical and non-medical costs	249 consecutive patients	About €25 493 during the 1st year
Dodel *et al.* 2004	Germany	Direct medical and non-medical costs	340 consecutive patients admitted for stroke (or TIA)	€3515 for ischemic stroke and €5131 for intracerebral hemorrhage (per admission)
Levy *et al.* 2003	France	Direct medical costs	Model + stroke pop. from CAPRIE trial	€6250 over 2 years (€3125 per year)
Patel *et al.* 2004	UK	Direct medical and non-medical costs	447 acute stroke patients randomly assigned to stroke unit, stroke team, or domiciliary stroke care	First year costs: €16 403 for stroke unit, €13 648 for stroke team, and €9799 for domiciliary stroke care
Terent *et al.* 1994	Sweden	Direct and indirect costs	162 +125 patients in two populations	€26 403 during the 1st year and €20 715 during the 2nd in the first population ($N = 162$). Slightly lower in the second pop.
Zethraeus *et al.* 1999	Sweden	Direct medical and indirect costs	25 consecutive patients	€23 666 during the 1st year

[a]Studies selected for the cost estimation of stroke in Europe.

of the available studies are of this kind. Incidence studies presenting the lifetime costs of stroke were not included (Grieve, 2001; Mamoli, 1999), primarily because there are fewer of them and it would be difficult to use these as a basis for the model. The exact studies that provide data for the estimation of the cost of stroke in Europe are marked in Table 3.

Discussion

The review of published stroke incidence and prevalence data from the EU, Iceland, Norway and Switzerland clearly demonstrate that there is an urgent need for more and better data. Especially East European countries have only few registries. The optimal goal is to establish community-based stroke incidence and prevalence studies in as many countries as possible including both hospitalized and non-hospitalized events, as well as fatal and non-fatal events. In addition, the development of a standard protocol or minimum data set would facilitate comparison between and within populations.

The experience from high-income countries is that 'ideal' stroke studies are extremely costly. It is unlikely that it will be possible in the near future to establish systems for complete registration of stroke events in all European countries. A first step may be to adhere to a standard protocol for collecting data on stroke patients admitted to health facilities, which is currently done, for example, in Sweden (RIKS STROKE) (Asplund, 2003). Development of a core set for surveillance of stroke is also known from, for example, the WHO where the Stepwise approach to Stroke Surveillance (STEPS Stroke) is currently tested in different countries within and outside Europe (Grieve, 2000).

The directions for further research in the economic burden of stroke in Europe follow naturally from the weaknesses of the data presently available. Cost studies on stroke would need to have longer follow-up, preferably at least 2 years after diagnoses. More focus on estimating the stroke-specific costs rather than the average costs of patients with stroke would also be valuable, even though it may be difficult to distinguish between costs for stroke and costs for comorbidities if prospective data are not available.

A common methodology for disease classification, standard cost variables, methods for projections of resource use, and survival over time is clearly needed in cost-of-illness studies of stroke, since there is presently a wide variety of methodologies and cost definitions (Porsdal, 1999). Different studies may not necessarily be comparable, since cost-of-illness studies can be conducted in a variety of ways with respect to methodology and the choice of diagnoses to include (Ekman, 2004; Porsdal, 1999; Payne, 2002). Further studies would also be needed to explain the differences in costs and treatment patterns across European countries.

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ORIGINAL ARTICLE

Cost of trauma in Europe

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Introduction

Approximately 1 600 000 head injured patients are admitted to hospital care in Europe (population 683 million), producing a brain injury rate of 235/100 000 and causing as many as 66 000 deaths per year (Kraus *et al.,* 2005). Costs of hospitalization vary by injury type, averaging according to US studies at $20 084 for gunshot wounds, $20 522 for motor vehicle crashes, $15 860 for falls, and $19 949 for blows to the head (McGarry *et al.,* 2002). Unfortunately, only scattered reports have been published on traumatic brain injury (TBI) epidemiology across Europe and very few include prevalence or cost data.

