Chapter 1

Epidemiology

In order to understand the clinical management of transient ischemic attacks (TIAs) and stroke, to plan clinical services or to design randomized controlled trials, and to measure the overall impact of treatments, it is important to understand the epidemiology of stroke.

Definitions of Transient Ischemic Attack and Stroke

A stroke is defined as rapidly developing clinical symptoms and/or signs of focal, and at times global (applied to patients in deep coma and to those with subarachnoid hemorrhage), loss of brain function, with symptoms lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin (Hatano 1976). Conventionally, a TIA is distinguished from stroke on the basis of an arbitrary 24-hour cutoff for resolution of symptoms (Box 1.1). Hence a TIA is defined as an acute loss of focal brain or monocular function with symptoms lasting less than 24 hours and that is thought to be caused by inadequate cerebral or ocular blood supply as a result of arterial thrombosis, low flow, or embolism associated with arterial, cardiac, or hematological disease (Hatano 1976).

Since the early part of the twentieth century, a variety of definitions of TIA have been used (Table 1.1). However, the definition given in Box 1.1 has recently been challenged since the 24-hour time limit is arbitrary rather than being based on clinical, imaging, or pathological criteria. The 24-hour cutoff does not reflect the fact that the majority of TIAs last for less than 60 minutes, nor does it indicate a lack of infarction on brain imaging. Some TIAs are associated with radiological evidence of cerebral infarction, but there is poor correlation between clinical and imaging findings (Table 1.2). An alternative, but controversial (Easton *et al.* 2004), definition for TIA has been proposed as comprising a transient episode of neurological dysfunction caused by focal brain or retinal ischemia without evidence of acute infarction on brain imaging (Albers *et al.* 2002). The proposed new definition for TIA has the problem that brain imaging does not correlate particularly well with pathological

BOX 1.1 Definitions of Transient Ischemic Attack and Stroke as Used in This Book

Transient Ischemic Attack An acute loss of focal brain or monocular function with symptoms lasting less than 24 hours and that is thought to be caused by inadequate cerebral or ocular blood supply as a result of arterial thrombosis, low flow, or embolism associated with arterial, cardiac, or hematological disease (Hatano 1976).

Stroke Rapidly developing clinical symptoms and/or signs of focal, and at times global (applied to patients in deep coma and to those with subarachnoid hemorrhage), loss of brain function, with symptoms lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin (Hatano 1976).

Table 1.1 History of the definition of transient ischemic attack

Year	Description
1914 Hunt (1914)	Characterized "the role of the carotid arteries in the causation of vascular lesions of the brain" and described "attacks of threatened hemiplegia and cerebral intermittent claudication"
1954 CM Fisher at the *First and Second Conferences on Cerebral Vascular Diseases*, Princeton, USA	Described "transient ischemic attacks . . . which may last from a few seconds up to several hours, the most common duration being a few seconds up to 5 or 10 minutes"
1961 CM Fisher at the *Third Conference on Cerebral Vascular Diseases*	TIA described as "the occurrence of single or multiple episodes of cerebral dysfunction lasting no longer than one hour and clearing without significant residuum"
1964 Acheson and Hutchinson (1964)	Series of patients with "transient cerebral ischemia" defined as "duration of attack less than an hour"
1964 Marshall (1964)	Series of 180 patients with TIAs defined as "of less than 24-hours duration"
1975 Advisory Council for National Institute of Neurological and Communicative Disorders and Stroke (1975)	TIA defined as lasting "no longer than a day (24-hours)," although typically lasting from 2 to 15 minutes
1976 World Health Organization bulletin (Hatano 1976)	TIA defined as lasting less than 24 hours
2002 for the TIA Working Group (Albers *et al.* 2002)	TIA definition proposed based on absence of infarction on brain scanning and a 1-hour time window

Note: TIA, transient ischemic attack.

infarction: brain imaging may be normal in clinically definite stroke, silent infarction may occur, and imaging sensitivity is highly dependent on both imaging method and area of the brain being examined. Moreover, there is uncertainty regarding the pathological correlates of imaging changes such as diffusion-weighted magnetic resonance imaging (DWI) hyperintensity (Chapters 10 and 11) and leukoaraiosis, and as imaging technology advances, what is defined as TIA will change. The definition of TIA used throughout this book is, therefore, the conventional one based on symptoms or signs lasting less than 24 hours.

