The global burden of cerebrovascular disease

Thomas Truelsen[1], Stephen Begg [2], Colin Mathers[2]

1. Introduction

The 1990 Global Burden of Disease (GBD) study provided the first global estimate on the burden of 135 diseases, and cerebrovascular diseases ranked as the second leading cause of death after ischemic heart disease [1]. The best possible sources of information on the different disease were used, and for countries or regions where no data were available, extrapolations from populations in neighboring countries were used to estimate the disease pattern. During the past decade the quantity of especially routine mortality data has increased, and is now covering approximately one-third of the world's population. The increase in data availability provides the possibility for updating the estimated global burden of stroke.

Data on causes of death from the 1990s have shown that cerebrovascular diseases remain a leading cause of death. In 2001 it was estimated that cerebrovascular diseases (stroke) accounted for 5.5 million deaths world wide, equivalent to 9.6 % of all deaths [2]. Two-thirds of these deaths occurred in people living in developing countries and 40% of the subjects were aged less than 70 years. Additionally, cerebrovascular disease is the leading cause of disability in adults and each year millions of stroke survivors has to adapt to a life with restrictions in activities of daily living as a consequence of cerebrovascular disease. Many surviving stroke patients will often depend on other people's continuous support to survive.

Cerebrovascular diseases can be prevented to a large extend and providing an entry point for public health initiatives to reduce the burden of stroke within a population. However, to direct such initiatives data on the burden of cerebrovascular disease are necessary and the GBD2000 is a means to provide such information for all regions of the world.

This document describes the background for the calculations behind the GBD2000 estimates on stroke. It outlines the estimated rates on incidence, prevalence, and prevalence of disability, mortality rates, case-fatality and duration of stroke related diseases.

1.1 Definition and pathogenesis of stroke

1.1.1. Definition of stroke

The World Health Organization (WHO) definition of stroke is: "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of

[1] Non-communicable Diseases and Mental Health Cluster, WHO Geneva (CCS/NMH)

[2] Epidemiology and Burden of Disease, WHO Geneva (EBD/GPE)

vascular origin" [3]. By applying this definition transient ischemic attack (TIA), which is defined to last less than 24 hours, and patients with stroke symptoms caused by subdural hemorrhage, tumors, poisoning, or trauma are excluded.

1.1.1 Types of stroke

The pathological background for stroke may either be ischemic or hemorrhagic disturbances of the cerebral blood circulation.

1.1.2 Ischemic stroke (infarction)

Thrombotic cerebral infarction results from the atherosclerotic obstruction of large cervical and cerebral arteries, with ischemia in all or part of the territory of the occluded artery. This can be due to occlusion at the site of the main atherosclerotic lesion or to embolism from this site to more distal cerebral arteries.

Embolic cerebral infarction is due to embolism of a clot in the cerebral arteries coming from other parts of the arterial system, for example, from cardiac lesions, either at the site of the valves or of the heart cardiac cavities, or due to rhythm disturbances with stasis of the blood, which allows clotting within the heart as seen in atrial fribrillation.

Lacunar cerebral infarctions are small deep infarcts in the territory of small penetrating arteries, due to a local disease of these vessels, mainly related to chronic hypertension.

Several other causes of cerebral infarction exist and are of great practical importance for patient management. As they are relatively rare they can be ignored for most epidemiological purposes.

1.1.3 Hemorrhagic stroke

Spontaneous intracerebral hemorrhages (as opposed to traumatic ones) are mainly due to arteriolar hypertensive disease, and more rarely due to coagulation disorders, vascular malformation within the brain, and diet (such as high alcohol consumption, low blood cholesterol concentration, high blood pressure, etc.).

Cortical amyloid angiopathy (a consequence of hypertension) is a cause of cortical hemorrhages especially occurring in elderly people and it is becoming increasingly frequent as populations become older.

1.1.4 Subarachnoid hemorrhage

This group of strokes is mainly due to the rupture of aneurysms at the bifurcations of large arteries at the inferior surface of the brain. Often they do not cause direct damage to the brain and some studies of stroke have therefore excluded them. However, patients with subarachnoid hemorrhage may develop symptoms that are in accordance with the stroke definitions and should as such be regarded as a stroke.

1.2 Natural history of stroke

In demographically developed countries, the average age at which stroke occurs is around 73 years reflecting the older age structure of these countries. The probability of a first stroke or first transitory ischemic attack is around 1.6 per 1,000 and 0.42 per 1,000, respectively [4]. In less developed regions, the average age of stroke will be

younger due to the different population age structure resulting from higher mortality rates and competing causes of death.

Stroke patients are at highest risk of death in the first weeks after the event, and between 20% to 50% die within the first month depending on type, severity, age, co-morbidity and effectiveness of treatment of complications. Patients who survive may be left with no disability or with mild, moderate or severe disability. Considerable spontaneous recovery occurs up to about six months [5]. However, patients with a history of stroke are at risk of a subsequent event of around 10% in the first year and 5% per year thereafter [6].

The proportion of patients achieving independence in self-care by one year after a stroke ranges from around 60% to 83% [7]. This wide variation relates to whether the studies are community based or hospital based, which activities are considered in estimating independence, and the methods used to rate ability. In established marked economies (EMEs), depending on the organization of hospital services, between 10% and 15% of survivors are resident in an institution at one year.

1.3 Distribution of stroke by type

In Caucasian populations approximately 80% of all strokes are ischemic, 10%-15% intracerebral hemorrhage (ICH), 5 % subarachnoid hemorrhage (SAH), and the rest is due to other causes of stroke [8]. Studies from Asian countries indicate that the proportion of ICH is higher than in Caucasians with approximately 20 % to 30% being hemorrhagic [9-12 13]. Higher numbers are criticized for being due to lack of CT scanning and for not complying with standard criteria for stroke identification [10;11]. A recent review on stroke epidemiology data in Hong Kong, Taiwan, South Korea, Singapore, Malaysia, Thailand, Philippines and Indonesia, reported that the proportion of ischemic and hemorrhagic strokes varied from 17 % to 33 % [12].

There are limited data sources on type of stroke from other parts of the world. For the Eastern Mediterranean Region (EMR) hospital-based studies have indicated that type of stroke pattern may be similar to that of Western countries [14] whereas others have found a higher proportion of hemorrhagic events [15;16]. The hospital-based stroke register from Buenos Aires, Argentina, have reported that ICH is more frequently occurring in natives than in Caucasians [17]. However, to what extend these findings from hospital registries can be generalized to the rest of the population remains unclear. Studies on stroke type from Africa are generally limited by small sample sizes and being hospital-based [18-20]. A recent review found that of scanned patients the proportion of cerebral hemorrhage was 26 % to 33 % [21].

Occurrence of ICH is related to level of blood pressure, and to level of blood cholesterol concentration where there seems to be an inverse relationship[22;23]. It is therefore plausible, that in areas with increasing blood pressure, with low-cholesterol intake, and with poor access to blood pressure lowering drugs/control of blood pressure there will be more hemorrhagic strokes than in for example Western populations. In addition, other risk factors such as tobacco smoking, physical activity, and alcohol intake may have an effect on the occurrence of ICH. Therefore, the proportion of hemorrhagic stroke is likely to vary from around 15% in affluent populations to a max. of 30 % in Asian countries. In the Comparative Risk Assessments analyses mean cholesterol levels were used to estimate the proportion of strokes that were due to hemorrhagic and ischemic stroke. The results from this study suggested a range in the proportion of hemorrhagic stroke from 15% in Europe and

North America, to 30% in the South-East Asian Region (SEAR) and Western Pacific Region (WPR).

As stroke patients with hemorrhagic stroke have higher short-term case fatality than patients with ischemic stroke events the 28-day case fatality will be higher in populations with higher proportions of hemorrhagic strokes. In the present analyses this is reflected in the higher 28-day case fatality rates in other regions than the EME. We have not been able to correct for possible differences in long-term survival for stroke survivors according to type.

1.4 Risk factors for cerebrovascular disease

Many risk factors for stroke have been described. They may refer to inherent biological traits such as age and sex, physiological characteristics that predict future occurrence such as high blood pressure, serum cholesterol, fibrinogen; behaviors such as smoking, diet, alcohol consumption, physical inactivity; social characteristics such as education, social class and ethnicity; and environmental factors that may be physical (temperature, altitude), geographical, or psychosocial [24]. In addition, medical factors including previous TIA or stroke, ischemic heart disease, atrial fibrillation, and glucose intolerance, all increase the risk of stroke.

At a population level, blood pressure and tobacco use are the two most important modifiable risk factors for stroke due to their strong associations, high prevalence and the possibility for intervention. Epidemiological research has shown that raised blood pressure is the single most important risk factor for ischemic stroke with a population attributable risk of 50% [25]. The risk of stroke rises steadily as blood pressure level rises and doubles for every 7.5 mm Hg increment in diastolic blood pressure, with no lower threshold. Treatment with anti-hypertensive treatment has been shown to reduce stroke risk by about 38 % [22;26].

Tobacco use increases the risk of ischemic stroke about two-fold and is furthermore also associated with a higher risk of hemorrhagic stroke [27]. There is a dose-response relationship so that heavy smokers are at a higher risk of stroke than light smokers. Until recently studies of tobacco use and stroke focused on smokers risk, however, exposure to environmental tobacco smoking is also an independent risk factor for stroke [28]. This study suggested that previous analyses based on reference groups without differentiating exposure between non-smokers might have led to a general underestimation of the risk of stroke in smokers.

While most studies of risk factors for ischemic stroke are based on data from populations in developed countries, there is some evidence from developing countries that many of the risk factors are similar including blood pressure, tobacco use, and obesity [29-32]. There is an estimated 1.2 billion smokers worldwide [33]. In China alone there are 300 million smokers. A review on obesity from Latin-American countries showed that the prevalence of over-weight people, especially in urban areas, may be as high as the prevalence reported in developed nations [34]. The present knowledge on the prevalence of major risk factors in developing countries is, however, very limited and it was not possible to integrate correction for trends in risk factors and the likely change in stroke rates for the calculations of the global burden of stroke. However, it is believed, that the prevalence of stroke risk factors globally has increased more than improvements in prevention, why stroke rates are likely to be higher in the GBD2000 study than in the GBD1990 study.

2. Mortality due to cerebrovascular disease (YLLs)

Cerebrovascular disease is a general term encompassing different disturbances of the vascularisation of the brain. In the International Classification of Diseases (ICD) 9th and 10th revision, cerebrovascular diseases are referred to with the codes 430 to 438 and I60 to I69. As indicated only a subgroup of cerebrovascular diseases is stroke according to the definition. The following diagnoses of cerebrovascular diseases are typical stroke diagnoses: subarachnoid hemorrhage (ICD9: 430;ICD10: I60), intracerebral hemorrhage (ICD9: 431; ICD10: I61), acute but ill-defined cerebrovascular disease (ICD9: 436), cerebral infarction (ICD10: I63), and stroke (ICD10: I64). The vast majority of deaths due to cerebrovascular diseases are due to stroke.

ICD 9 and 10 codes for cerebrovascular diseases

ICD-9 code	ICD-10
430: Subarachnoid hemorrhage	I60: Subarachnoid hemorrhage
431: Intracerebral hemorrhage	I61: Intracerebral hemorrhage
432: Other and unspecified intracranial hemorrhage	I62: Other non-traumatic hemorrhage
433: Occlusion and stenosis of precerebral arteries	I63: Cerebral infarction
434: Occlusion of cerebral arteries	I64: Stroke
435: Transient cerebral ischemia	I65: Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction
436: Acute but ill-defined cerebrovascular disease	I66: Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction
437: Other and ill-defined cerebrovascular disease	I67: Other cerebrovascular diseases
438: Late effects of cerebrovascular disease	I68: Cerebrovascular disorders in diseases classified elsewhere
	I69: Sequelae of cerebrovascular disease

2.1 GBD 2000 analyses of deaths by cause

Causes of death for the WHO sub-regions and the world were estimated for Version 1 of the GBD 2000 based on data from national vital registration systems that capture about 17 million deaths annually. In addition, information from sample registration systems, population laboratories and epidemiological analyses of specific conditions have been used to improve estimates of the cause of death patterns [35-38]. WHO is intensifying efforts with Member States to obtain and verify recent vital registration data on causes of death and Version 2 of the GBD 2000 estimates of deaths by cause were published in the World Health Report 2002 [2]. Estimates for stroke by 17 WHO regions are presented in Table 1.

The Years of life Lost due to stroke is presented in the Figures 1 to 4 for 8 WHO regions.

The world estimate for YLL to stroke for men and women in 1990 and 2000 is almost identical for both men and women. However, the overall estimate covers that the YLLs to stroke have decreased substantially especially in the African region. The devastating AIDS epidemic on the African continent has profoundly altered the cause of death pattern within the past 10 to 15 years. In contrast, the YLLs have increased markedly in the Former Socialistic Economies (FSE).

Cause of death data have been analyzed to take into account incomplete coverage of vital registration in countries and the likely differences in cause of death patterns that would be expected in the uncovered and often poorer sub-populations. Techniques to undertake this analysis have been developed based on the global burden of disease study and further refined using a much more extensive database and more robust modeling techniques.

Special attention has been paid to problems of misattribution or miscoding of causes of death in cardiovascular diseases, cancer, injuries and general ill-defined categories.

A correction algorithm for reclassifying ill-defined cardiovascular codes has also been developed and applied.

Table 1: Estimated stroke mortality rates per 100,000 in 17 WHO regions, the GBD2000

	AFRO-D		**AFRO-E**		**AMRO-A**		**AMRO-B**		**AMRO-D**		**EMRO-B**		**EMRO-D**		**EURO-A**		**EURO-B1**	
Age groups	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
0-4	2	3	2	3	1	1	1	1	2	6	2	2	20	12	1	0	6	6
5-14	1	1	1	0	0	0	1	0	1	2	1	1	8	5	0	0	2	1
15-29	4	4	5	5	1	1	2	2	4	4	2	1	8	3	1	1	6	5
30-44	24	17	31	15	5	4	13	13	13	12	6	6	9	5	5	4	21	17
45-59	87	113	89	104	22	17	75	57	60	48	41	46	56	46	25	16	111	73
60-69	274	366	269	377	78	60	257	177	193	142	209	173	257	242	117	66	467	327
70-79	778	1086	781	1,155	270	230	666	499	544	429	680	614	752	741	453	338	1,206	1,041
80+	2091	3696	2,092	3,591	1,018	1,180	1,792	1,792	1,595	1,554	2,318	2,221	1,963	1,967	1,779	1,797	3,227	3,182
All ages	37	60	36	57	46	74	52	53	35	35	32	33	41	43	89	130	134	158
	EURO-B2		**EURO-C**		**SEARO-B**		**SEARO-D**		**WPRO-A**		**WPRO-B1**		**WPRO-B2,**		**WPRO-B3**			
Age groups	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F		
0-4	0	0	1	1	2	2	3	2	0	0	2	1	2	2	6	5		
5-14	0	0	0	0	1	1	1	1	0	0	0	0	0	0	2	1		
15-29	1	1	4	2	3	2	2	1	1	1	2	1	2	1	8	3		
30-44	16	9	31	14	12	10	6	4	8	4	11	7	10	8	20	16		
45-59	131	92	188	101	79	73	96	67	42	21	104	73	100	70	137	112		
60-69	550	433	767	451	319	309	476	408	139	68	519	333	521	384	518	465		
70-79	1,156	1,157	1,809	1,451	941	951	1,140	1,141	435	257	1,537	1,273	1,413	1,214	1,606	1,400		
80+	3,346	3,155	4,772	5,219	1,902	1,968	2,086	2,207	1,840	1,549	3,725	3,700	3,126	3,185	2,791	2,212		
All ages	78	103	229	347	54	62	65	68	99	109	116	124	80	81	61	55		

Figure 1: Years of Life Lost (YLL) to stroke per 1,000 in men in 1990 and 2000

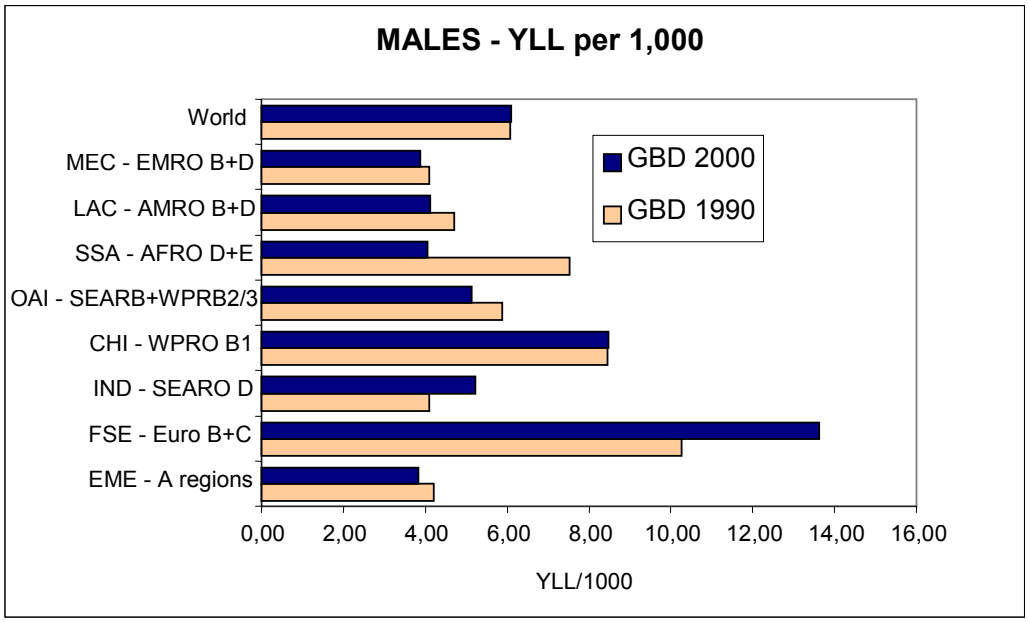


Figure 2: Years of Life Lost (YLL) to stroke per 1,000 in women in 1990 and 2000

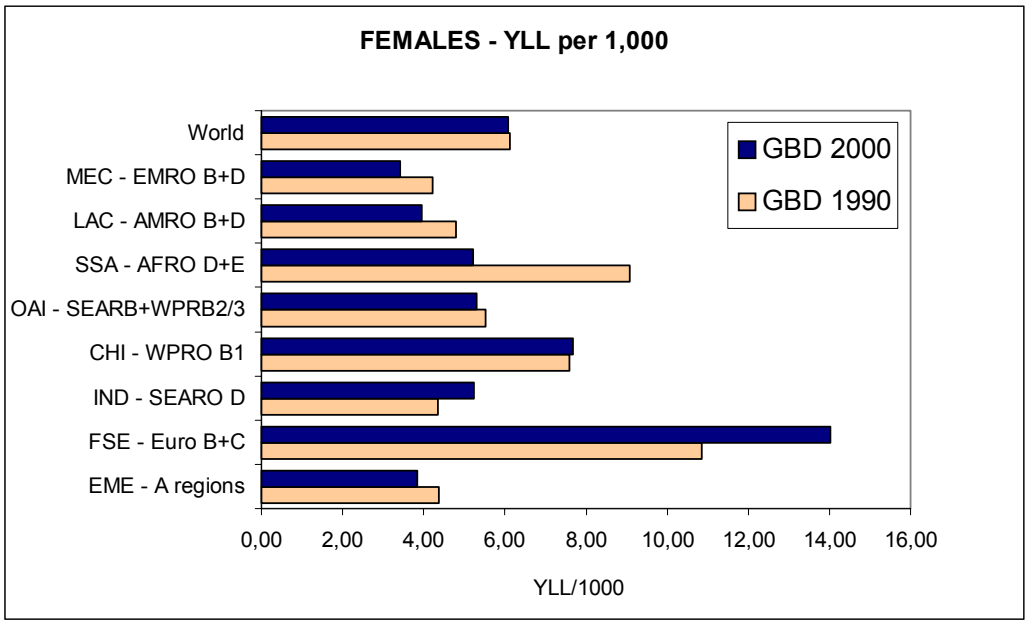


Figure 3: Years of Life Lost (YLL) to stroke per 1,000 in men in 1990 and 2000, by age