TBI is defined as an insult to the brain that leads to temporary or permanent impairments of cognitive abilities and physical functioning. Head injury results from an interaction between an individual and an external agent such as a mechanical force and contributes significantly to the outcomes in one half of all deaths from trauma (Kraus, 1987). This mechanical force may be related to road traffic accidents, falls (with or without alcohol consumption) and work/sport accidents. Trauma injures neural tissue by primary (direct brain tissue injury) or secondary mechanisms (increased intracranial pressure, ischemia related to general hypoxia and hypotension). The consciousness level is a valuable index of injury severity. Impairment of consciousness is stratified according to the Glasgow Coma Scale Scores (GCS) in terms of the responses to external stimuli. The lower the level of GCS on admission, the worse the outcome. Those patients with moderate or severe TBI who survive are often unable to return to full employment and require some degree of rehabilitation. This means that TBI is related to significant direct medical and non-medical costs in terms of hospitalization, outpatient care and rehabilitation, indirect costs due to lost productivity, and intangible costs due to reduced quality of life. This review provides an overview of existing epidemiological and economic evidence in TBI, and discusses the possibility of estimating the total costs of TBI in Europe. The results presented in this summary are described in more detail in previous publications (Kraus, 1987; Tagliaferri 2005).

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Methodology

We searched Medline for epidemiological articles published between 1980 and 2004. The search was undertaken using the terms 'epidemiology', 'head injury', 'trauma', 'brain injury' and 'Europe'. These terms were linked using the following combinations: 'epidemiology' plus 'head injury' or 'brain injury' and 'trauma' and 'Europe'. References from the retrieved reports were checked to identify other possible reports. The reports selected for review were limited to studies of European populations, without restrictions on age, gender or severity of TBI. While the search language was English, articles in French, German, Italian, Spanish and Portuguese were also included in the review if relevant. We studied the abstract in English of those papers in other languages. Data extracted (when available) included: country, number of patients, severity of trauma, incidence, male/female incidence ratio, hospital days, mortality, prevalence, cost of care and other relevant factors.

We identified 21 articles focusing on epidemiological descriptions of TBI. Nine reports were national population studies (Denmark, Spain, UK, Sweden, Finland, Portugal and Germany) and 12 studies focused on countries, provinces, or regions in Norway, Sweden, Italy, Switzerland, Spain, France, The Netherlands and the UK.

The review methodology and results of relevant health economic studies have been described in detail previously (Berg, 2004). Based on a literature search for studies containing cost data on TBI, three studies were identified containing some selected costs of TBI in European countries. Two of these studies focused on inpatient costs per treatment episode for TBI and mild TBI in Germany (Firsching and Woischneck, 2001) and Spain (Brell and Ibanez, 2001), respectively, while the third study contained a rough estimate for the costs of care and rehabilitation following severe TBI in the UK (Wood *et al.,* 1999). None of the studies were truly population based, but instead used secondary data, surveys or cohort information for their analysis. To complement the literature studies, data from the Swedish Hospital Discharge and Causes of Death registers were used to obtain comprehensive estimates for the costs of hospitalization and an estimate of the indirect costs due to early mortality. The ICD-10 codes most related to brain injuries were used for the register ana-

lysis: S02.1, S02.9, S06.0-S06.9 (intracranial injury) and S07.1. Cost data were inflated to the year 2004 with consumer price index, and converted to Euros adjusted for purchasing power (Eurostat, 2004a, b; European Central Bank, 2004).

Results

The incidence, gender ratio, age groups and the highest incidence by age are given in Table 1 for regional and national studies. A range of incidence rates for hospitalized patients has been reported from a high of 365/10^5/year in western Sweden (Andersson *et al.,* 2003) to a low of 83/10^5/year in Glasgow in the UK (Kay *et al.,* 2001). The overall average rate for hospitalized patients was about 235/10^5/year. Five out of 21 articles reported the incidence of TBI by age (Andersson *et al.,* 2003; Engberg Aa and Teasdale, 2001; Peloso *et al.,* 2004; Steudel *et al.,* 2004; Santos *et al.,* 2003). Peaks of incidence were reported in the second/third decades and over 70 years of age. There were no published reports on TBI prevalence rates in Europe and no data on the duration of sequalae from TBI at any level of severity or in different age groups.

Of the 21 studies included in this report, nine provided data on mortality rates directly or gave the basic elements of the rate to make a best guess. A range of in-hospital mortality rates has been reported from a high of 11.5/10^5/year in a German national study (Firsching *et al.,* 2001) to a low of 2/10^5/year in north Staffordshire, UK (Hawley *et al.,* 2003). In Table 1 the mortality rates for different studies are given. An average mortality rate of about 9.7/10^5/year of in-patients is derived from the available reports. Mortality rates vary in different groups of age. Peaks of mortality rates were reported in the third decade and over 70 years of age (Steudel *et al.,* 2004; Santos *et al.,* 2003; Masson *et al.,* 2001; Nardi *et al.,* 1999; Servadei *et al.,* 2002a, b).