Anything that causes a TIA may, if more severe or prolonged, cause a stroke (Sempere *et al.* 1998). There are many non-vascular conditions that may cause symptoms suggestive of TIA or stroke, and these are referred to in this book as "TIA mimics" or "stroke mimics." The separation of TIA from stroke on the basis of a 24-hour time limit is useful since the differential diagnosis of the two syndromes is different to some extent (i.e., the spectrum of TIA mimics differs from that of stroke mimics).

Given the common mechanisms underlying TIA and stroke, the investigation of patients with these syndromes is similar. However, in TIA and minor stroke, the emphasis is on rapid identification and treatment of the underlying cause in order to prevent a recurrent

Table 1.2 Advantages and disadvantages of conventional and imaging-based definitions of transient ischemic attack

Definition	Advantages	Disadvantages
Conventional definition	Diagnosis can be made at assessment (provided that symptoms have resolved) either prior to imaging or in centers where imaging is unavailable	Diagnosis based on an arbitrary cut-point of no physiological or prognostic significance
	Comparisons with previous studies using conventional definition possible	Diagnosis based on patient recall, which may vary with time
		Diagnosis cannot be made with certainty within 24 hours in a patient with resolving (but persistent) symptoms
Imaging-based definition	Based on pathophysiological endpoint and emphasizes prognostic importance of cerebral infarction	Diagnosis based on interpretation of imaging, which is likely to vary between individuals and centers; also, sensitivity of imaging techniques is likely to increase with time with developments in computed tomography and magnetic resonance technology
	Majority of transient ischemic attacks last less than 60 minutes	Pathophysiological significance of changes on new imaging techniques not fully understood
	Encourages use of neurodiagnostic investigations	Classification of events lasting more than 1 hour without infarction unclear
	Consistent with the distinction between unstable angina and myocardial infarction	Diagnosis cannot be made in centers where no imaging is available

and possibly more severe event, whereas in severe stroke, the initial emphasis of investigation is on targeting treatment to minimize subsequent deficit. Therefore, in this book, we have considered TIA and minor stroke separately from severe stroke to reflect the difference in clinical approach to minor versus more severe cerebrovascular events.

There is no accepted definition for what constitutes "minor" stroke. This distinction between minor and major stroke is sometimes based on a score on the National Institutes of Health Stroke Scale (NIHSS) at assessment of ≤ 3 (Wityk *et al.* 1994) or a score of ≤ 2 on the modified Rankin Scale (mRS) at 1 month. Such distinctions are problematic because the NIHSS score will vary with time after the stroke and the mRS at 1 month may increase if a minor stroke is followed by a major stroke. We take the pragmatic view that minor stroke includes those strokes mild enough for patients to be seen in an emergency outpatient setting or to be sent home after initial assessment and treatment in the hospital.

Approximately 85% of all first-ever strokes are ischemic; 10% are caused by primary intracerebral hemorrhage, and approximately 5% are from subarachnoid hemorrhage (Rothwell *et al.* 2004). Within ischemic stroke, 25% are caused by large artery disease, 25% by small vessel disease, 20% by cardiac embolism, 5% by other rarer causes, and the remaining 25% are of undetermined etiology. Ischemic stroke may also be classified by anatomical location, using simple clinical features, as total anterior circulation stroke, partial anterior circulation stroke, lacunar stroke, and posterior circulation stroke. This is of some help in identifying the likely underlying pathology and gives information as to prognosis (Chapter 9).