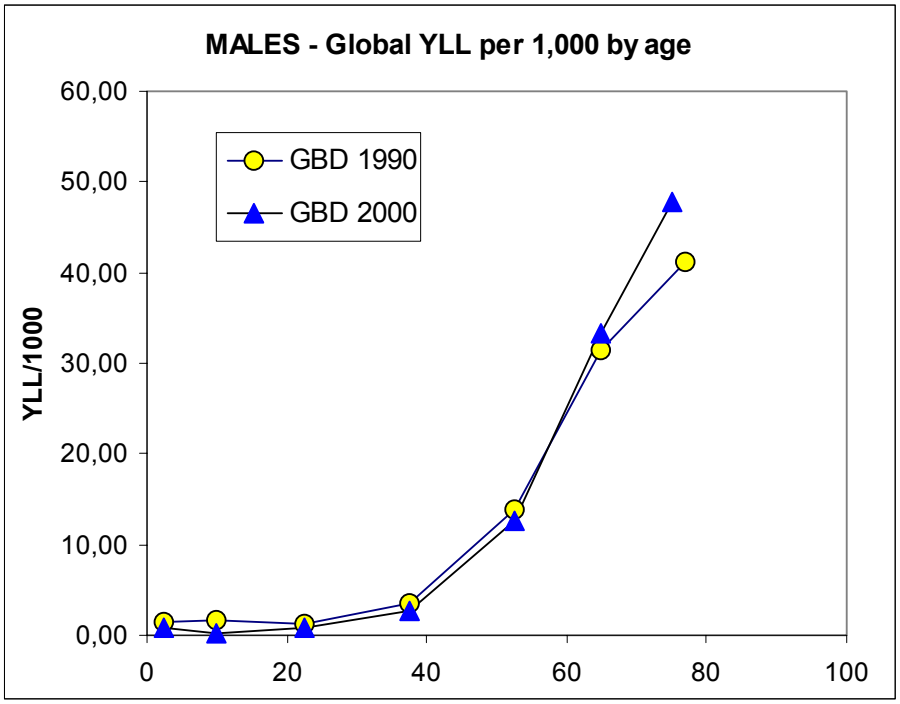
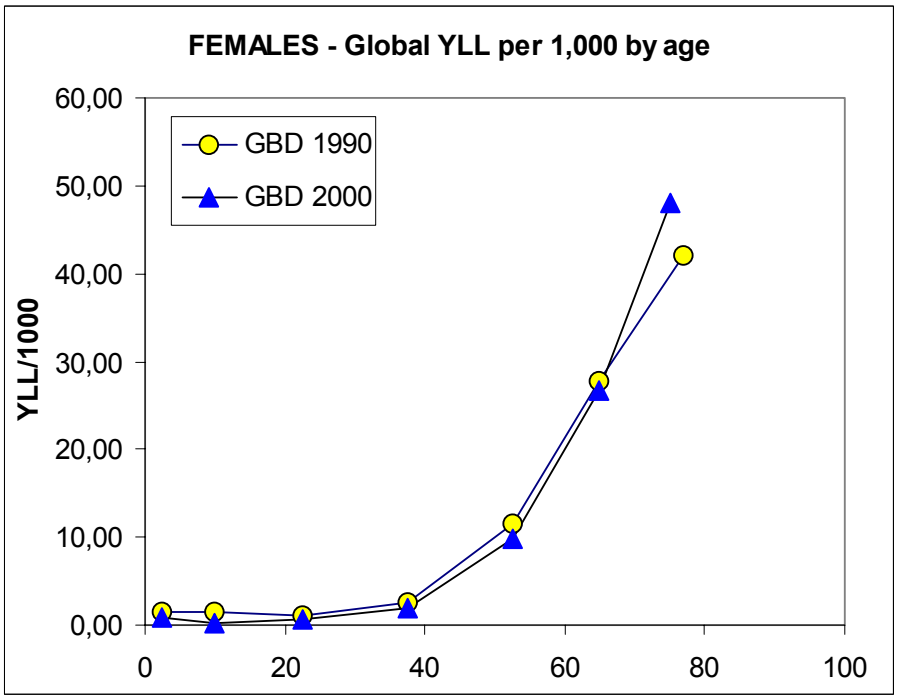


Figure 4: Years of Life Lost (YLL) to stroke per 1,000 in women in 1990 and 2000, by age



As a general rule, vital registration data, suitably corrected for ill-defined coding and probable systematic biases in certifying deaths to non-specific vascular, cancer and injury codes were used to estimate cause of death patterns. Vital registration data to do so was available for 65 countries for Version 1 of the GBD 2000. In a further 28 countries, cause of death models were used to correct vital registration data by age and sex to yield patterns across Groups I, II and III adjusted for under-registration. The distribution of specific causes within groups was then based on the recorded cause of death patterns from vital registration data. The resulting estimates were then systematically corrected on the basis of other epidemiological evidence from registries, community studies and disease surveillance systems.

For China and India, cause patterns of mortality were based on existing mortality registration systems, namely the Disease Surveillance Points system (DSP) and the Vital Registration System of the Ministry of Health in China, and the Medical Certificate of Cause of Death (MCCD) for urban India and the Annual Survey of Causes of Death (SCD) for rural areas of India. For all other countries lacking vital registration data, cause of death models were used to firstly estimate the maximum likelihood distribution of deaths across the broad categories of communicable, non-communicable and injuries, based on estimated total mortality rates and income *(26)*. A regional model pattern of specific causes of death was then constructed based on local vital registration and *verbal autopsy* data and this proportionate distribution was then applied within each broad cause group. Finally, the resulting estimates were then adjusted based on other epidemiological evidence from specific disease studies.

Using these methods, deaths due to cerebrovascular disease (ICD 9 codes 430 through 438, and ICD 10 codes I60-I64 and I67) were estimated by age and sex for all 191 WHO Member States. The Version 1 estimates of deaths by cause are available for 14 subregions of the 6 WHO regions on the WHO website at www.who.int/evidence/bod.

2.2 Identification of stroke deaths in vital registration data

Information form routine mortality statistics were essential for calculating the YLLs. Validity studies of routine mortality data on stroke have shown that this source of information is of varying quality [10;39-45]. A validation study from the Northern Sweden MONICA population found that routine mortality statistics based on death certificates with cerebrovascular disease (ICD codes 430-438) provided a fair estimate of fatal stroke cases [40].The study included stroke patients aged 25 to 74 years, thus, the age groups where the bulk of stroke events occur were not included. The authors estimated the proportion of non-stroke events that was classified as stroke (false-positive) and the proportion of stroke events that were misclassified as non-stroke deaths (false-negative). Of 980 true stroke deaths, routine mortality statistics provided an estimated 899 (91.7%) stroke deaths, which emerged as a result of 10% false positive, 17% false-negative, and the remainder correctly registered.

In the Auckland stroke study (NZ) it was reported that only one third of cases where the underlying cause of death was attributed to stroke, did the event meet the WHO criteria for a stroke [39]. Most of the excluded events occurred in very elderly people in whom diagnosis was difficult in the presence of multiple pathology, or where unwitnessed sudden death had occurred. However, the study did not provide information on what diagnoses was applied instead, and there were no data on how

common misclassification of stroke events were to other disease categories (false-negative).

In the POLMONICA study the study stroke deaths were compared with the stroke deaths registered at the Central Statistical Office (CSO) [44]. The comparison was done for subjects aged 25 to 64 years and using ICD 9 codes 430-436. The data showed that of 326 registered stroke deaths in the POL-MONICA study only 206 (63%) were registered as stroke in the CSO. There were 7 stroke deaths registered in the CSO that were found not to have been a stroke in the POL-MONICA. The overall agreement was 64.4 % and use of the routine statistics alone would have provided a total of 213 stroke deaths whereas the study register identified 326 stroke deaths.

Validation studies from Japan have also shown that there are inaccuracies with regard to the correctness of routine death certificates. In the Hisayama study autopsy results from 846 post-mortem examinations in subjects aged 20 years or older (over-all autopsy rate 79%) were compared with information from death certificates during the period 1961-1983 [41]. Stroke was a part of the study and according to the autopsy reports stroke was the cause of death in 199 subjects whereas the routine data provided a total of 214 stroke deaths (ICD9 codes 430-438). The sensitivity was 84 % while the positive predictive value of being a positive diagnosis of stroke on death certificates was 78 %. There was a statistical significant decrease in the positive predictive value with advancing age indicating that in elderly subjects stroke was certified as underlying cause of death where autopsy results differed. Also, the sensitivity rates declined with advancing age indicating that routine death certificates listed other causes of death in subjects where the autopsy found it was stroke the person died from. In many countries autopsy rates are declining and in some countries they are rarely done. This is likely to lead to less valid data on stroke as a cause of death.

Results from the Framingham study (US) have shown that during a 30-year period there were 214 stroke deaths registered in routine mortality statistics while according to the study criteria 280 stroke deaths had occurred [46]. The false-negative rate was 40 % while the false-positive rate was 22 %. The proportion of false negative diagnoses increased significantly with increasing age, and increased both for men and women, while there was a decrease in the proportion of false positives stroke diagnosis in men with increasing age, while the opposite was found in women. The authors also found that there was a trend toward an increase in the false-negative rate and a decrease in the false positive rate.

The validation studies are based on data from developed countries and there is no current knowledge about the validity of stroke diagnoses in routine mortality statistics from developing countries. It is possible that less access to scanning facilities and laboratories will lower the validity of the diagnoses. It should be noted that most of the validation studies cited, are from before scanning became widely used, but it remains unclear to what extend the results reflect validity of death certificates in developing regions.

The quality of routine mortality data is likely to vary between and within populations and it seems likely that the validity decreases with increasing age. The number of false-positive and false-negative registrations may counter balance each other and increased access to scanning facilities may improve the validity of stroke events. Decreasing autopsy rates seen in many countries will have the opposite effect. Scanning is more often done in younger stroke patients, whereas there may be more deaths in elderly patients where the deceased person was neither scanned nor was autopsy done [47]. It is therefore possible that in the oldest age group in the GBD 2000

study there might be an overestimation of the burden of stroke. Subjects aged 80+ years contribute with 8.3 % of all DALYs and it is unlikely that our overall result would be seriously biased. Until evidence is available on magnitude of such possible misclassification, and on the actual causes of death, we have not attempted to adjust mortality estimates for stroke, beyond a proportional redistribution of ill-defined causes of death across all non-injury causes including stroke.

In addition to variation in the validity of death certificates on stroke deaths, several studies from different countries have shown that the specificity and sensitivity of stroke diagnoses varies [48]. A recent publication estimating the total occurrence of strokes in the US provided a combined estimate for the positive predictive value of ICD-9 codes from hospitalized stroke patients based on four studies. [49-52]. These results indicate that the inclusion of the codes 432, 437, and 438 is likely to increase the number of false-positive events. The study is only suggestive for the validity of stroke codes in death certificates, as it is based on hospitalized stroke patients which may be less accurate than mortality data [40]. Vital registration data from countries in all 6 WHO regions were analyzed to examine the distribution of type of stroke. Pooled estimates from these countries showed that 4 % of stroke deaths were due to subarachnoid hemorrhage, 18 % due to intracerebral and other intracranial hemorrhages, 16 % due to cerebral infarction, 48 % due to acute but ill-defined cerebrovascular disease, 3 % due to cerebral arteriosclerosis, and 9 % were due to the remaining diseases in the group of cerebrovascular diseases. Because of the large proportion of acute but ill-defined cerebrovascular disease, it was not possible to use these data to refine estimates of stroke type distributions across the WHO regions.

3. Methods for calculating the burden of stroke (YLDs)

3.1 Population studies of stroke epidemiology

A global estimation of the burden of stroke should ideally be based on data from real study populations providing data on stroke incidence, prevalence, mortality, morbidity, and disability. In 1987, Malmgren et al published the "ideal" stroke study criteria [53]. The paper was a benchmark in stroke epidemiology providing a set of standards for how to collect population data on stroke. A key issue was to include both hospitalized and non-hospitalized events, as well as fatal and non-fatal events. Stroke registries meeting all the "ideal" criteria are expensive and requires a well-defined population where it is possible to identify and follow-up all stroke patients. Studies providing "good" stroke data are summarized in table 2. All of them provide incidence rates but more detailed descriptions such as prevalence, survival, and disability are available from only some of them.

In the early 1980s the WHO MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Project was initiated [77]. The aim was to continuously register the occurrence of myocardial infarction and stroke among populations in different countries and to analyze the relationship between trends in incidence and mortality rates and changes in major cardiovascular risk factors. Uniform procedures and methods were used in all participating centers and between 1982 and 1986, 19 of 39 MONICA Collaborating Centers (MCC) entered the stroke component of the MONICA Project. Four MCCs withdrew from the stroke study after a few years of registration, however, since some of the remaining 15 MCCs covered more than one study population the stroke component of the WHO MONICA Project involved 21

populations in 11 countries (China, Denmark, Finland, Germany, Hungary, Italy, Lithuania, Poland, Russia, Sweden, Yugoslavia). The WHO MONICA Project data are one of the best sources to study differences in stroke occurrence and stroke trends in different countries. However, there is only complete registration for subjects aged 35 to 64 years thereby excluding the age groups where the majority of strokes occur. In addition, some of the studies did not distinguish between first-ever or recurrent strokes, and the majority of data are from populations in EMEs and FSEs. Because of these limitations data from the WHO MONICA Project are not ideal for the calculation of the global burden of stroke.

The available stroke studies with good data are from different years and the WHO MONICA Project was terminated in the mid 1990s. It is known from stroke mortality studies, based on routine mortality statistics, that there are constant changes in stroke rates with decreasing stroke mortality rates in many EME countries while increasing in FSE [78]. There is conflicting evidence on whether changes in stroke mortality rates are due to changes in incidence or case fatality. While some stroke studies have concluded that changes in case fatality are the most likely explanations for trends in stroke mortality rates [74;79] others have found that changes in the frequency of stroke, rather than its outcome, is chiefly responsible for the trends in stroke mortality rates [72;80-82]. Results from the WHO MONICA Project suggest that one-third is explained by changes in incidence while two-thirds are due to changes in case fatality[83]. The inconsistency of the results made it impossible to extrapolate from previous studies.

Table 2 Population studies for cerebrovascular disease epidemiology

Study population	Ref.	Years	WHO Region	Sample size	Information available
Sweden (S)	[54 55]	1975-78 and 1983-86	EUR-A	723 first-ever strokes	Incidence, 3 years survival
Arcadia (G)	[56 57]	1993-95	EUR-A	555 first-ever strokes	Incidence, 28 day case fatality, one year survival, disability in stroke survivors
Oxfordshire Community Stroke Project (UK)	[58 59]	1981-86	EUR-A	675 first-ever strokes	Incidence, 30 day case fatality, 6 years survival, one year disability
London (UK)	[60 61]	1995-197	EUR-A	911 first strokes	Incidence, 28 day case fatality, one year survival
Innherred (N)	[62]	1994-96	EUR-A	593 strokes; 432 first-ever strokes	Incidence, 30 day case fatality
Frederiksberg (DK)	[63]	1972-90	EUR-A	262 first-ever strokes (1989-90)	Incidence
L'Aquila (I)	[64]	1994-98	EUR-A	819 first-ever strokes	Incidence, 30 day case fatality, survival at one year, disability at one year
Belluno (I)	[65]	1992-93	EUR-A	474 first-ever strokes	Incidence, 30 day case fatality
Valle D'Aosta (I)	[66 67]	1996-97	EUR-A	343 first-ever strokes	Incidence, 30 day case fatality, disability at 30 days
Finland (three populations)	[68]	1972-91	EUR-A	244, 255, and 594 first-ever strokes	Incidence, one month case fatality
Erlangen (G)	[69 61]	1995-97	EUR-A	572 first strokes	Incidence, 28 day case fatality, one year survival
Dijon (F)	[61]	1995-97	EUR-A	591 first strokes	Incidence, 28 day case fatality, one year survival
NW England (UK)	[70]	1994-95	EUR-A	932 strokes; 642 first-ever strokes	Incidence, 28 day case fatality

NEMESIS (AU) [71]		WPR-A	381 strokes; 276 first-ever strokes	Incidence, 28 day case fatality, disability in stroke survivors, one year survival
Perth (AU) [72 73]	1995-96	WPR-A	290 strokes; 213 first-ever strokes	Incidence, 28 day case fatality, stroke severity, five year survival, cause of death, long term disability
Auckland (NZ) [74 75]	1991	WPR-A	953 first-ever strokes	Incidence, 28 day case fatality, stroke prevalence, follow-up of survivors
Rochester (US) [76]	1955-89	AMR-A	496 first-ever strokes (1985-89)	Incidence, 28 day case fatality, stroke severity, follow-up of survivors, prevalence

As the available stroke literature providing reliable data is dominated by studies from developed regions, in particular EME and to a lesser extent FSE, extrapolation of the results to other regions of the world was considered unrepresentative for the global burden of stroke. Therefore, for the purpose of estimating the global burden of cerebrovascular disease a model was developed. However, the data from the population-based studies were used to calibrate and compare the estimated results. More detailed review of data from the studies presented in this section will be discussed below in relevant sections.