Road traffic accidents and falls were the two main causes of TBI. While in southern Europe road traffic crashes constitute the vast majority of cases, falls (with or without alcohol consumption) are the leading cause of trauma in northern Europe. Only two studies, both in the UK, report assaults as a second cause of TBI after falls.

Based on the limited existing cost estimates, the average cost per inpatient with TBI in 2004 ranges from €2500 in Germany to €2800 in Spain and around €3000 in Sweden (cf. Table 2). Using conservative assumptions, the incidence-based inpatient costs derived from the Swedish Hospital Discharge register for patients admitted for TBI in 2001 were €4562 for the first year following admission. If all readmissions, regardless of diagnosis, were included, the corresponding 1-year cost would amount to €7120 per TBI patient. The costs for men were 16% higher than for women. Inpatient costs also increased with age, with relative peaks seen for the age groups 15–24, 50–59 and 70–84 years.

Based on analysis of the Swedish Causes of Death register, the average number of life years lost per person dying of TBI as a multiple cause of death is 20 years, of which almost 10 years still could be productive working years. Men accounted for 71% of all deaths due to TBI, with an average age of death of 58 years, compared with 68 years for women. This results in considerable lifetime costs due to TBI mortality, on average €375 000 per death in Sweden.

Discussion

While the incidence describes the occurrence of new cases in the population over a period of time, the prevalence describes all cases in the population at a particular time and is a measure of both new and established cases. Therefore, the prevalence rate is better for an accurate cost calculation. As mentioned before, there are no published reports on TBI prevalence rates in Europe and no data on the duration of sequalae from TBI, which makes even best guesses impossible.

The rate of hospital admissions for TBI across Europe is high (235/10^5/year) when compared with a recent 98/10^5/year published by Thurman for the USA (Thurman *et al.,* 1999). This difference is entirely due to broader admission criteria for mild head injured patients (GCS 14–15) in Europe compared with the USA. The main problem in comparing different European incidence results is that some studies in this review present different case definitions and patient inclusion rules. Most rates include hospitalized patients (regardless of outcome) plus deaths identified from local authorities (Firsching, 2001; Andersson *et al.,* 2003; Engberg Aa and Teasdale, 2001; Santos *et al.,* 2003; Tiret *et al.,* 1990). Some include only hospitalized patients (Ingebrigtsen *et al.,* 1998; Vazquez-Barquero *et al.,* 1992), others include patients only if treated neurosurgically (Annoni *et al.,* 1992) and some others include patients from national registers (Kleiven *et al.,* 2003; Alaranta *et al.,* 2000). These features obviously contribute to the large range of incidence and mortality rates of TBI across Europe.

A somewhat surprising finding of our study is the systematic difference concerning the causes of trauma observed between northern Europe (UK and Scandinavia) on the one hand and continental and southern Europe on the other hand. The prevalence of falls as the main cause of trauma in the north and of road traffic accidents in the south is also confirmed by a recent multicentre study (Hukkelhoven *et al.,* 2002). This may

Table 1 Incidence, mortality rate, severity of trauma, gender ratio and highest incidence by age[a]