The Burden of Transient Ischemic Attack and Stroke

Data from the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD), one of the most comprehensive observational epidemiological studies to date, estimated the absolute numbers of people with first stroke in 119 countries (58 high-income, 61 low- and middle-income) to be 16.9 million in 2010 (Feigin *et al.* 2014). More than 38% of new strokes (50% in high-income and 32% in low- and middle-income countries) were in people aged 75 years and older. In the UK alone, there were about 150,000 new strokes in 2010 (Feigin *et al.* 2014), making it by far the most common neurological disorder (MacDonald *et al.* 2000) (Table 1.3). The Framingham Study estimated 1 in 6 men and 1 in 5 women may suffer from a stroke if they lived to be 75 years old (Seshadri *et al.* 2006). Stroke is the second most common cause of death worldwide (Lozano *et al.* 2012). However, mortality data underestimate the true burden of stroke since, in contrast to coronary heart disease and cancer, the major burden of stroke is chronic disability rather than death (Wolfe 2000), and in 2010, GBD noted 102 million disability-adjusted life-years (DALYs) were lost due to stroke (Feigin *et al.* 2014).

Stroke is the third-leading cause of premature death and disability, and approximately a third of stroke survivors are functionally dependent at 1 year (Murray et al. 2012; MacDonald *et al.* 2000). Stroke also causes secondary medical problems, including dementia, depression, epilepsy, falls, and fractures. Globally, with an increasing number of people with stroke (ischemic and hemorrhagic), stroke-related deaths, and DALYs lost due to stroke, the burden of stroke is increasing (Krishnamurthi *et al.* 2013; Feigin *et al.* 2014). This will probably increase further, unless there are substantial decreases in age- and sex-specific incidence (Rothwell *et al.* 2004). Furthermore, while ischemic stroke is the main pathological stroke subtype, the burden of hemorrhagic stroke (mortality-to-incidence ratio and DALYs lost) is much higher (Krishnamurthi *et al.* 2013).

In the UK, the treatment of and productivity lost arising from stroke result in total society costs of approximately £9 billion per year, accounting for about 6% of the total National Health Service (NHS) and Social Services expenditure (Rothwell 2001; Saka *et al.* 2009). However, a significant bulk of the global stroke burden is borne by low- and middle-income countries, due partially to a disproportionate higher incidence of hemorrhagic stroke in these countries (Krishnamurthi *et al.* 2013).

Additionally, TIAs are also common, and it is estimated that 54,000 TIAs occur each year in England (Giles and Rothwell 2007). By definition, TIA causes transient symptoms only and, therefore, has no long-term sequelae per se. However, the importance of TIA lies in the high early risk of stroke and the longer-term risk of other vascular disease. Indeed, it has been estimated that approximately 20% of strokes are preceded by TIA (Rothwell and Warlow 2005).

Table 1.3 Comparative incidence and prevalence rates of common neurological conditions measured in a population-based study of approximately 100,000 people registered with 13 general practices in London, UK, and conducted between 1995 and 1996

Condition	Incidence rate (95% CI)[a]	Prevalence rate (95% CI)[a]
First TIA or stroke[b]	2.05 (1.83–2.30)	
Second TIA or stroke[b]	0.42 (0.33–0.55)	
Intracranial hemorrhage	0.10 (0.05–0.17)	0.5 (0.2–0.8)
Any stroke		9 (8–11)
Epilepsy[c]	0.46 (0.36–0.60)	4 (4–5)
First seizure	0.11 (0.07–0.18)	
Primary CNS tumor	0.10 (0.05–0.18)	
Parkinson's disease	0.09 (0.12–0.27)	2 (1–3)
Shingles	1.40 (1.04–1.84)	
Bacterial infection of CNS	0.07 (0.04–0.13)	1 (0.8–2.0)
Multiple sclerosis	0.07 (0.04–0.11)	2 (2–3)
Myasthenia gravis	0.03 (0.008–0.070)	
Guillain-Barré syndrome	0.03 (0.01–0.06)	
Motor neuron disease	0.02 (0.003–0.050)	0.1 (0.01–0.30)

Notes: CI, confidence interval; TIA, transient ischemic attack; CNS, central nervous system.
[a] Age- and sex-adjusted rates per 1,000 population.
[b] Includes ischemic and hemorrhagic stroke.
[c] Two or more unprovoked seizures.
Source: From MacDonald *et al.* (2000).