3.2 National burden of disease stroke models

The Australian Burden of Disease studies for 1996 used a model to estimate the burden of stroke, based on incident cases of first-ever stroke. These were divided into people who died within 28 days, those who survived this period with a permanent disability and those who recovered completely. Incidence and duration estimates were derived using DISMOD from the numbers of hospitalized stroke patients and modeling assumptions drawn from a community stroke study in Perth and a study of Perth and Auckland population-based stroke registers.

Based on national hospital inpatient data for Australia in 1996, admissions for stroke were adjusted to account for stroke managed outside hospitals and used to calculate the incidence of hospitalized first-ever stroke. Data on short-term case fatality rates and on the proportion of stroke cases who die prior to hospitalization from the Perth stroke study [84] were used to estimate the total incidence of first-ever stroke. Assuming fatality rates in Australia in 1990 were similar to those in the Perth study, the Perth case fatality rates were reduced to reflect half the declines in Australian stroke mortality between 1990 and 1996. As a check on these estimates, the incidence rates of first-ever stroke in the Perth study for 1990 [85] were extrapolated to 1996 by adjusting them downwards by half the average annual decline in mortality rates. The two methods gave very consistent incidence of FES incidence rates for Australia in 1996.

Anderson et al [86] found that 58% of deaths in stroke patients were attributed to stroke. Deaths with stroke as underlying cause were multiplied by 100/58 to obtain total deaths in stroke cases and 28-day deaths subtracted to obtain number of deaths in stroke survivors. DISMOD was then used to model duration of survival for stroke survivors. Resulting average annual case fatality rates for long-term stroke survivors were around 10% for 65-74 years and 20% for 75 years and over. The estimated prevalence of 28-day stroke survivors in 1996 from this model was 121,000 persons, quite consistent with an estimate of 110,507 persons with prevalent stroke or stroke aftereffects in the 1995 National Health Survey.

The US Burden of Disease study, currently close to completion, has used a very similar model of stroke, together with US hospital admission data, data from stroke studies, and health survey data of stroke survivors to calculate the burden of stroke in the USA for 1996. Estimates of hospitalized stroke were derived from the 1996 nationwide inpatient sample (NIS) using the approach described by Williams et al (1999) in which first-ever and recurrent stroke hospitalizations were identified by ICD-9 codes 430-438 in any diagnosis field. Adjustments were also made to account for multiple admissions for the same event. There is conflicting evidence in the USA on the proportion of total stroke events that fail to present to hospital [87;88]. Based on expert opinion, the US BOD study assumed a flat 10% for non-fatal strokes below 75 years of age and 15% above 75 years, and for fatal strokes, an exponential increase with age based on the proportions reported by Wein et al [89]. The resulting envelope of total stroke burden (first-ever and recurrent) in the US was estimated to be closer to three quarters of a million strokes annually, rather than the often-quoted figure of 500,000 from the American Heart Association.

The Australian burden studies modeled stroke survivors past the first 28 days based on an extrapolation of mortality in this group. Using findings reported by Anderson et al [86], it was assumed that only 58% of deaths in stroke cases are actually attributed to stroke. Recorded stroke deaths were therefore multiplied by 100/58 to obtain an extrapolation of total stroke deaths. Modeled 28-day deaths were then deducted from this total to obtain the number of deaths in 28-day survivors and average duration of survival in this group was modeled in DISMOD I to match estimated incidence, remission and mortality. Case-fatality estimates from this model were considered reasonably consistent with reports from Anderson et al (1993), and prevalence estimates were considered consistent with estimates of self-report prevalence of current and chronic stroke from national health survey data. The validity of this extrapolation is difficult to verify from the literature reviewed on stroke in the US. Estimates of self-reported current and chronic stroke from the National Health Interview Survey are available, however, and Dismod II was used to model duration from incidence and prevalence assuming zero remission and a RR of 4.36 for males and 3.63 for females from Framingham. The overall proportion of estimated stroke attributable deaths to coded stroke deaths was lower than Anderson et al's estimate [86].

Figure 5 Estimated incidence of first-ever stroke, Australia and USA

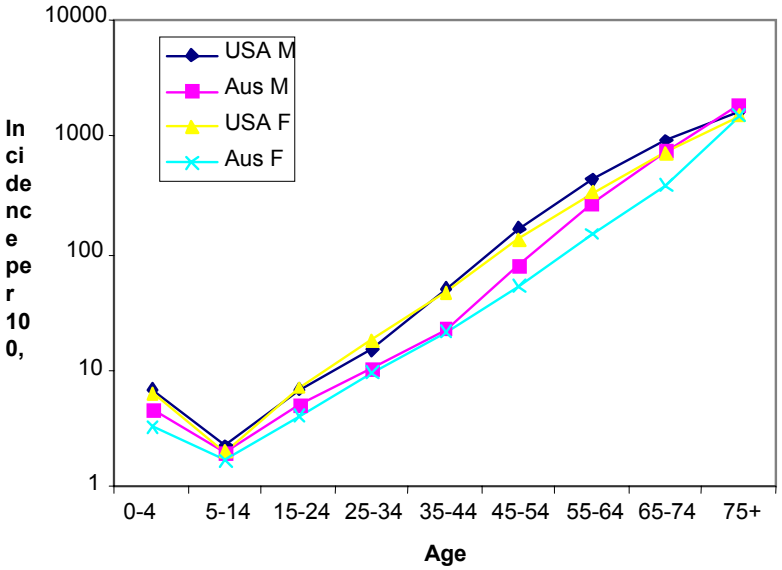


Figure 6 Estimated 28-day case fatality rates, Australia and USA 1996

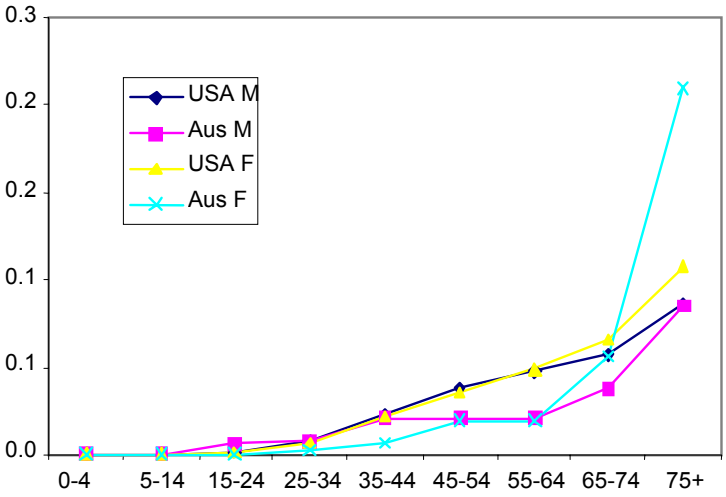


Figure 7 Estimated average duration for long-term stroke survivors, Australia and USA 1996

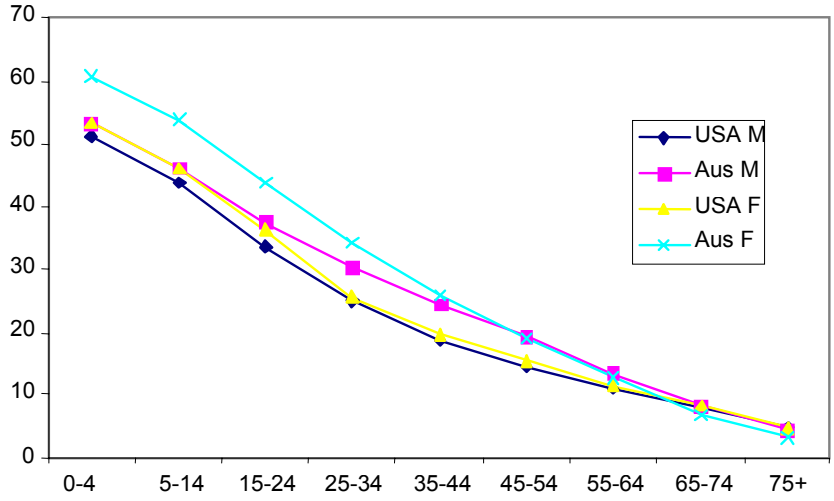
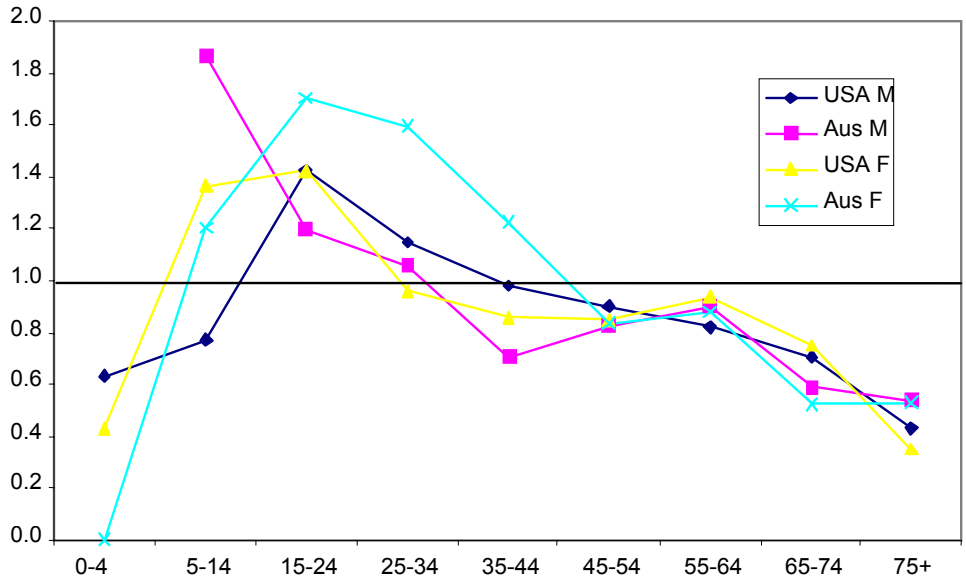


Figure 8 Estimated ratio of 28-day deaths to total recorded stroke deaths, Australia and USA 1996



3.3 The global burden of stroke in 1990

In the GBD1990 study [1], the analysis of stroke burden was based on a literature review by Bonita and Asplund. Calculations of DALYs for cerebrovascular disease were based on estimates on the total number of stroke deaths, and incidence and average duration of stroke in the EME (established market economies) region. Mortality to incidence ratios were calculated for the EME and adjusted for higher case fatality rates in developing regions, by multiplying them by the following factors:

Age group:	
15-29	2.0
30-44	2.0
45-59	2.0
60-69	2.0
70+	1.5

For the age group 0-4 and 5-14 years the incidence rates of stroke were based on the number of deaths, assuming that the non-fatal strokes in children were undetectable. DisMod was used to determine relative risk (RR) of death for stroke survivors in the EME. These results were extrapolated to other regions, by multiplying the RR-1 by the factors given above for all other regions.

3.4 Disease model for estimation of stroke burden in 2000

Since the GBD 1990 was completed, more stroke studies have become available and the experience from the two national burden of disease studies have contributed to the development of a more sophisticated model for estimating the global burden of stroke (Figure 9). This model builds on the existing national models and allows for the incorporation of available population-level information on the global epidemiology of stroke in a consistent way.

We start with the simplifying assumption that in a country with good vital registration, all deaths within 28 days of a stroke event are recorded by certifying practitioners as stroke deaths. The total number of deaths due to stroke in this country's vital register, therefore, can be defined as:

$$M_C = M_{28} + M_S$$

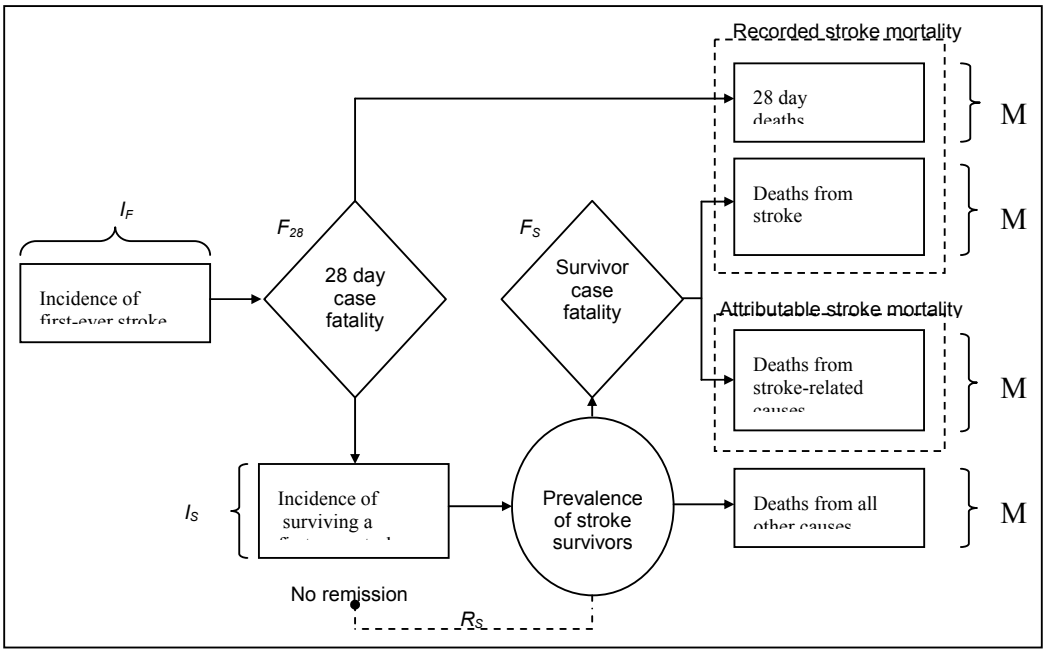
where M_{28} is the number of stroke deaths within 28 days of a stroke and M_S is the number of deaths for which a certifying practitioner has determined stroke as the underlying cause of death in 28 day survivors. Given that M_{28} is a product of the hazard of dying within 28 days, M_S can be expressed as:

$$M_S = M_C - I_F F_{28}$$

where I_F is the incidence of first ever stroke and F_{28} is the 28 day case-fatality. The remaining mortality in survivors can be divided into deaths due to causes closely related to stroke M_A (such as ischemic heart disease and other cardiovascular diseases) and deaths due to causes unrelated to stroke M_O.

Although M_A cannot be directly observed, it is possible to derive indirectly using a generic disease model known as Dismod which calculates an internally consistent description of disease epidemiology from at least three known parameters relating to the epidemiology of the disease of interest. The allowable parameters are incidence, prevalence, remission, disease specific mortality, duration, relative risk of mortality

Figure 9: Schematic diagram for estimating the global epidemiology of stroke



and case-fatality (although for a given level of background mortality, the last two are equivalent). Their relationship can be represented by the following function:

$$f_x(P_1, P_2, P_3, ...)$$

where $_x$ is any of the unknown parameters and P_1 to P_3 are at least three of those that are known. Figure 9 presents a schematic diagram of stroke epidemiology in terms of each of the parameters identified above.

We can now consider the epidemiology of stroke in the US, a country with good vital registration and for which I_F and F_{28} have been investigated in detail. To find M_A we can model stroke survivors in Dismod using at least three of the allowable parameters. From Figure 9 we can identify the first as:

$$I_S = I_F(1-F_{28})$$

where I_S is the incidence of survivors of first-ever stroke. The second is derived from the observation that there is no remission from ever having had a stroke (accept through death, which is treated separately). With regard to the final parameter, cause specific mortality in stroke survivors might appear to be the most readily available information. Unfortunately, it is not directly observable since it is defined by the following equation:

$$M_D = M_S + M_A$$

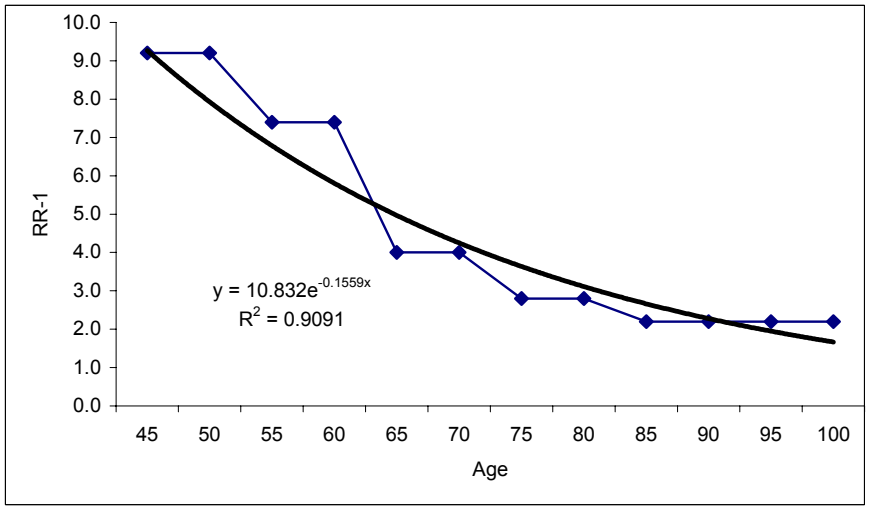
and M_A is unknown. While there are various sources of information on the remaining parameters as they relate to stroke in the US, we would expect information on prevalence to be the least reliable due to recall problems to the question "has a doctor ever told you that you have had a stroke?". A more robust strategy, therefore, is to use information on relative risk of mortality and case-fatality.

In the absence of population-level survival information in the US, we have used data on survival in stroke patients from a study in Perth, Australia [90] on the assumption that the risk profiles between the two countries are similar. This study provides an overall estimate of the relative risk of mortality in stroke survivors compared to the general population of around 2.5 (95% CI, 2.1 to 3.0) in the five years proceeding their initial stroke, which the authors equate to an annual case fatality of around 10 per cent. Age specific relative risks are also reported, but these relate to all cases of stroke, not just 28 day survivors. We can integrate these various figures by fitting the following log-linear regression to the age-specific relative risks minus one:

$$RR_a - 1 = ke^{\left(\frac{-0.1559(a-40)}{5}\right)}$$

where a is age in years and k is the y intercept (which for all stroke cases is 10.8). This equation explains around 90 per cent of variance in the reported figures if those below 45 years are excluded, Figure 10.