Country	Year of study	Incidence	Mortality/10^5/ year	Severity of trauma	Highest incidence by age (years)	Male/female	First cause of TBI	Second cause of TBI
France (Aquitaine) (Masson *et al.*, 2001)	1996	17.3	5.2	severe TBI	> 70	2.4	RTA (48%)	fall (42%)
Italy (Friuli,Venezia,Giulia) (Nardi *et al.*, 1999)	1998	176[BG]	N/A	H.P.	N/A	N/A	N/A	N/A
Italy (Romagna) (Servadei *et al.*, 2002a)	1998	250	N/A	H.P.	1–4	1.6	RTA (48%)	fall (33%)
Italy (Romagna & Trentino) (Servadei *et al.*, (2002b)	1998	314	7.7	H.P.	20 to 30 & > 70	1.6	fall (33%)	RTA (48%)
Netherlands (Maastricht) (Meerhoff *et al.*, 2000)	1997	88	N/A	H.P.	[a]	2	fall (43%)	RTA (22%)
Norway (Troms) (Ingebrigtsen *et al.*, 1998)	1993	169	N/A	H.P.	10–24 & > 80	1.7	fall (62%)	RTA (21%)
Sweden (Western) (Andersson *et al.*, 2003)	1992	365[BG]	4	H.P.	0–9	1.46	fall (58%)	RTA (16%)
UK (Glasgow) (Kay *et al.*, 2001)	1995	83[BG]	N/A	H.P.	N/A	N/A	fall (43%)	assault (34%)
UK (North Staffordshire) (Hawley *et al.*, 2003)	1992	280	2[BG]	H.P.*	< 2 (18%)	1.9	fall (60% under 2)	RTA (37% from 10 to 15)
Spain (Cantabria) (Vazquez-Barquero *et al.*, 1992)	1992	91	N/A	[a]	[a]	2.7	RTA (60%)	fall (24%)
Switzerland (St. Gallen) (Annoni *et al.*, 1992)	1992	20	N/A	NS treated^	N/A	3.1	N/A	N/A
France (Aquitaine) (Tiret *et al.*, 1990)	1986	282	22	H.P.	< 5 & 15–24 & > 75	2.1	RTA (60%)	fall (33%)
Denmark (Engberg Aa and Teasdale, 2001)	1991–1993	157	10.7	H.P.	> 60	1.7	N/A	N/A
Germany (Firsching and Woischneck 2001)	1996	341[BG]	11.5	H.P.°	N/A	2.4	RTA (56%)	RTA (56%)
Germany (Steudel *et al.*, 2004)	1998	337	9.7	H.P.	N/A	N/A	N/A	N/A
United Kingdom (Kay, 2001)	2001	322[BG]	10	H.P.	N/A	N/A	fall (40%)	assault (20%)
Sweden (Peloso *et al.*, 2004)	1987–2000	175	N/A	mild TBI	0–25 & > 65	1.4	N/A	N/A
Sweden (Kleiven *et al.*, 2003)	1987–2000	259	N/A	all TBI	15–19 & > 75	2.1	fall (54%)	RTA (26%)
Spain (Brell and Ibanez 2001)	1999	227[BG]	N/A	mild TBI	N/A	N/A	N/A	N/A
Finland (Alaranta *et al.*, 2000)	1991–1995	100	N/A	H.P.	[a]	[a]	fall (61%)	RTA (26%)
Portugal (Santos *et al.*, 2003)	1996	137	N/A	H.P.	20–29	1.8	N/A	N/A

[a][BG] best guess; N/A not available; [a] data from the abstract, * children only, ^ neurosurgically treated, ° moderate and severe H.P; H.P: hospitalised patients; RTA road traffic accident.

Table 2 Average cost (€ 2004) per inpatient with traumatic brain injury in three European countries[a]

Country	Average inpatient with TBI (€)	Inpatient with concussion (€)	Inpatient with severe brain injury (€)
Germany	2529	1071	6647[b]
Sweden[d]	3024	927[b]	6045
Spain[c]	2833	987	6362

[a]Costs were inflated with consumer price index, and converted to Euros adjusted for purchasing power (Eurostat, 2004a, b; European Central Bank, 2004).

[b]Average of several relevant costs in each country.

[c]For Spain, ratios between costs in Sweden and estimated costs for minor head injury (concussion) using German data on length of hospital stay were used to estimate average cost per inpatient with TBI and with severe brain injury.

[d]Estimate used in the model estimation for cost of trauma in Europe.

cause differences in the admitted population since TBI related to falls are milder than road traffic related accidents. Except for the UK, assault- and violence-related injuries do not constitute a problem in Europe yet, differently from the USA (Adekoya, 2004). European data on mortality are lower than published data for the US ($30/10^5$/year) (Kraus *et al.,* 1984) and much lower than data from South Africa ($81/10^5$/year) (Nell and Brown 1991) and Colombia ($120/10^5$/year) (Gutierrez *et al.,* 2000).

It is at this stage not possible to provide any sound estimate for the total costs of TBI in Europe due to the lack of essential data on medical outpatient care, direct non-medical services and indirect costs. The little existing data mainly focuses on hospital care, and often only applies to selected TBI patients. In this respect, the Swedish register analysis is likely to provide the most up-to-date and comprehensive assessment of inpatient costs. The differences in healthcare systems between the USA and Europe make the Swedish inpatient statistics more suitable for a conservative estimate of the cost of TBI as part of the European cost of brain disorders. While these costs are probably not representative of either common care patterns or of TBI patients overall, they suggest that costs due to acute hospitalization are only a small part of the direct and total costs of TBI.