Understanding of the epidemiology of stroke has lagged behind that of coronary heart disease because of a lack of research funding for stroke (Rothwell 2001; Pendlebury *et al.* 2004; Pendlebury 2007) and because stroke is a much more heterogeneous disorder. Separate assessment of the different stroke subtypes should ideally be made in epidemiological studies of stroke. Stroke subtype identification was often not possible in early studies because of a lack of brain and vascular imaging, and it remains problematic today because of the frequent difficulty in ascribing a cause for a given stroke even when imaging is available. The epidemiology of TIA is more challenging even than stroke since patients with TIAs are more heterogeneous and present to a variety of different clinical services, if they present to medical attention at all. Furthermore, reliable diagnosis of TIA requires early and expert clinical assessment (there is no diagnostic test for TIA), making epidemiological studies labor intensive and costly.

Mortality

Stroke mortality rises rapidly with age (Rothwell *et al.* 2005). The increase in mortality in the elderly is mainly a result of the steep rise in the incidence of stroke with age but also, to

a lesser extent, reflects the increase in case fatality in older patients. In other words, older people are more likely to have a stroke (incidence), and if they do have one, it is more likely to be fatal (case fatality). GBD estimated that in 2010, there were 5.9 million stroke deaths, 71% of which occurred in low- and middle-income countries (Feigin *et al.* 2014). Mortality-to-incidence ratio was 0.35 (0.32 in high-income countries and 0.36 in low- and middle-income countries). Although the overall age-adjusted mortality rate reduced by 25% (37%, 95% CI, 31–41% in high-income countries and 20%, 95% CI, 15–30% in low-income and middle-income countries) during 1990–2010, the absolute numbers of stroke-related deaths increased by 26%, much of which was accounted for by patients aged 75 years and older. Age-standardized rates of stroke mortality in people aged 75 years and older in low- and middle-income countries exceeded mortality rates by a third compared to those of high-income countries of the same age group and by more than twofold in those younger than 75. When stratified by geographical region, mortality-to-incidence ratios of stroke decreased in all GBD regions, with the exception of south Asia, eastern Europe, and high-income Asia Pacific, where they remained largely unchanged (Feigin *et al.* 2014).

Mortality-to-incidence ratios decreased for both ischemic (21%, 95% CI, 10–27%) and hemorrhagic (27%, 95% CI, 19–35%) stroke in high-income countries during 1990–2010. While mortality-to-incidence ratio also decreased for hemorrhagic stroke in low- and middle-income countries (36%, 95% CI, 16–49%), this was not significant for ischemic stroke (16%, 95% CI, –5 to 37%) (Krishnamurthi *et al.* 2013).

Incidence, Prevalence, and Time Trends

The incidence of new cases of first-ever TIA or stroke can only be reliably assessed in prospective population-based studies (Sudlow and Warlow 1996; Feigin *et al.* 2003; Rothwell *et al.* 2004) since hospital-based studies are subject to referral bias (Table 1.4). One of the most comprehensive population-based studies of stroke and TIA incidence is the Oxford Vascular Study (OXVASC), which has near-complete case ascertainment of all patients, irrespective of age, in a population of 93,000 defined by registration with nine general practices in Oxfordshire, UK (Coull *et al.* 2004). This is in contrast to previous studies, such as the MONICA project and the Framingham study, which had an age cutoff at 65 or 75 years or relied on voluntary participation.