Figure 10 Relative risk minus one of mortality in all stroke cases with respect to the general Perth population

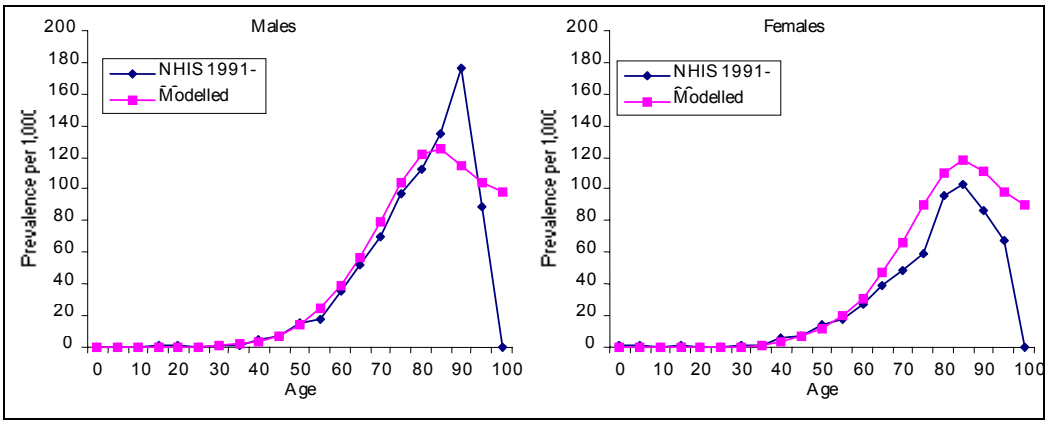


The above equation can then be re-expressed in terms of case-fatality thus:

$$F_S = M_O\left[1 + ke^{\left(\frac{-0.1559(a-40)}{5}\right)}\right] - M_O$$

where M_O is all mortality unrelated to stroke. We can now resolve this equation for stroke survivors in the US by using it as the third parameter in Dismod and varying k until estimates of overall case fatality and relative risk are as near to 10 per cent and 2.5, respectively, as possible. Figure 11 presents self-reported prevalence of stroke survivors from the National Health Interview Survey and Dismod derived estimates assuming a k of 4.5 in males and 5.8 in females. As expected, self-reported prevalence follows the same age distribution but is slightly lower at all ages compared to the modelled figures, accept in elderly men which is most likely due to sampling errors.

Figure 11 Comparison of self-reported and modelled prevalence of stroke in the United States



Once k is specified, M_D is also specified and we can define a new parameter α which is the proportion of deaths in 28 day survivors that gets coded as stroke in the US. This can be expressed as:

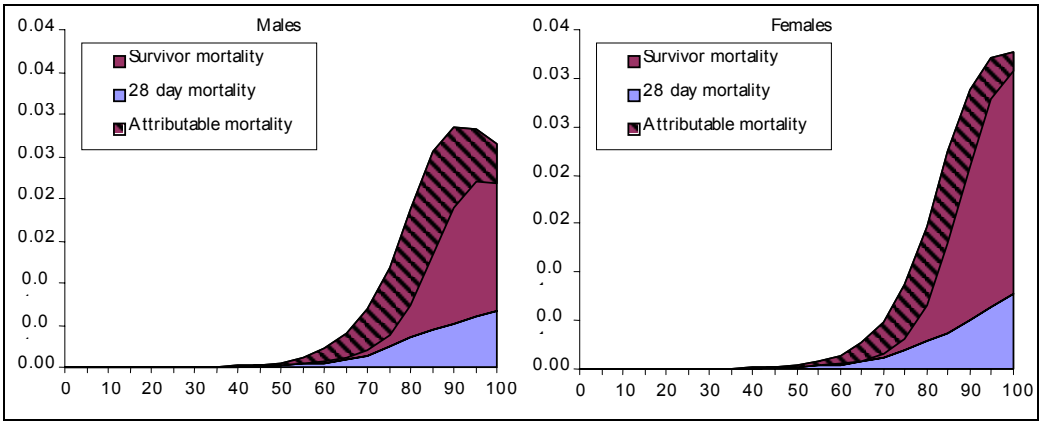
$$\alpha = \frac{M_C - I_F F_{28}}{M_D}$$

where

$$M_D = \underset{mort}{f}\left(I_F(1-F_{28}), R_S, M_O\left[1 + ke^{\left(\frac{-0.1559(a-40)}{5}\right)}\right] - M_O\right)$$

Figure 12 shows stroke mortality in the United States graphically using these methods. M_D is represented by the area in red (including the shaded area), α is the unshaded red area over the entire red area, and M_C is represented by the unshaded red and blue areas combined.

Figure 12 Stroke mortality in the United States



We can now proceed to the global estimation of stroke epidemiology. If we assume α is constant across all regions of the world, the epidemiology of stroke for any one region can be derived simply by specifying F_{28} and F_S and finding the value for I_F that is consistent with its relationship to both M_D and M_C.

The estimation of F_{28} in each region is discussed in section 3.5. Briefly, we have used GDP to predict regional estimates of F_{28} for all ages combined and have applied the ratio of predicted F_{28} to observed US F_{28} (σ_{gdp}) to the age specific US F_{28} figures to derive estimates of F_{28} for each region at each age. If we assume the excess risk in 28 day deaths applies to survivors as well, then σ_{gdp} can also be used to adjust the age specific US mortality assumptions for survivors. This can be written as:

$$F_S = M_O\left[1+\sigma_{gdp}ke^{\left(\frac{-0.1559(a-40)}{5}\right)}\right]-M_O$$

where k has been calibrated for the US population and σ_{gdp} is the ratio of predicted F_{28} in the population of interest to observed US F_{28}.

If the above assumptions hold, then the epidemiology of stroke for any one region is fully described when the following statement is true:

$$\underset{mort}{f}\left[I_F(1-F_{28}\sigma_{gdp}),R_S,M_O\left(1+\sigma_{gdp}ke^{\left(\frac{-0.1559(a-40)}{5}\right)}\right)-M_O\right]\equiv\frac{M_C-(I_F F_{28}\sigma_{gdp})}{\alpha}$$

where I_F is the only parameter to be resolved in the population of interest.

3.5 Estimation of regional 28 day case fatality rates

The 28-day case-fatality is a common parameter for the short-time survival in stroke patients [91]. In the first weeks after stroke symptoms onset death directly related to the

stroke is the main cause of death [80;92;93]. As described in section 4.0 in this study it was assumed that all deaths occurring within 28 days were due to stroke. As mean duration for short-term survival in different regions is unknown it was set to 10 days in all age groups, regions and in men and women. Population-based studies of stroke case fatality were identified and the available estimates of 28-day case fatality rates were used as the basis to estimate 28-day CF rates by age and sex for the 17 GBD 2000 epidemiological regions. Studies are summarized in Table 3.

The methodology and sampling methods varies between the stroke studies and especially in developing regions the results were based on data from hospitalized stroke patients. Such studies are likely to underestimate case fatality and for example the studies from EMR-B and D were hospital based with remarkably low case fatality rates. While some studies include all age groups others are restricted and include only middle-aged subjects, which for example is the case for the WHO MONICA Project where only data on stroke events in patients aged 35 to 64 years have been included. Some of the studies provided age and sex specific case-fatality rates while the majority provided an over-all case fatality estimate. Over-all case fatality rates are likely to differ as a result of different stroke types, admission rules, and the age and sex distribution. In those studies that provided a case-fatality for men and women separately, women had often a higher rate than men although it was not a consistent finding.

Based on the results from these studies it seemed reasonable to assume that the lowest 28-day case fatality rates were among countries in the EME, where the lowest rates have been reported in the USBOD (15% for both men and women) [117]. For countries in the remaining regions the case-fatality rate would be higher reflecting lower income, less developed health care infra structure, and less resources to prevention and medication. Furthermore, it was expected that the 28-day CF would be higher in developing countries than in developed countries, because of a higher proportion of hemorrhagic strokes. The great diversity of study types provided an idea about the magnitude of the overall 28-day CF but rendered it futile to consider meta-analyses as a means of estimating a regional 28-day CF.

Results from the WHO MONICA Project have indicated that the 28-day CF differs in different populations from different countries [91;93;118], and populations in less resourced countries are likely to have a higher 28-day case-fatality as compared to populations from more affluent populations. An association between income and stroke mortality and stroke incidence has been described from different studies [119;120]. In an overview of the association between socioeconomic status and stroke mortality in men aged 30 to 64 years in the 1980s (including data from England and Wales, Ireland, Finland, Sweden, Norway, Denmark, Italy, Spain, United States, France, Switzerland, and Portugal) it was reported that manual occupational classes had higher stroke mortality rates than non-manual occupational classes [121]. The author also found that in most of these countries, inequalities were much larger for stroke mortality than for ischemic heart disease mortality.

As a means to estimate the overall regional 28-day case-fatality it was therefore assumed that plotting results from different stroke studies against the respective national GDP could be used as a way to predict CF from regions with little or no stroke data, Figure 13. For Africa a case fatality of 0.35 was entered in the model[21].

Table 3: Case fatality studies according to region

Region	Year	Country	Ref.	Type of study	Case fatality Men Women Sex specific Not provided	Comments
AFR	1998	Zambia	[94]	Hospital based	50 %	Few events. No stroke definition. High CF but observation length not indicated
	1984-85	South Africa	[20]	Hospital based	34 %	116 events
	1973-75	Nigeria	[95]	Community based, WHO criteria	35 %	Case fatality at 3 weeks 229 men and 89 females
	1986-87	Kenya	[96]	Hospital based	46 %	Few events. Only over-all case-fatality provided
	1986-87	South Africa	[19]	Hospital based	33 %	304 patients
	1991	Zimbabwe	[97]	Hospital based	35 %	488 events. One week case fatality
AMR B+D	1997-99	Peru	[98]	Hospital based	23 %	9 deaths in 40 patients
AMR A	1985-89 *	US	[99] [76]	Community based Community based	17 % 14 % 25 %	

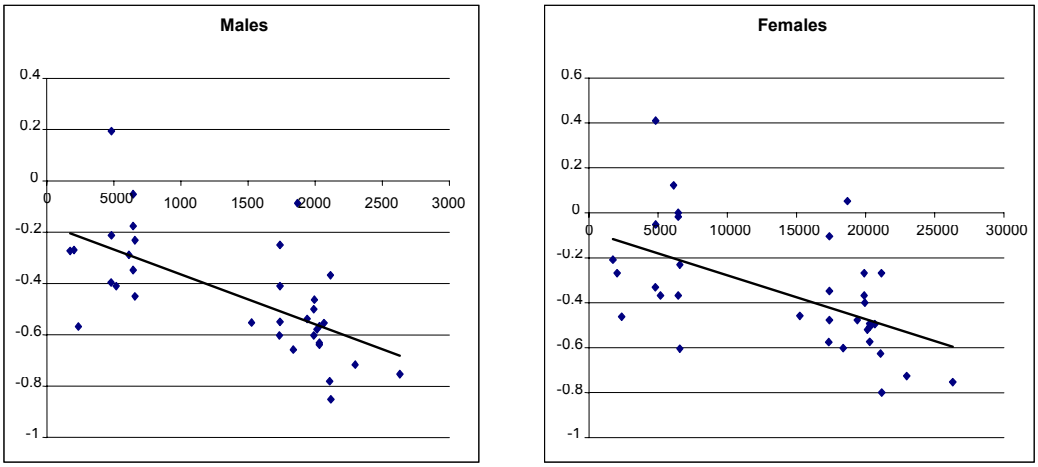
EMR D+B	1989;1992;1993	Kuwait	[100]	Hospital based			10 %	30 day case fatality
	1982-1992	Saudi Arabia	[101]	Hospital based			12 %	30 day case fatality
	1997-2000	Saudi Arabia	[102]	Hospital based			31 %	Observation period not indicated
	1984-1989	Saudi Arabia	[14]	Hospital based			8 %	Observation period not indicated
	1989-1993	Saudi Arabia	[15]	Hospital based			15 %	30 day case fatality
EUR A	1977-92 *	Denmark	[80]	Community based			24 %	28 day case fatality. Age and sex specific rates
	1985-87 *	MONICA	[91]	MONICA population				
	-	- Denmark (GLO)			22 %	26%		Age group 35 to 64 years
	-	- Finland (KUO)			17 %	18 %		-
	-	- Finland (NKA)			27 %	31 %		-
	-	- Finland (TUL)			21 %	22 %		-
	-	- GER (HAC)			36 %	36 %		-
	-	- GER (KMS)			32 %	34 %		-
	-	- GER (RDM)			30 %	36 %		-
	-	- GER (RHN)			16 %	23 %		-
	-	- ITA (FRI)			34 %	39 %		-
	-	- SWE (GOT)			18 %	25 %		-
	-	- SWE (NSW)			15 %	21 %		-
	1994-96 *	Erlangen (GER)	[103]				19%	All age groups
	1995-97 *	London (GB)	[61]	Community –based			27 %	
	1995-97 *	Dijon (FR)	[61]	-			13 %	
	1990-92 *	FINMONICA	[82]	-	20 %	21 %		35-74 years

	1994-96 *	(SU)	62	MONICA population			19 %	∃ 15 years. First-ever stroke.
	1993-95 *	Innherred (N)	56	Community based	26 %	27 %		
	1994-98 *	Arcadia (GR)	64	Community based			25 %	
		L'Aquila (I)		Community based				
EUR B1 + B2	1991-92 *	Praga (P)	104	Community based	38 %	47 %		35-64 years
	1991-92 *	Mokotóv (P)	104	MONICA population	35 %	34 %		35-64 years
	?? *	Warsaw (P)	105	Hospital based			24 %	
EUR C	1992 *	Novosibirsk (R)	106	Community based	26 %	20 %		
	1994-95 *	Novosibirsk (R)	93	MONICA population	35 %	31 %		35-64 years
	1991-93 *	Tartu (EST)	107	Community based			30 %	All ages
	1999-2000 *	West Ukraine (U)	108	Community based			23 %	All ages
	1986-88 *	Kaunas (Lit)	109	MONICA population	20 %	21 %		35-64 years
WPR A	1991 *	Auckland (NZ)	74	Community based	22 %	26 %		15 years and older
	1989-90 *	Perth (AU)	85	Community based			24 %	All ages
	1996-97 *	Melbourne (AU)	71	Community based			20 %	All ages
	?	Okinawa (JP)	110	Cross-sectional survey			13 %	?
	1989-93 *	Shiga (JP)	111	Hospital based	16 %	16 %		35 years or older
	1987-91 *	Oyabe (JP)	112	Community based	14 %	19 %		25 or older. Rural area.
WPR B + C	1984-86 *	Beijing (C)	113	MONICA population	33 %	40 %		
	1984-86	Shanghai	114					
	1984-91 *	Shanghai (C)	114	MONICA criteria	***46 %***	***33 %***		35-74 years
	1989-90	Korean hospitals	115	Hospital based (types)		5 %		
	??	Korea	116					

				Hospital based		
SEAR B + D		No Studies found				

Legend: * indicates a study that was included in estimating the regression between GDP and case fatality.

Figure 13 Plot of logit of over-all 28 day case fatality versus GDP (PPP dollars)



Information on regional GDPs was subsequently used to derive a regional estimate for 28 day CF, Table 4. This method provided a graded increase in over-all 28-day case fatality that was consistent with the results from the stroke studies. In the regression equation the CF for AMR-A men and women was 0.14 and 0.16, which is close to the estimated 15% in the USBOD. For EMR-B and D the CF rates were of the same magnitude or higher than reported in the studies from that region. Considering that the studies were hospital based it was assumed that the estimated rates were acceptable. The region with the highest CF rates were AFRO D and E in both men and women, and the estimates are in accordance with results from local studies [21]. (AFR: During the review process it was suggested that the estimates for case-fatality were too low and the over-all 28 day case fatality was therefore increased to 40 % in men and 42 % in women for AFRO D and E so that the lowest age- and sex specific 28 day CF would be around 33%. The presented results for both short- and long-term stroke survivors are based on these case-fatality estimates).

Table 4: 28 day case fatality rates used in the GBD2000 calculations

	AFRO-D		**AFRO-E**		**AMRO-A**		**AMRO-B**		**AMRO-D**		**EMRO-B**		**EMRO-D**		**EURO-A**		**EURO-B1**	
Age groups	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
30-44	0.38	0.28	0.40	0.28	0.14	0.11	0.26	0.21	0.29	0.23	0.26	0.20	0.29	0.23	0.18	0.14	0.27	0.21
45-59	0.29	0.28	0.29	0.28	0.10	0.11	0.20	0.21	0.22	0.23	0.20	0.21	0.22	0.23	0.13	0.14	0.20	0.22
60-69	0.29	0.30	0.29	0.30	0.10	0.11	0.20	0.22	0.22	0.24	0.20	0.22	0.22	0.25	0.13	0.15	0.20	0.23
70-79	0.37	0.36	0.37	0.36	0.13	0.14	0.25	0.27	0.28	0.30	0.25	0.27	0.28	0.29	0.17	0.19	0.25	0.27
80+	0.53	0.46	0.52	0.46	0.18	0.18	0.36	0.35	0.39	0.39	0.35	0.34	0.39	0.38	0.24	0.24	0.37	0.36
All ages	0.40	0.38	0.40	0.38	0.14	0.16	0.26	0.28	0.32	0.36	0.29	0.29	0.43	0.37	0.19	0.21	0.27	0.29
	EURO-B2		**EURO-C**		**SEARO-B**		**SEARO-D**		**WPRO-A**		**WPRO-B1**		**WPRO-B2**		**WPRO-B3**			
Age groups	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F		
30-44	0.29	0.24	0.27	0.22	0.29	0.23	0.31	0.24	0.16	0.13	0.28	0.23	0.28	0.24	0.29	0.24		
45-59	0.22	0.24	0.21	0.22	0.22	0.23	0.22	0.24	0.12	0.13	0.21	0.23	0.22	0.24	0.22	0.24		
60-69	0.22	0.25	0.21	0.23	0.22	0.24	0.22	0.25	0.12	0.14	0.22	0.24	0.23	0.25	0.22	0.25		
70-79	0.27	0.30	0.25	0.28	0.28	0.29	0.28	0.303	0.16	0.17	0.28	0.30	0.29	0.31	0.28	0.30		
80+	0.42	0.41	0.38	0.37	0.38	0.38	0.40	0.39	0.23	0.23	0.39	0.39	0.40	0.40	0.39	0.38		
All ages	0.28	0.31	0.26	0.30	0.28	0.30	0.28	0.30	0.17	0.20	0.27	0.30	0.29	0.32	0.32	0.30		

3.6 Case fatality/Relative Risk of death in stroke survivors

The relative risk of death in stroke survivors and case fatality in stroke survivors are two measures that both relate to the number of stroke survivors that die each year. Both are related to duration, prevalence rates, access to medication, rehabilitation, and stroke severity, and the magnitude is also associated to the underlying death intensity in the population.

In the two national burden of disease studies different methodologies were used. In the AUBOD study mortality rates in 28 survivors were extrapolated based on death registrations for which stroke was the recorded cause of death assuming this represented only 58 per cent of all stroke deaths [86]. It was assumed that a proportion (50 per cent of males and 37 per cent of females) had six months at the Dutch weight for mild disability but no permanent impairment [75]. For the remainder, an average duration before death was derived using DISMOD after subtracting the estimated deaths within 28 days of first ever stroke. In the USBOD study duration in stroke survivors was calculated using DISMOD based on data on incidence, prevalence (extracted from the National Health Interview Survey) and an assumption of zero remission.