To obtain a ballpark figure for total costs, it is of interest to consider evidence from the USA, where more research has been conducted in this area. According to a US study (Max *et al.,* 1991) using 1984–86 data, the average lifetime cost per TBI case was $197 163 (scaled to 2004 price levels). Total lifetime costs associated with all head injuries resulting in death or hospitalization in 1985 were thus estimated to $64.6bn (2004 prices), with 65% of costs being attributable to survivors and 35% to fatalities. The study also showed that the lifetime economic costs of TBI are dominated by indirect costs, which account for 88% of the total burden, and most of the direct costs are incurred in the acute hospital setting. However, only the cost of brain injuries resulting in hospitalization were included and the results did not cover direct medical and non-medical costs such as cognitive rehabilitation, neuropsychological services, or different types of living and support services, nor did they consider the costs of informal care. Therefore, it is likely that that direct costs actually account for a larger proportion of total costs; overall, the above figures are likely to be conservative estimates. Thompson and colleagues (Thompson *et al.,* 2001) also highlighted the difficulties of obtaining comprehensive and consistent data on resource use related to TBI, such as the identification of all relevant patients, the inclusion of injuries that do not result in hospitalization, and the tracking of long-term outcomes.

In the case of TBI, the incidence and care patterns can vary substantially across countries. Therefore, it is extremely difficult to generate any European-wide estimate of the total costs of TBI on the basis of the scarce existing data. Furthermore, the little existing evidence refers to different timeframes, which makes combination of the data impossible. Any estimate can only constitute speculation at this point. There are two ways in which the limited existing evidence could be used for two types of best guess:

- Using the 1-year cost of inpatient care for Sweden (€4562 per admitted patient) as a basis for extrapolation to other countries, adjusting for relative and absolute differences in price levels, combined with an average incidence rate for Europe. While there is not a well-defined pattern for the incidence of TBI across Europe, the incidence rate of $235/10^5$/year for hospitalized patients can be considered a best guess for a European average at this stage.
- Applying the conservative US estimate of total lifetime costs per TBI case of $197 163 (€168 100, not adjusted for price level index), adjusting for differences in price levels between the USA and Europe, as well as between European countries. This can again be combined with the assumed incidence rate of $235/10^5$/year for hospitalized patients across Europe. Since the distribution of direct and indirect costs for TBI is likely to vary across countries and is not necessarily similar to the one found in the USA, the assumption that indirect costs account for 88% of total lifetime costs in Europe would have to be used bearing this important caveat in mind.

The first estimate has the benefit of being based on inpatient data for one European country, whereas the second estimate is a rough application of total lifetime costs from the USA to the whole of Europe. Both approaches are based on the assumption that epidemi-

ological and treatment patterns do not vary across countries or regions. Although this is likely not to be the case, particularly considering the heterogeneity within Europe, it is the best estimate that can be derived on the basis of currently existing information. The differences in healthcare systems between the US and Europe make the Swedish inpatient statistics more suitable for a conservative estimate of the cost of TBI as part of the European burden of brain disorders.

Conclusions

Twelve countries in Europe have reported their epidemiological data regarding TBI. These reports contain incidence of TBI on a national or regional level, main causes of trauma and gender features. There are few data about incidence by age, mortality rates and practically no data about prevalence of TBI and the costs of the condition. European data (mainly for incidence and trauma causes) differ from US-based studies and therefore a straightforward application of US studies to Europe is not feasible. Future study directions will include prevalence data that are now unavailable in Europe.

Overall, economic evidence on TBI is presently scarce in Europe. Available information is mostly related to hospital treatment, which probably only constitutes a relatively small component of overall costs resulting from TBI. In light of this, there is a strong need for comprehensive cost-of-illness studies in this area that address both direct and indirect costs. The lifetime costs of TBI should be assessed through long-term population and register studies. Since mild TBI cases may not always be captured in national databases, it is also important to stratify the costs by severity, using a standard measurement scale. As a longer term goal, a relevant measurement tool to assess quality of life in patients should be developed, as the intangible costs of TBI are likely to be substantial.

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