In the GBD2000 there were insufficient data for calculating the case fatality or relative risk of death in stroke survivors from most parts of the world, and another method was developed. It was assumed that a higher proportion of stroke survivors would die every year in developing regions than in EME. Case-fatality rates in long-term stroke survivors from developed countries are approximately 5 to 10 % per year with no major differences between men and women [73;122 123] which is what was estimated, Table 5. There was no information on long-term case fatality from developing countries and it was therefore assumed that the excess risk in 28-day deaths applied to stroke survivors as well, and used to adjust correspondingly the age specific US mortality assumptions for survivors.

The lowest long-term case fatality rate for all ages combined was calculated for AMR-A and the highest was calculated for AFR-E. The diversity between the regions is only moderate which was expected as it was anticipated that surviving stroke patients in developing countries probably would have suffered a less severe stroke for surviving beyond the initial 28 days. However, the over-all estimates hide that in the age groups where most strokes occur, the case fatality rates varies two to three fold.

In addition to the case-fatality in stroke survivors the DISMOD calculations also provided estimates on the relative risk of death in stroke survivors. Information on relative risk of death in stroke survivors was available from some studies, Table 6 [59;117;124;125] and used as a further control of the estimated data. The estimates for USBOD and AUBOD shown in the table were derived from the results provided and applying these to the GBD2000 populations for AMR-A and WPR-A, thus, they are not directly comparable with the results from the two reports as the populations differ. Generally, the relative risk decreases by increasing age, which reflects that the difference in risk of death in stroke survivors and the general population decreases when the underlying death intensity increases. There is considerable uncertainty on the estimates in the younger age groups reflecting that few events are occurring. From the age of 45 years and onwards the relative risk estimates are relatively consistent across the studies. The two population studies (Oxfordshire and Perth) both reported that the difference in long-term relative risk in male and female stroke survivors was small and insignificant. The relative risks from the AUBOD and the USBOD are also of similar magnitude in the older age groups.

Table 5: Long-term case fatality in stroke patients surviving the initial 28 days after symptoms onset.

	AFRO-D		**AFRO-E**		**AMRO-A**		**AMRO-B**		**AMRO-D**		**EMRO-B**		**EMRO-D**		**EURO-A**		**EURO-B1**	
Age groups	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
30-44	0.16	0.16	0.35	0.35	0.01	0.01	0.04	0.02	0.06	0.05	0.02	0.02	0.03	0.03	0.01	0.01	0.04	0.02
45-59	0.17	0.15	0.25	0.20	0.02	0.02	0.06	0.05	0.08	0.07	0.05	0.06	0.08	0.07	0.03	0.02	0.08	0.05
60-69	0.25	0.23	0.28	0.25	0.04	0.04	0.11	0.19	0.13	0.12	0.11	0.12	0.15	0.14	0.05	0.03	0.13	0.10
70-79	0.40	0.40	0.42	0.41	0.07	0.16	0.17	0.16	0.22	0.21	0.20	0.22	0.26	0.28	0.10	0.08	0.20	0.19
80+	0.63	0.67	0.64	0.66	0.13	0.14	0.31	0.32	0.41	0.44	0.36	0.42	0.44	0.55	0.19	0.20	0.37	0.42
All ages	0.27	0.27	0.32	0.32	0.06	0.07	0.12	0.11	0.15	0.14	0.13	0.14	0.17	0.19	0.09	0.11	0.16	0.15
	EURO-B2		**EURO-C**		**SEARO-B**		**SEARO-D**		**WPRO-A**		**WPRO-B1**		**WPRO-B2**		**WPRO-B3**			
Age groups	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F		
30-44	0.06	0.04	0.09	0.03	0.05	0.04	0.06	0.06	0.01	0.01	0.03	0.02	0.06	0.05	0.08	0.09		
45-59	0.10	0.08	0.14	0.07	0.08	0.07	0.11	0.10	0.02	0.01	0.06	0.05	0.09	0.08	0.11	0.12		
60-69	0.17	0.16	0.21	0.12	0.14	0.13	0.18	0.17	0.04	0.02	0.12	0.10	0.15	0.15	0.17	0.17		
70-79	0.25	0.26	0.27	0.23	0.23	0.24	0.28	0.28	0.07	0.05	0.23	0.19	0.26	0.28	0.26	0.26		
80+	0.45	0.44	0.42	0.49	0.39	0.44	0.44	0.44	0.15	0.14	0.40	0.39	0.45	0.50	0.37	0.40		
All ages	0.18	0.21	0.22	0.21	0.15	0.16	0.20	0.21	0.06	0.07	0.15	0.15	0.19	0.21	0.18	0.19		

Table 6: Relative Risks (RRs) from different studies

	Oxfordshire	Perth	USBOD	USBOD	AUBOD	AUBOD
	1993	1989-90	1996	1996	1996	1996
	M+W	M+W	Men	Women	Men	Women
0-4			178	224.48	569	572
5-14			223.1	438.2	772.0	886.0
15-24			42.7	287.9	2.5	3.6
25-34			69.1	317.5	13.4	1.1
35-44	37.5 (62.87.7)	201 (70-333)	19.6	103.9	7.6	2.8
45-54	25.8 (11.1-50.8)	10.2 (0.2-20.2)	5.7	5.4	6.3	12.7
55-64	10.6 (7.3-14.9)	8.4 (4.5-12.3)	6.0	8.3	2.8	5.9
65-74	4.8 (3.8-6.0)	5.0 (3.4-6.5)	3.0	5.0	1.8	4.7
75+	3.3	3.8	2.2	3.1	2.0	4.7
85+	2.7	3.2				
Total	3.7	4.2	5.6	14.4	4.9	5.7

The results from these studies were regarded as insufficient to be used on a global scale due to the uncertainty around the estimates, and because weighted averages would be favoring the two BOD studies. However, it was expected that estimated relative risk results from the GBD2000 DISMOD computations would be of approximately similar magnitude, Table 7.

Table 7: Over all relative risk of death in stroke patients surviving the initial 28 days after stroke onset

	AFR-D		**AFR-E**		**AMR-A**		**AMR-B**		**AMR-D**	
All ages	M	F	M	F	M	F	M	F	M	F
	7.2	8.1	8.2	8.1	2.5	2.8	4.7	5.7	5.2	6.6
	EMR-B		**EMR-D**		**EUR-A**		**EUR-B1**		**EUR-B2**	
All ages	M	F	M	F	M	F	M	F	M	F
	4.6	5.7	5.1	6.3	3.0	3.3	4.6	5.4	5.3	6.2
	EUR-C		**SEAR-B**		**SEAR-D**		**WPR-A**		**WPR-B1**	
All ages	M	F	M	F	M	F	M	F	M	F
	5.1	5.4	5.2	6.4	5.3	6.5	2.9	3.2	4.9	5.8
	WPR-B2		**WPR-B3**							
All ages	M	F	M	F						
	5.1	6.3	5.5	7.1						

3.7 Stroke as a cause of death in stroke patients

The total number of deaths attributed to cerebrovascular disease is the sum of stroke deaths occurring in short- and long term stroke survivors. It was assumed that all deaths within 28 days were due to stroke, thus subtracting these from the total number of deaths provided the number of cerebrovascular deaths that have occurred in long-term stroke survivors. However, simple addition of number of deaths in short- and long term stroke survivors was not possible as not all long-term stroke survivors eventually die from a stroke.

Data on causes of death in long-term survivors require a follow-up period for several years (ideally until all stroke survivors have died), which is difficult unless the population is stable within a geographical area that can be surveyed, or if there is established central identification systems of the subjects. In the absence of data, it is assumed that the proportion of all long-term stroke survivors that die from stroke is relatively stable between regions.

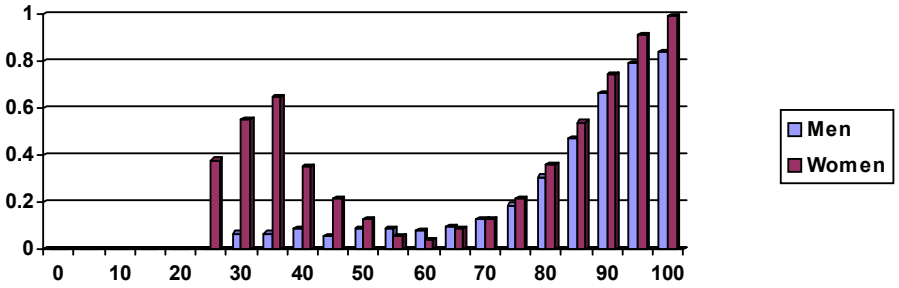
Studies, all from developed countries, indicate that approximately half of all stroke patients die from a stroke, Table 8 [59 123 124 126]. There was no information from developing countries.

Table 8: Proportion of stroke patients dying from stroke

Region	Ref.	Country	Data	Results	Comments
EUR-A	[59]	Oxfordshire Community Stroke Project	Community based	A total of 347 deaths of which 195 (56 %) were due to stroke during a 6.5 years follow-up.	First stroke was the cause of death in 157 (45 %) patients whereas 38 (11%) deaths were du to recurrent stroke.
EUR-A	[123]	DANMONICA	MONICA study	In men 268 (27 %) of stroke survivors died from cerebrovascular disease. In women 318 (38 %) of stroke survivors died from cerebrovascular disease.	Follow-up for vital status for 5.5 to 15.5 years; follow-up for causes of death for 4 to 14 years. Data were obtained from central disease and cause of death registers. ICD 8 codes: 430-438; ICD10: I60-I69.
EUR-A	[126]	Three provinces of the Netherlands	Community based	Three years of follow-up of 221 stroke patients of whom 120 deceased. From 30 days to 3 years index stroke was the cause of death in 23 % and recurrent stroke in 21 %.	Information on stroke events through general practitioners not including nursing homes.
WPR-A	[124]	Perth Community Stroke Study	Community based	In 370 30-day stroke survivors there were 210 deaths during a 5 year follow-up period. 27 % of deaths were due to stroke.	Two-thirds of the stroke deaths were due to the index stroke and one-third due to recurrent stroke.

Based on the results from the USBOD we developed a smoothened model for the proportion of stroke survivors that died from a stroke, figure 14. This factor, denoted α, was multiplied with the total number of deaths providing the estimated number of cerebrovascular deaths in stroke survivors. Due to shortage of data from other than developed countries it was furthermore assumed that α was constant across regions.

Figure 14 Proportion of stroke survivors that die from stroke (α), GBD2000.



The estimated proportion of deaths due to stroke is shown in Table 9. The proportion is higher in women than in men reflecting the generally higher 28-day case-fatality in women and the difference in age distribution.

Table 9: Proportion of stroke patients dying from stroke

	AFR-D		**AFR-E**		**AMR-A**		**AMR-B**		**AMR-D**	
All ages	M 50 %	F 51 %	M 49 %	F 51 %	M 42 %	F 53 %	M 44 %	F 50 %	M 46 %	F 52 %
	EMR-B		**EMR-D**		**EUR-A**		**EUR-B1**		**EUR-B2**	
All ages	M 46 %	F 48 %	M 49 %	F 49 %	M 46 %	F 58 %	M 43 %	F 50 %	M 42 %	F 49 %
	EUR-C		**SEAR-B**		**SEAR-D**		**WPR-A**		**WPR-B1**	
All ages	M 40 %	F 51 %	M 44 %	F 47 %	M 42 %	F 46 %	M 46 %	F 60 %	M 45 %	F 52 %
	WPR-B2		**WPR-B3**							
All ages	M 45 %	F 50 %	M 44 %	F 45 %						

3.8 Health state descriptions and disability weights

In the calculation of YLDs due to stroke for the GBD2000 study the same disability weights were used as the ones from the GBD1990 study. The out-come after a stroke event is outlined in Table 10**;** either the patient has a full recovery, or has mild to severe long-term disability.

Table 10: The out-come after stroke

Sequela/stage/severity level	*Health state description*
First ever stroke – acute event	Acute stroke event and period immediately following. Severe pain, unable to self-care or carry out usual activities, severe mobility limitations, likely cognitive and motor deficits. The average duration of this period for those who die within 28 days is around 6 days. Model this health state with duration of 6 days for all first strokes.
First ever stroke with full recovery	After 1 year, no impairments or limitations in activities. The model assumes approximately 50% of long-term stroke survivors have full recovery.
First ever stroke with long-term disability - mild	Permanent impairments and disability after one year. Motor impairment resulting in some problems with usual activities, some pain and discomfort, some depression or anxiety. No problems in self-care or cognition.
First ever stroke with long-term disability - moderate	Permanent impairments and disability after one year. Cognitive or cognitive plus motor impairment resulting in some problems with mobility, usual activities, some pain and discomfort, some depression or anxiety, and some problems in self-care.
First ever stroke with long-term disability – severe	Severe permanent impairments and disability after one year. Severe cognitive problems, unable to perform usual activities or self-care., Severe pain or discomfort. Some problems in mobilty and some depression or anxiety.

Different disability weights for cerebrovascular disease have been used in different studies, Table 11. The lack of disability data from the vast majority of the worlds regions made it impossible to try estimating regional disability rates divided into level of severity.

Table 11: Disability weights for cerebrovascular disease

Stage/sequela	**GBD 1990**	**Netherlands Study**	**Australian BOD Study**
First-ever stroke with full recovery	0	0	0
First-ever stroke with long-term disability	0.224 (Treated) 0.262 (Untreated)	0.360 (Mild) 0.630 (Moderate) 0.920 (Severe)	0.36 (younger ages) –0.58 (older ages)

It should be noted that the vast literature on impairment, disability and handicap indicates the problems of developing a simple, easy, reliable and valid measure for measuring the outcome of a disease like stroke which can have a wide spectrum of residual disability not covered in a simple measure of dependence on another for daily activities [127]. Different disability rating scales are likely to provide a different estimates [128], and scales that may provide an appropriate estimate of disability in one population may be inadequate in others [129]. The approach used in this study is a simplified method but until more data and knowledge on how to assign disability for the worlds regions we have chosen to use the same strategy as was used in the GBD 1990 study.

4 Results from the GBD2000 study

4.1 Incidence rates of cerebrovascular disease

The estimated incidence rates refer to incidence of first-ever stroke (FES) and age and sex specific rates are shown in Table 12 while age standardized incidence rates are shown in Figure 15.

The Americas, the Eastern Mediterranean Region, the Western Pacific Region, and Euro-A are the regions with the lowest stroke incidence rates, whereas high rates are estimated for the remaining European regions, and Western Pacific region. Age specific stroke incidence rates are generally higher among men compared with women except for a few regions where especially the two African regions have considerably higher rates in women than in men.

Age-standardized rates reflect the marked differences between the regions. In men 11 regions have incidence rates that are less than 600/100,000 and the regions with higher rates are EUR-B1, B2, C, WPR-B1, B2, and B3. In women 13 regions have incidence rates below 600/100,000 with the highest stroke incidence rates calculated for EUR-B1, B2, C, WPR-B1, B2, and B3. The age-standardized stroke incidence rates are remarkably high in the two African regions.

EUR-C is the region with the highest estimated stroke incidence rates both in men and women. Stroke incidence studies from this region have reported high rates although not as high as estimated in the GBD2000 [106-108].

The stroke model used for calculating the GBD2000 stroke estimates were partly based on assumptions from the USBOD. Therefore, it was expected that the estimates would be close to local US studies, and populations from EUR-A and to a lesser extend also WPR-A as the populations in these regions are predominantly Caucasians and industrialized. Graphs comparing the estimated regional incidence rates for AMR-A, EUR-A, and WPR-A with local stroke studies are shown in Figure 16 to 21 (approximated age groups as different age categories were used in the different studies). In both men and women the estimated stroke incidence rates from the GBD2000 study are either in within the range of estimate from local stroke studies or slightly lower than reported especially in AMR-A when compared with the USBOD [117] and data from the Minnesota study [79]. WPR-A is special stroke region, as it is known that Japan has high stroke rates compared with other industrialized countries. However, in the WPR-A estimate Japan is combined with Australia and New Zealand, but because the population in Japan is much bigger than in Australia and New Zealand the estimated rates were expected to be closer to the Japanese rates. However, they are very much alike rates from the Australian NEMESIS study [71].

Table 12: Estimated stroke incidence rates per 100,000 in 17 WHO regions, the GBD2000

	AFRO-D		**AFRO-E**		**AMRO-A**		**AMRO-B**		**AMRO-D**		**EMRO-B**		**EMRO-D**		**EURO-A**		**EURO-B1**	
Age groups	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
0-4	2	3	2	3	1	1	1	1	2	6	2	2	20	12	1	0	6	6
5-14	1	1	1	0	0	0	1	0	1	2	1	1	8	5	0	0	2	1
15-29	4	4	5	5	1	1	2	12	14	4	2	1	8	3	1	1	6	5
30-44	47	50	89	30	30	31	54	53	40	40	34	28	23	20	39	24	66	68
45-59	249	342	274	329	219	180	335	240	247	197	192	204	233	174	174	94	498	269
60-69	792	1,095	781	1,115	651	491	1,067	708	721	507	878	680	698	870	700	384	1,917	1,284
70-79	1,654	2,369	1,693	2,539	1,137	1,043	1,868	1,312	1,446	1,087	2,011	1,622	1,947	1,797	1,816	1,326	3,410	2,716
80+	2,936	5,418	2,995	5,233	2,091	1,956	2,846	2,694	2,453	2,297	3,825	3,545	3,145	2,997	3,181	2,845	4,935	4,518
	EURO-B2		**EURO-C**		**SEARO-B**		**SEARO-D**		**WPRO-A**		**WPRO-B1**		**WPRO-B2,**		**WPRO-B3**			
Age groups	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F		
0-4	0	0	1	1	2	2	3	2	0	0	2	1	2	2	6	5		
5-14	0	0	0	0	1	1	1	1	0	0	0	0	0	0	2	1		
15-29	1	1	4	2	3	2	2	1	1	1	2	1	2	1	8	3		
30-44	58	34	122	50	45	31	20	13	59	28	46	29	50	40	56	36		
45-59	544	312	765	404	341	278	378	248	323	138	450	302	403	257	546	415		
60-69	2,000	1,547	3,009	1,723	1,222	1,048	1,736	1,434	934	442	2,003	1,226	1,931	1,362	1,774	1,651		
70-79	3,088	2,784	5,150	3,694	2,546	2,355	2,840	2,724	1,930	1,123	4,116	3,260	3,656	2,899	4,361	3,551		
80+	4,840	4,374	7,360	7,529	2,885	2,846	3,148	3,224	3,427	2,680	5,793	5,321	4,694	4,638	4,254	3,101		

Figure 15: Age-standardized incidence rates for men and women in 17 WHO regions, the GBD2000

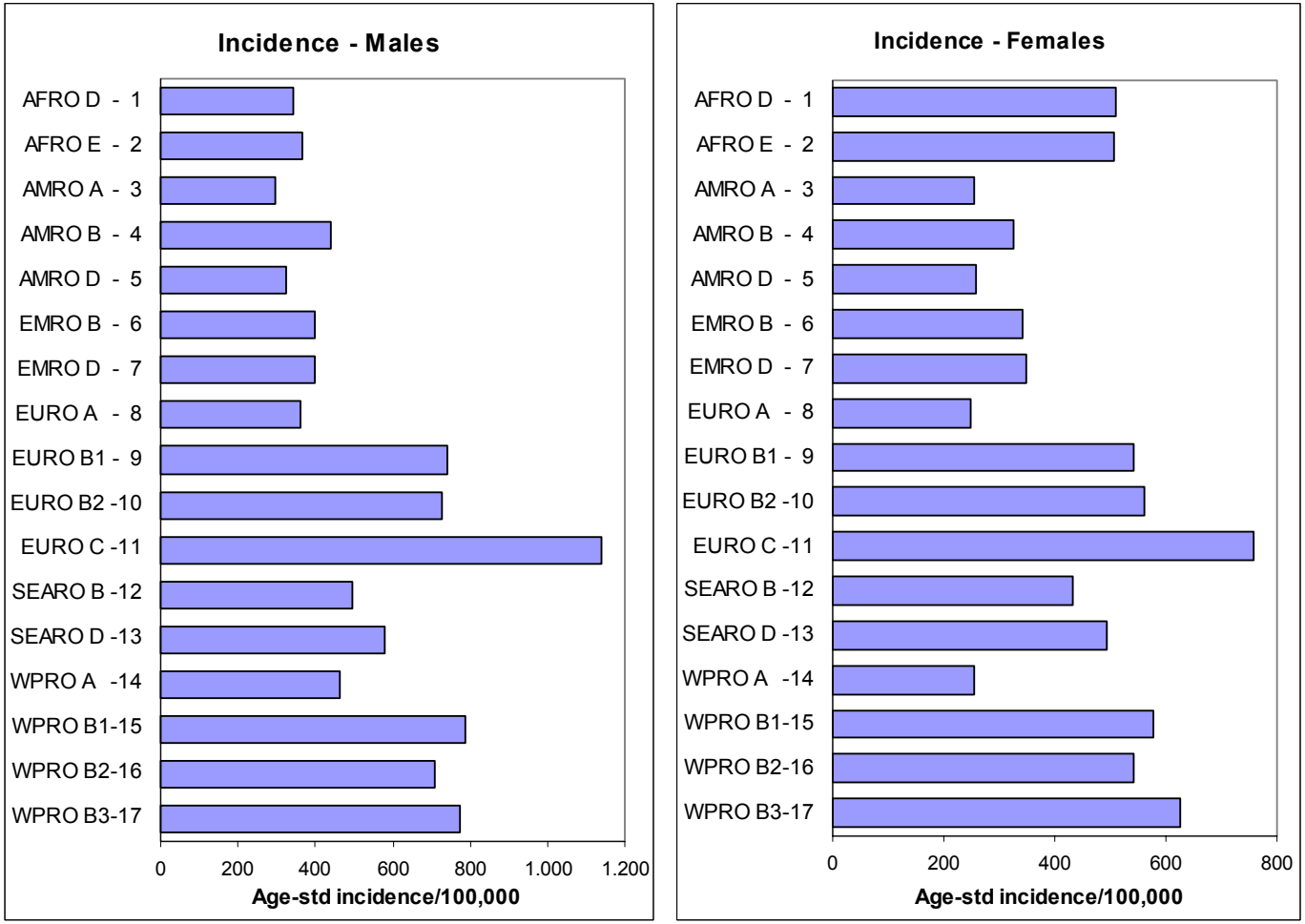


Figure 16: Stroke incidence in WPR-A in the GBD2000 Study compared with local stroke studies, men.

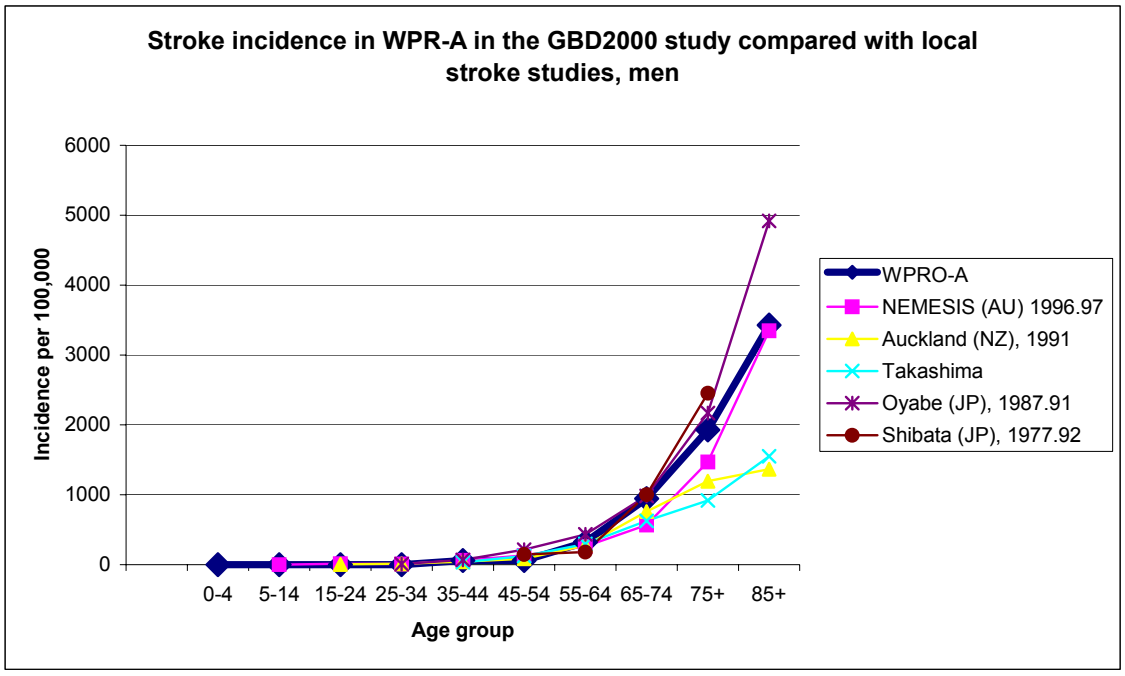


Figure 17: Stroke incidence in EUR-A in the GBD2000 study compared with local stroke studies, men.

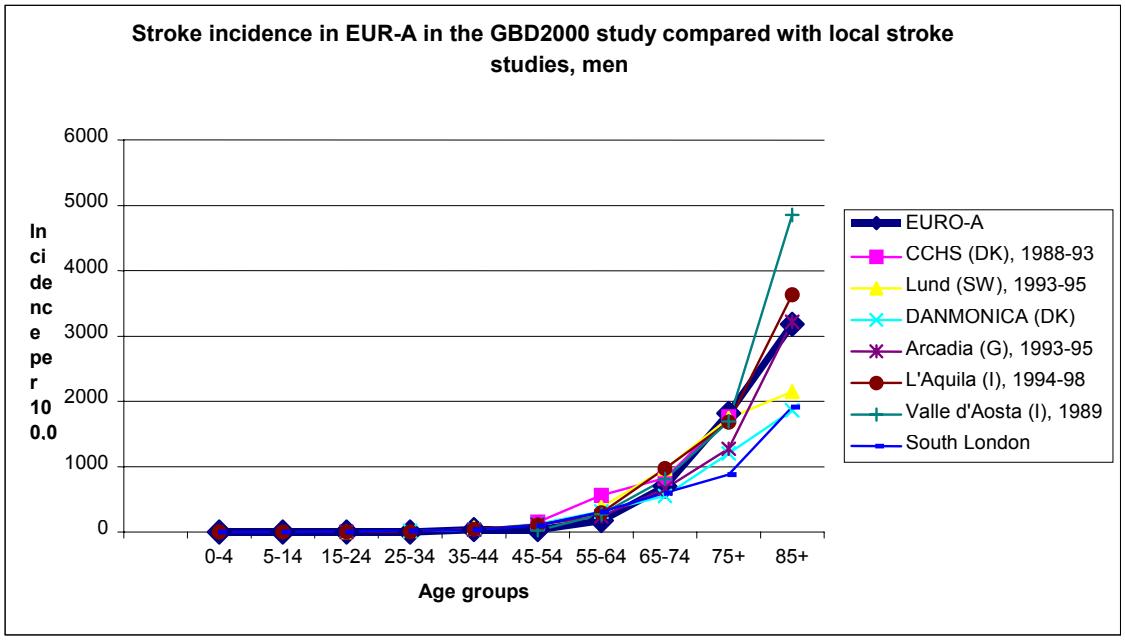


Figure 18: Stroke incidence in AMR-A in the GBD2000 study compared with local stroke studies, men.

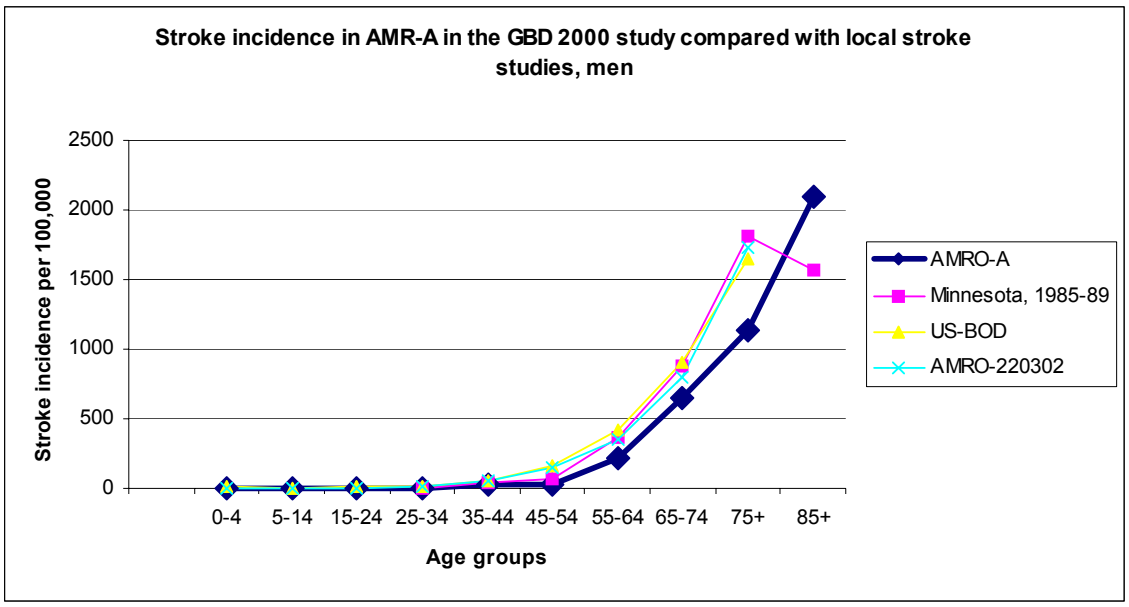


Figure 19: Stroke incidence in WPR-A in the GBD2000 study compared with local stroke studies, women.

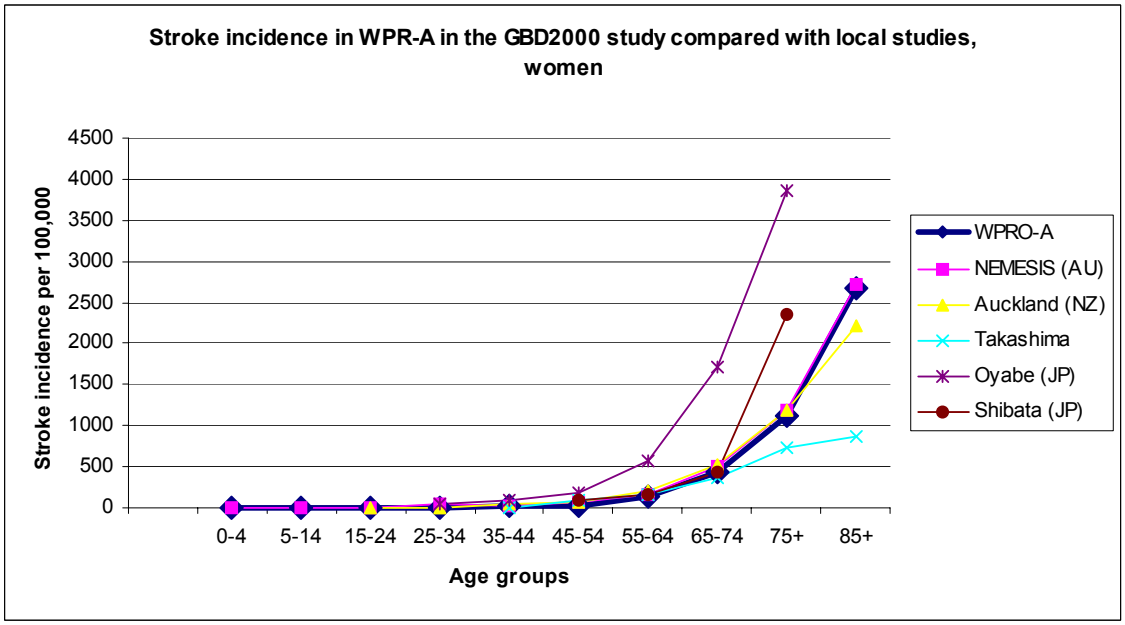


Figure 20: Stroke incidence in EUR-A in the GBD2000 study compared with local stroke studies, women.

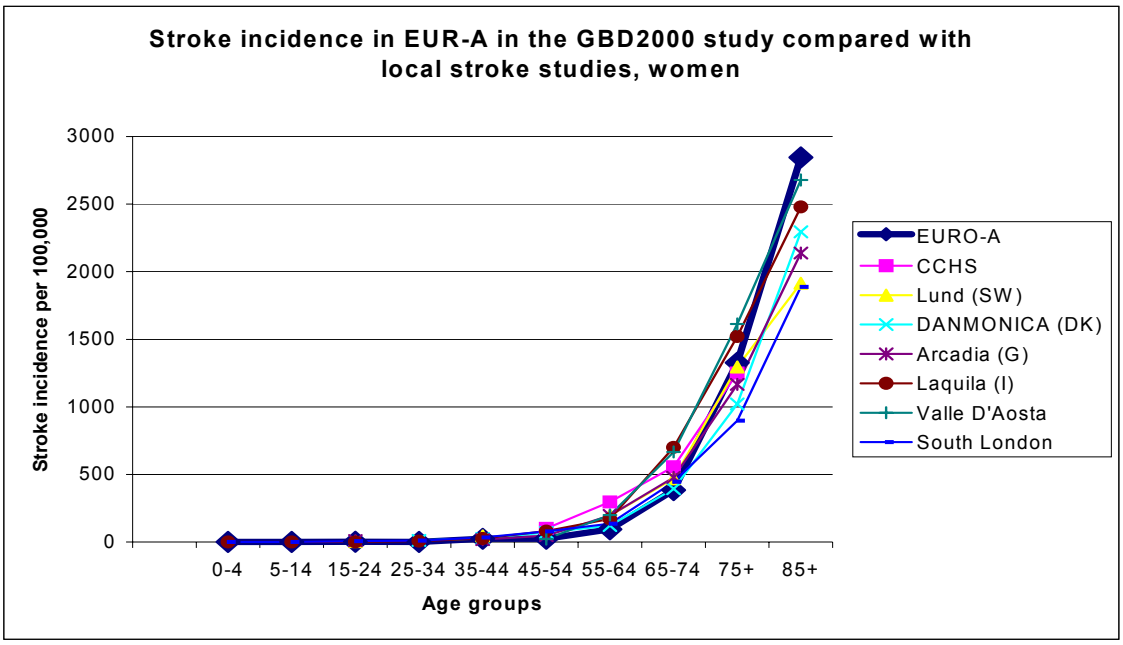
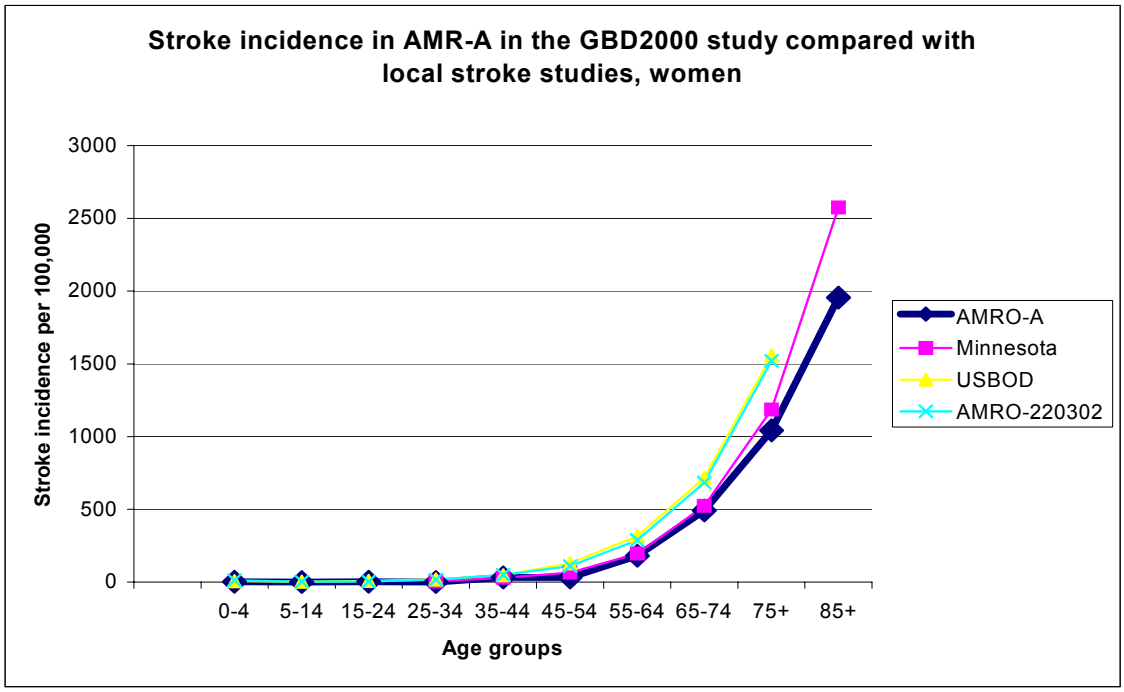


Figure 21: Stroke incidence in AMR-A in the GBD2000 study compared with local stroke studies, women.



4.2 Prevalence of stroke survivors

The estimated stroke prevalence rates are shown in Table 13 and age standardized incidence rates are shown in Figure 22.

The prevalence rates of stroke are a combined measure of the incidence, survival, and duration. Thus, it includes all patients who have had a stroke irrespective how they have recovered. Studies on stroke prevalence have estimated that two thirds to three quarters of people who claim to have experienced a stroke in the past are independent in self care activities [130-135].

In all regions the prevalence increases with increasing age. The two African regions had the smallest prevalence rates while WPR-A had the largest prevalence rates. Age standardized prevalence rates in men range in most regions from 500 to 1,000 per 100,000 with the highest age-standardized stroke prevalence rate calculated for the EUR-C region. In women the range in stroke prevalence rates are slightly smaller than for men and with the highest age-standardized rates calculated for EUR-C. The estimates are in good agreement with prevalence rates from stroke studies that report rates in the range from 600-1,000 per 100,000 population in most EME populations [130-132;136-138].

Prevalence studies in developing countries are mostly restricted to house-hold-surveys where only patients with disability are likely to be registered. Prevalence in China has been reported as 200-300 per 100,000 [139;140]. A study from NW India reported prevalence rates of 630 per 100,000 [141] and 420 per 100,000 in Bombay based on a door to door survey of 14,000 subjects [142]. In rural Kashmir the prevalence rate of stroke was 630 per 100,000 in subjects aged > 40 years but based on only 81 cases [143]. In another study in the OAI region [144], prevalence of stroke was estimated to 690 per 100,000 population. In a house-hold survey in Taiwan including 11,925 subjects 71 were identified as stroke patients with a crude point prevalence rate of 595 per 100,000 [145]. Prevalence in Tunesia was 720 per 100,000 in people 45 years and over [146]. A study of hemiplegic stroke survivors from Tanzania reported crude prevalence rates of disability resulting from stroke ranging from 208 to 2,345 per 100,000 among men and women aged 55 to 85+ years [147]. The most likely explanation for the wide variation in crude prevalence is the difference in the age structure of the different populations age the age groups measured. Also definition of stroke varied widely between studies.

Graphs comparing prevalence studies are shown in the figures 23 and 24. The estimates are remarkably overlapping both when compared with the two national BOD studies and stroke studies from different populations such as for example the prevalence rates from the Auckland stroke study [75]. The rates from the NHANES study are based on self-reported stroke, which is likely to lead to an underestimation of the stroke prevalence. Nevertheless, in men the rates are slightly higher than the estimated rates for AMR-A especially in the older age groups, while of similar magnitude in women.

Table 13: Prevalence of stroke

	AFRO-D		AFRO-E		AMRO-A		AMRO-B		AMRO-D		EMRO-B		EMRO-D		EURO-A		EURO-B1	
Age groups	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
30-44	81	120	117	44	169	144	189	222	139	160	176	133	66	66	180	104	224	287
45-59	627	900	518	689	1,228	1,297	1,496	1,348	998	926	872	920	841	674	1,120	736	1,965	1,491
60-69	1,865	2,686	1,655	2,426	4,783	3,865	4,872	3,588	3,046	2,197	3,481	2,924	3,326	2,750	4,027	2,348	7,087	5,266
70-79	2,539	3,732	2,406	3,825	8,749	7,357	7,330	5,348	4,463	3,209	6,377	4,787	5,101	4,581	8,926	6,432	11,386	9,320
80+	2,335	4,238	2,302	4,185	11,257	10,463	6,717	5,620	4,028	3,352	7,033	5,449	4,569	3,591	12,218	10,319	9,670	7,893
All ages	159	263	139	218	1,285	1,478	646	609	331	301	365	320	292	294	1,520	1,487	1,393	1,390

	EURO-B2		EURO-C		SEARO-B		SEARO-D		WPRO-A		WPRO-B1		WPRO-B2		WPRO-B3	
Age groups	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
30-44	148	104	375	182	147	98	65	47	304	133	143	123	163	146	174	100
45-59	1,728	1,110	2,297	1,613	1,265	1,072	1,060	778	2,127	1,047	1,738	1,279	1,334	983	1,626	1,236
60-69	6,593	4,789	8,320	6,300	4,677	3,845	5,079	3,858	6,727	3,271	7,568	4,974	6,242	4,158	5,879	4,739
70-79	8,880	7,189	12,994	10,657	7,183	6,272	7,233	6,509	12,427	7,401	11,944	9,502	9,822	6,846	10,263	8,500
80+	6,967	6,254	11,611	10,088	6,030	5,110	5,183	5,038	16,656	12,555	10,524	9,549	7,524	6,093	8,758	6,306
All ages	691	661	548	520	548	520	510	456	2,467	1,845	1,154	988	643	520	450	419

Figure 22: Age-standardized stroke prevalence rates for men and women in 17 WHO regions, the GBD2000.

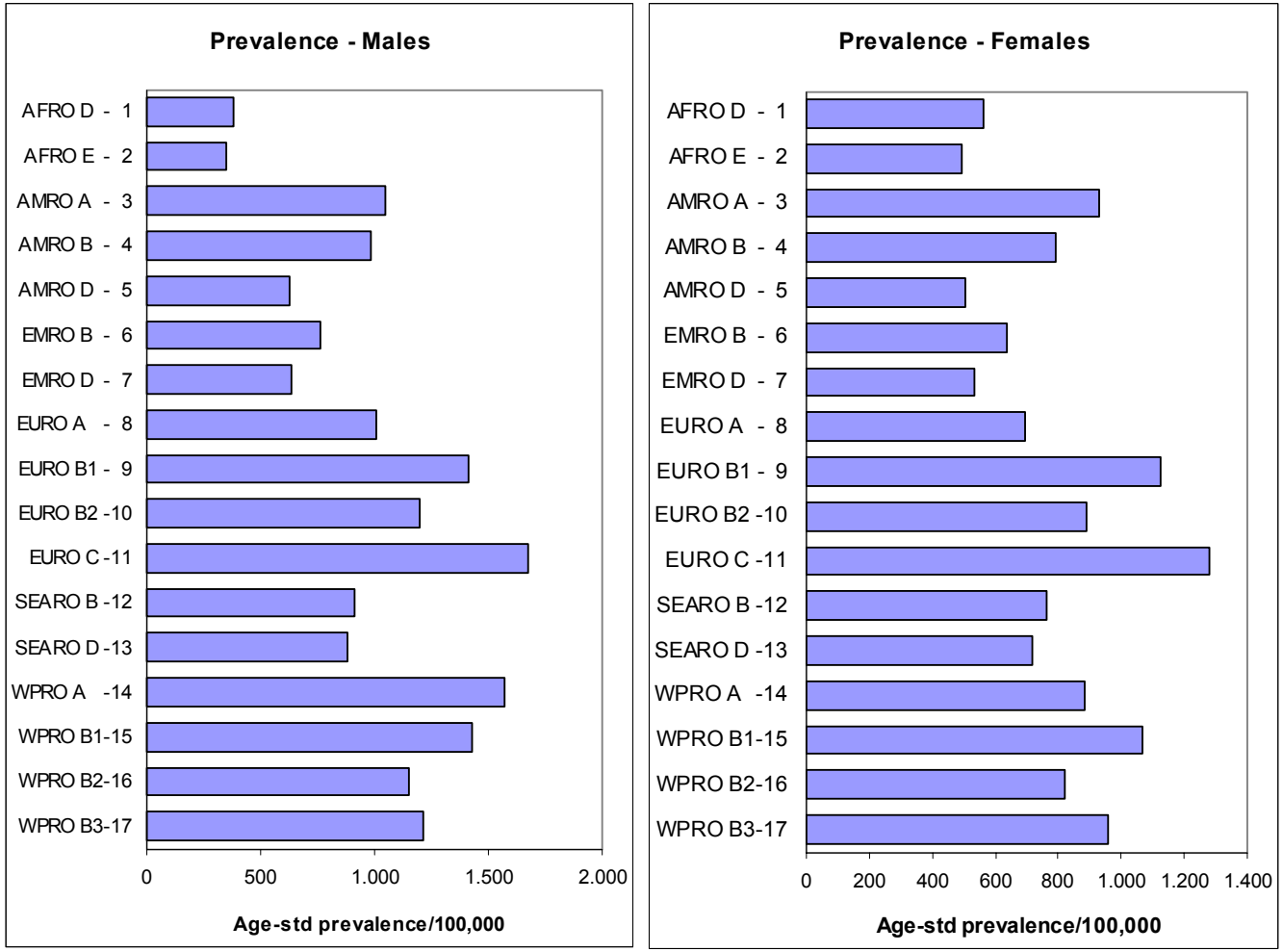


Figure 23: Stroke prevalence rates in men in the GBD2000 study compared with selected stroke studies.

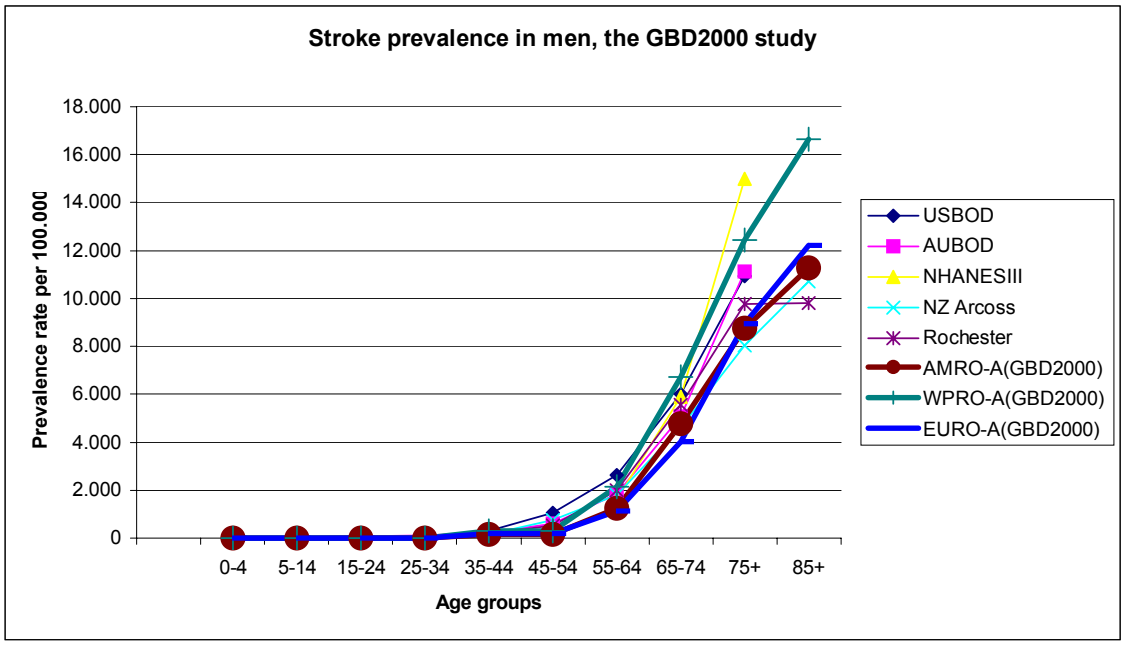
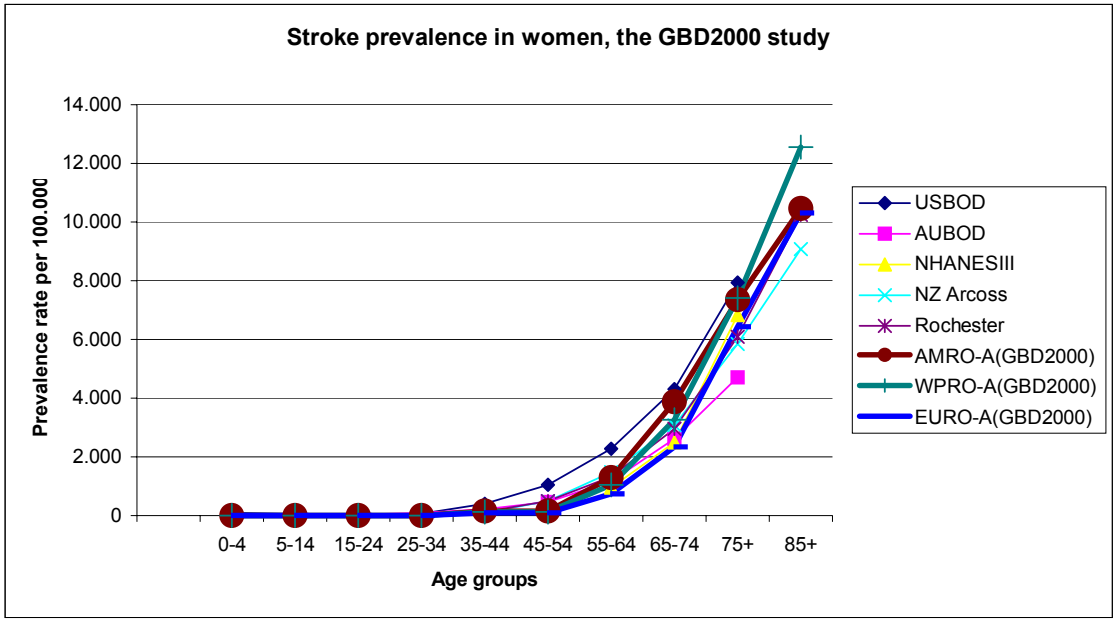


Figure 24: Stroke prevalence rates in women in the GBD2000 study compared with selected stroke studies.



4.3 Years Lost to Disability (YLD) and Disability Adjusted Life Years (DALYs) in the GBD2000 study

Table14 summarizes the global burden of cerebrovascular disease estimates for the GBD 2000 compared with the cerebrovascular disease estimates from the GBD 1990 (27).

Table 14: Cerebrovascular disease: global total YLD, YLL and DALY estimates, 1990 and 2000

Global totals

	Males	*Females*	*Persons*
YLD ('000)			
*GBD 1990**	3.288	3.120	6.408
GBD 2000	5.911	5.227	11.139
YLL ('000)			
*GBD 1990**	16.098	16.017	32.115
*GBD 2000**	18.558	18.246	36.804
DALY ('000)			
*GBD 1990**	19.387	19.136	38.523
GBD 2000	24.469	23.473	47.943

*Total for all sequelae

The total number of DALYs has increased from 38.523 in 1990 to 47.943 in the GBD2000 study. The increase was due to almost a doubling of the YLDs in both men and women and an increase in YLLs each contributing with 50% of the increase. In 1990 the YLDs constituted 17 % of the DALYs while 23% in the GBD2000 study.

The contribution of DALYs from each region to the total number of DALYs varied markedly, Table 15. WPR-B1 was the single region with most DALYs followed by SEAR-D and EUR-C. Both WPRO-B1 and EURO-C had high YLL and YLD rates, and all three regions are populous. In all regions except SSA the estimated YLDs increased, especially in the former socialistic countries and China (FSC and WPR-B1), Figure 25 and 26. The decreases in SSA are strongly related to the altered cause of death pattern in this region as a consequence of the AIDS epidemic. When examining the contribution of YLDs according to age, the increases in YLDs are predominantly due to higher rates in subjects aged 50 years or more for both men and women, Figure 27 and 28.

Graphs comparing the ratio between YLDs and YLLs in the GBD1990 and GBD2000 studies are shown in Figure 29 and 30. Generally the YLD/YLL ratio is higher in the GBD2000 study especially in EME, China, LAC, and OAI. The ratio between YLDs and YLLs in the 1990 and the 2000 GBD study are of almost the same magnitude in the FSE, India, and MEC.

Table 15: Cerebrovascular disease: YLD, YLL and DALY estimates for WHO regions, 2000

	Incidence YLD/100,000 Males	*Incidence YLD/100,000 Females*	*YLL*/100,000 Males*	*YLL/100,000 Females*	*Total YLD ('000)*	*Total YLL* ('000)*	*Total DALYs ('000)*
AFR D	40,2	66,4	386,4	523,5	178	1.520	1.698
AFR E	36,3	52,5	422,1	518,6	150	1.589	1.739
AMR A	248,4	258,7	251,8	290,2	785	840	1.625
AMR B	157,4	147,1	425,4	405,6	673	1.838	2.511
AMR D	80,5	74,7	330,2	324,0	55	233	289
EMR B	94,1	80,7	264,7	263,0	122	368	491
EMR D	73,2	72,1	513,9	420,3	100	646	746
EUR A	287,4	246,5	427,3	446,5	1.095	1.796	2.891
EUR B1	303,9	282,6	1026,5	1017,0	487	1.696	2.183
EUR B2	164,7	145,8	653,1	684,8	79	341	420
EUR C	416,1	423,3	1758,6	1793,5	1.032	4.366	5.398
SEAR B	140,8	130,4	483,9	522,6	535	1.985	2.520
SEAR D	124,7	109,4	522,2	522,9	1.581	7.045	8.627
WPR A	484,6	314,3	537,3	402,9	595	701	1.295
WPR B1	279,5	228,5	848,2	768,4	3.459	10.992	14.451
WPR B2	152,3	132,5	584,0	553,2	202	807	1.010
WPR B3	146,1	126,5	646,9	554,0	9	41	51
Total	*194,2*	*174,2*	*609,6*	*608,1*	*11.139*	*36.804*	*47.943*

Figure 25: cerebrovascular disease YLD rates in the GBD 1990 and 2000 studies, men.

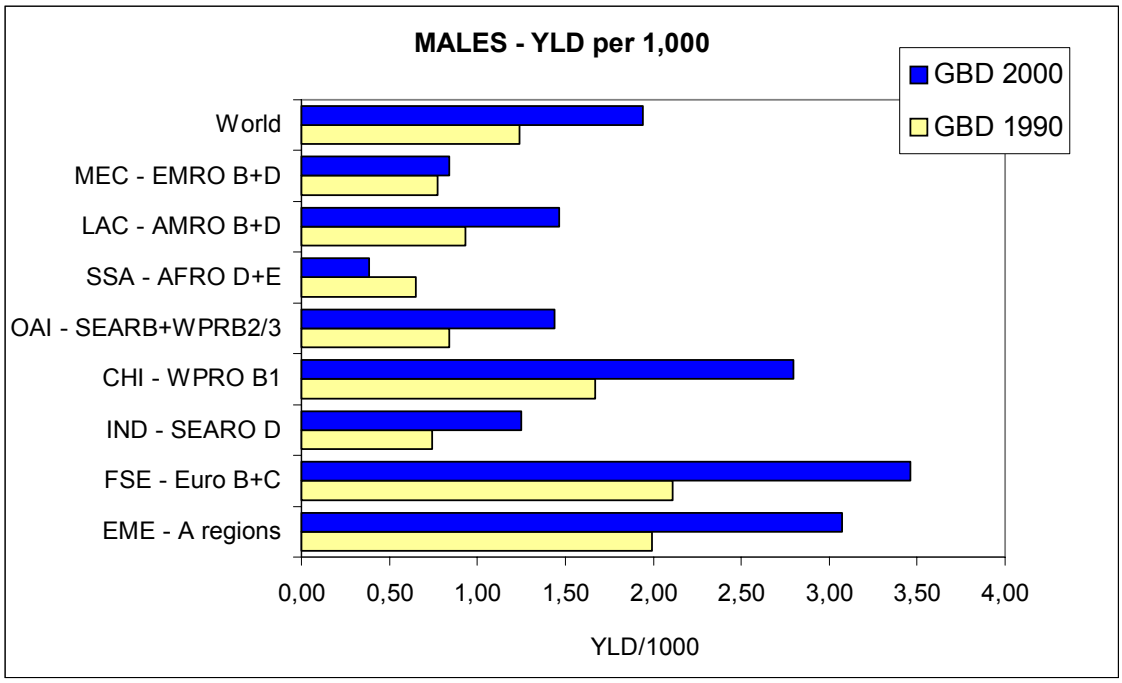


Figure 26: cerebrovascular disease YLD rates in the GBD 1990 and 2000 studies, women.

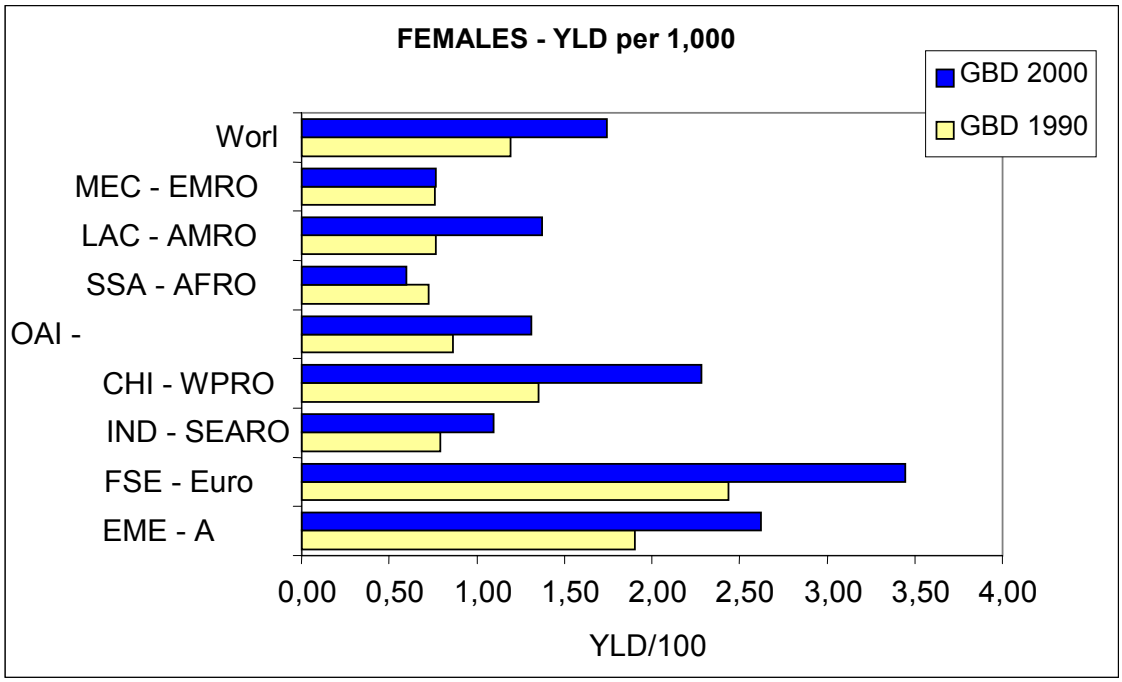


Figure 27: cerebrovascular disease YLD rates, by age group in the 1990 and 2000GBD studies, men. .

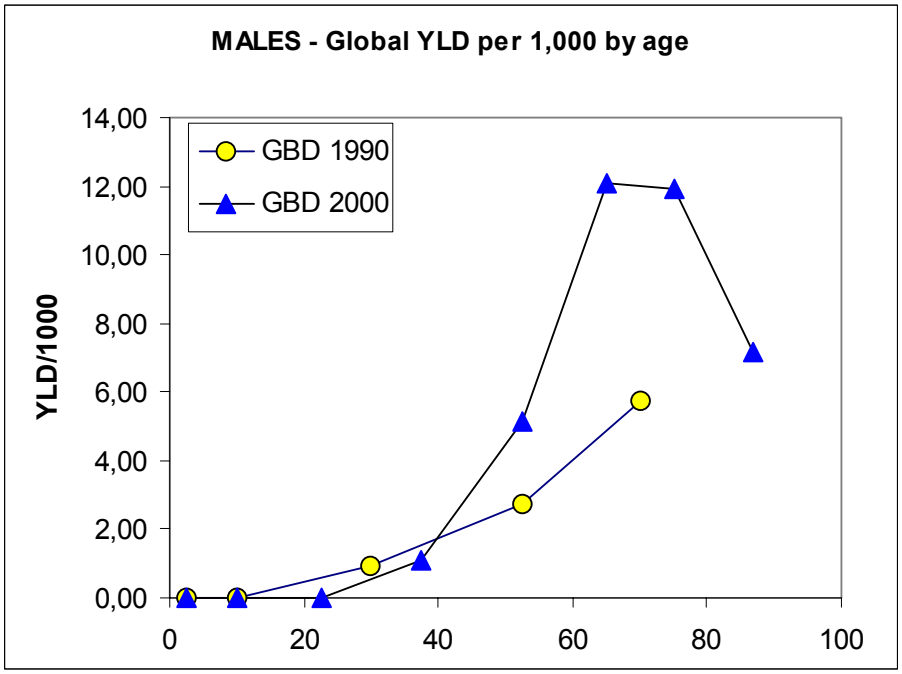


Figure 28: cerebrovascular disease YLD rates, by age group in the 1990 and 2000GBD studies, women.

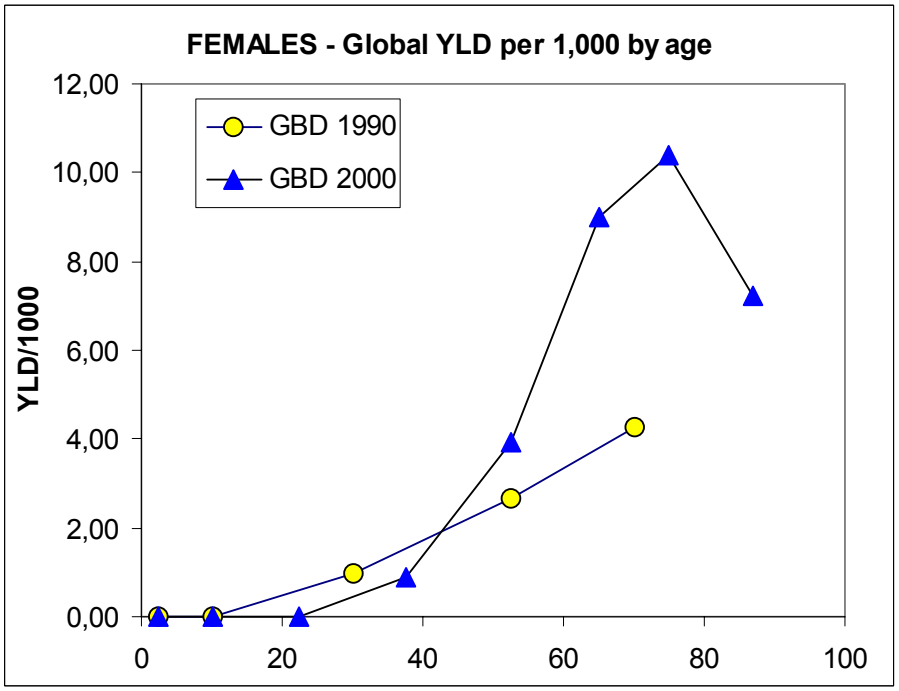


Figure 29: Ratio between YLD and YLL for 8 WHO regions in 1990 and 2000, men.

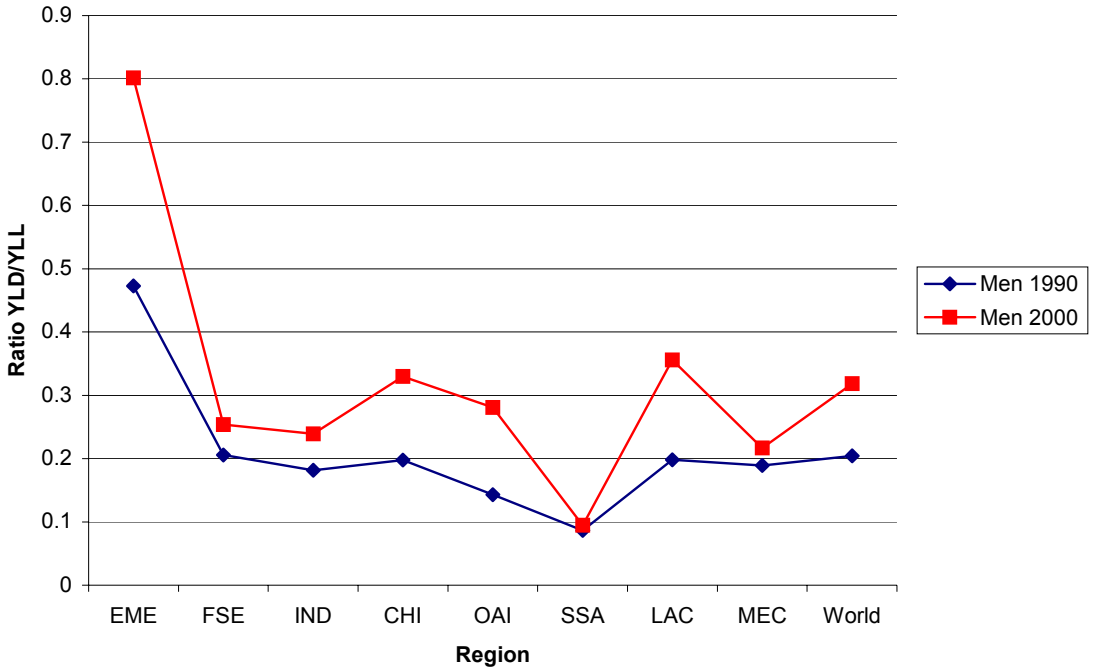
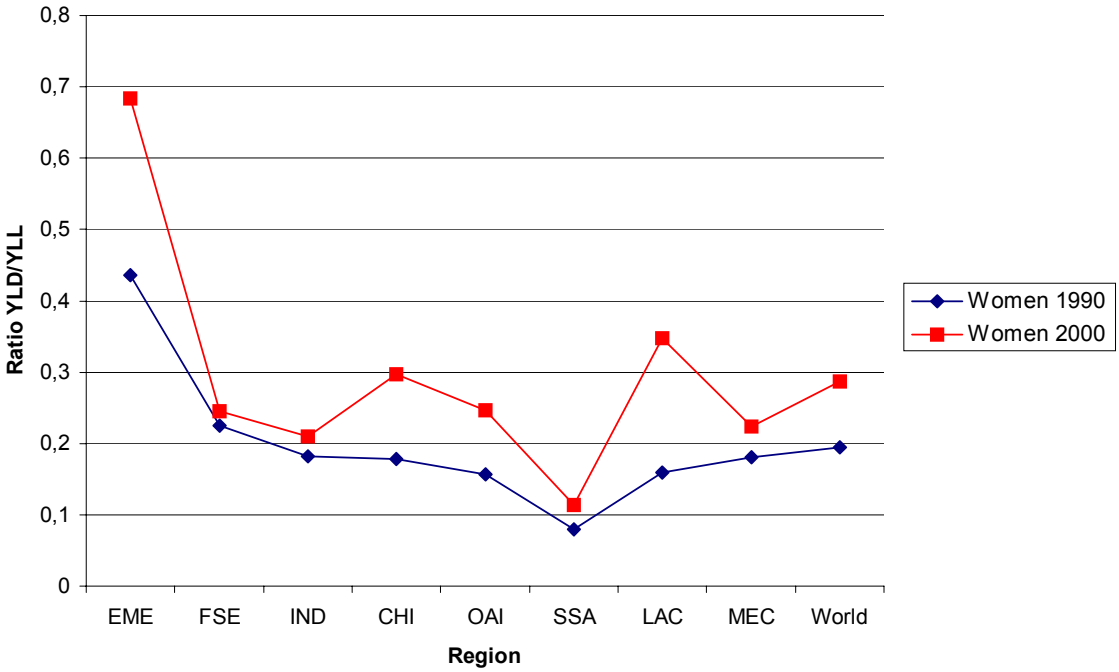


Figure 30: Ratio between YLD and YLL for 8 WHO regions in 1990 and 2000, women



5 Discussion

The global burden of cerebrovascular disease has increased from 38,523,000 DALYs in the 1990 GBD study to 47,943,000 DALYs in the GBD2000 study. The increase is equally due to increases in YLLs and YLDs. The estimates have especially increased for WPR-B1 and EUR-C, whereas there are decreases in both YLLs and YLDs for the two African regions.

In both the GBD1990 and the GBD2000 study was approximately four-fifth of the DALYs due to YLLs. The difference in the proportion, which is related to YLDs from 17% in the GBD1990 study to 23% in the GBD2000, is remarkably small considering the difference methodologies that were used. It was expected that the total number of DALYs would increase as the population in many regions are ageing and more subjects are likely to reach the age where stroke becomes a more common disease. In accordance, the increase in YLDs is predominantly in subjects aged more than 50 years. In addition, in many countries the prevalence of major risk factors for stroke has increased as discussed in section 1.2.2. An ageing population and increased exposure to major risk factors are both related to the theory of changing disease pattern as populations undergo the epidemiological transition [148]. This transition is characterized by a shift in the disease pattern from nutritional deficiencies and infectious disease, to noncommunicable diseases. Increasing stroke rates are early markers of a population having started the epidemiologic transition, with the emergence of stroke preceding other major NCDs such as ischemic heart disease and cancer. The epidemiologic transition model provides the best basis for understanding the disease pattern in countries such as China and other Asian countries where stroke is the leading cause of death with rates several times higher than for both infectious diseases and ischemic heart disease [149].

As the YLLs are the largest component of DALYs the validity of death certificates for stroke as a cause of death is a central issue. In section 2.2 we have discussed several studies on the validity of the stroke diagnoses in routine mortality statistics. The most common conclusion is that there is a tendency to underestimate the number of deaths due to stroke, although there are several limitations. Elderly subjects often have several co-morbidities and the uncertainty about the cause of death may be less reliable than in younger subjects. However, subjects aged more than 80 years only contribute 8% of the total DALYs for cerebrovascular disease. As long as there is no better way to re-classify these deaths to other causes they have remained in the calculations as provided by the routine mortality statistics. Another limitation is that coding practices may differ between countries and cultures and validation studies have only been conducted in developed countries. By using routine mortality statistics we have used the presently only data source available that covers entire countries. It is well known that the agreement between issuing health professionals differs, and the procedure for issuing death certificates differ between countries. In the majority of deaths in EME it is a medically trained person who is responsible for applying the diagnosis of the cause of death. However, in other countries where there is a shortage of medical or medical-legal professionals, a certain proportion of death certificates are issued by administrative workers who have varying levels of medical knowledge. Thus, there is no information about the validity of stroke diagnoses as a cause of death in most developing countries. Furthermore, routine mortality statistics are only available for approximately one-third of the world population. For the remaining regions estimates were based on the demographic structure and disease pattern from neighboring countries, and it is unknown how correctly this method estimates the disease pattern.

The estimated incidence and prevalence rates for the GBD2000 were compared with data from regional stroke studies. The age specific rates were in good agreement with the published data with rates around the mean of the reported range or on the low side. According to these comparisons the estimates from the GBD2000 study seem to be in accordance with the literature or to provide conservative estimates. This is an indication of that the calculated YLDs may not be too high. However, as several of the model assumptions related to the USBOD it could be expected that the AMR-A, EUR-A, and WPR-A regions which have disease and population patterns that are relatively similar to that of the US. There is more uncertainty about the validity of the model when estimating the stroke burden in developing countries where the racial, economic, and social structure is very different.

It is possible to estimate the stroke burden using many different disease models. An alternative approach to estimating the global burden of stroke than used in the GBD200 study could have been to use data from "ideal "stroke studies [8;53 150]. However, this was abandoned, as the number of such studies is very limited and mostly restricted to EME countries. Extrapolation to the remaining regions would be based on considerable uncertainty. In addition, the few ideal stroke studies are almost exclusively restricted to urban populations and several studies have shown that stroke rates differ between urban and rural populations [109]. Another model that was tried was to integrate the occurrence of other cardio-vascular disease. In developed countries the stroke occurrence in the population is to some extent related to the occurrence of other cardio-vascular disease such as ischemic heart disease. As a means to further elaborate the stroke model it was tested whether simultaneously incorporation of data on ischemic heart disease would improve the estimates. However, that generated very low stroke estimates especially from the WPR because of low rates of ischemic heart disease, which was regarded as incorrect as it is known that stroke in countries in this region is the leading cause of death, well in accordance with the theory of the epidemiological transition. This method was therefore regarded as insufficient for estimating stroke.

Each step of estimating the stroke burden included assumptions such as length of time for survival, the survival rate in stroke survivors, survival distribution according to age and sex, and the proportion of subjects who died due to stroke or other causes. It is clear that the ideal was to have comparably data from all countries about stroke occurrence, case-fatality rates, survival rates with and without disability etc. However, is it remarkable that there are very few stroke studies outside of AMR-A, EUR- A, and WPR-A when data indicate that the majority of strokes occur in developing countries. Even within developed countries there are only ideal stroke studies from a minority of these and including only a fraction of the total population. Until more and better data become available the knowledge about the stroke burden will be based on model assumptions.

6 Conclusions

Stroke is a leading cause of DALYs and the majority of stroke DALYs are from developing countries.

The current study has aimed at using existing data and to estimate the burden of stroke. The calculations are based on several assumptions where the value of each component is uncertain. The results of the GBD2000 burden of stroke study were compared with results from stroke studies in different parts of the world, predominantly developed regions. There was a good agreement and it is believed that the current data provide a reliable estimate for

the global burden of stroke. However, the amount of data on stroke occurrence and prognosis is sparse especially from developing countries hampering the possibility for a thorough evaluation of the correctness of the estimates.

With more data on stroke becoming available adjustments may be applied. These are version 2 estimates for the GBD 2000. Apart from the uncertainty analysis, updating estimates to reflect revisions of mortality estimates and any new or revised epidemiological data or evidence, it is not intended to undertake any major addition revision of these estimates.

We welcome comments and criticisms of these draft estimates, and information on additional sources of data and evidence: please contact Colin Mathers (EBD/GPE) on email mathersc@who.ch.

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