The OXVASC study showed that the annual incidence of stroke in the UK in the first few years of this century, including subarachnoid hemorrhage, was 2.3/1,000 and the incidence of TIA was 0.5/1,000 (Rothwell *et al.* 2005), with about a quarter of events occurring in those under the age of 65 and about half in those above the age of 75 (Fig. 1.1). The incidence of cerebrovascular events in OXVASC was similar to that of acute coronary vascular events in the same population during the same period (Fig. 1.2), with a similar age distribution (Rothwell *et al.* 2005). Incidence rates, however, measure first-ever-in-a-lifetime definite events only and exclude possible, recurrent, and suspected events and so do not represent the true burden of a condition. This is especially true for TIA, where a significant proportion of cases referred to a TIA service have alternative, non-vascular conditions. Thus consequently, although the annual incidence of definite, first-ever-in-a-lifetime TIA in OXVASC was 0.5/1,000, the rate of definite or possible, incident or recurrent TIA was 1.1/1,000, and the rate of all referrals to a TIA clinic including all TIAs, suspected events with non-vascular causes and minor strokes was 3.0/1,000 (Giles and Rothwell 2007) (Table 1.5).

Table 1.4 Population- and hospital-based incidence studies

Study type	Description	Advantages
Population-based	Multiple overlapping, prospective methods of case ascertainment used to identify all individuals with condition of interest from a predefined population; includes searches of both primary and secondary care and databases of diagnostic tests and death certification/ mortality statistics	More accurate measurement of incidence through minimizing referral bias; individuals who are not managed in the hospital are included, particularly elderly, those with mild conditions, and fatal events occurring outside the hospital
		Results of studies conducted in different populations and over different time periods can be directly compared (after statistical adjustment for age and sex)
		Representative of the requirements of an entire population
Hospital-based	Methods of case ascertainment used to identify all cases that are referred, admitted, managed, or discharged from a hospital setting from a predefined population	Less time consuming and less resource intensive
	Typically, hospital-based databases only searched	Representative of the requirements for hospital services

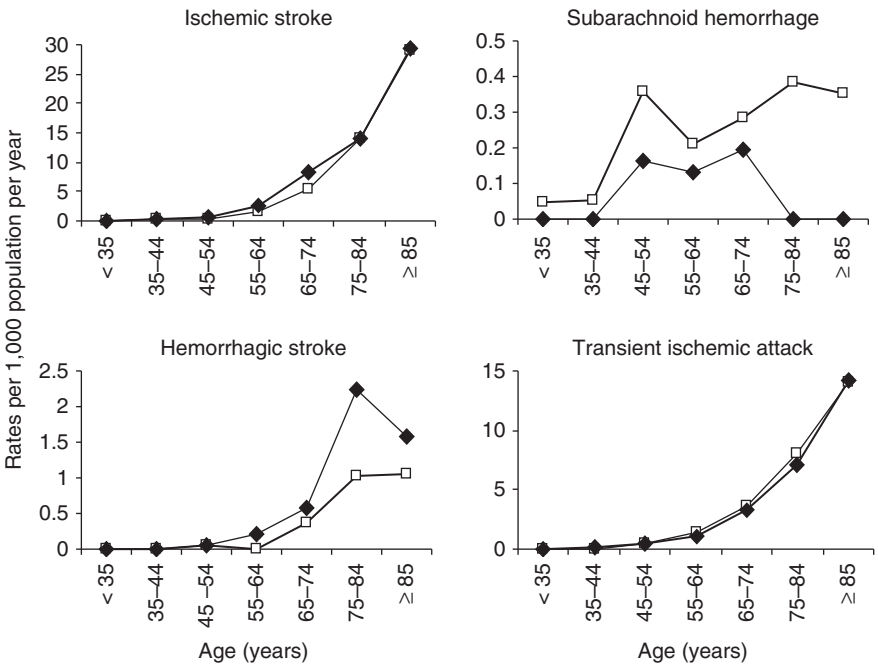

Fig. 1.1 Age-specific rates of all events for different types of acute cerebrovascular event in men (diamonds) and women (open squares) in Oxfordshire from 2002 to 2005 (Rothwell *et al.* 2005).

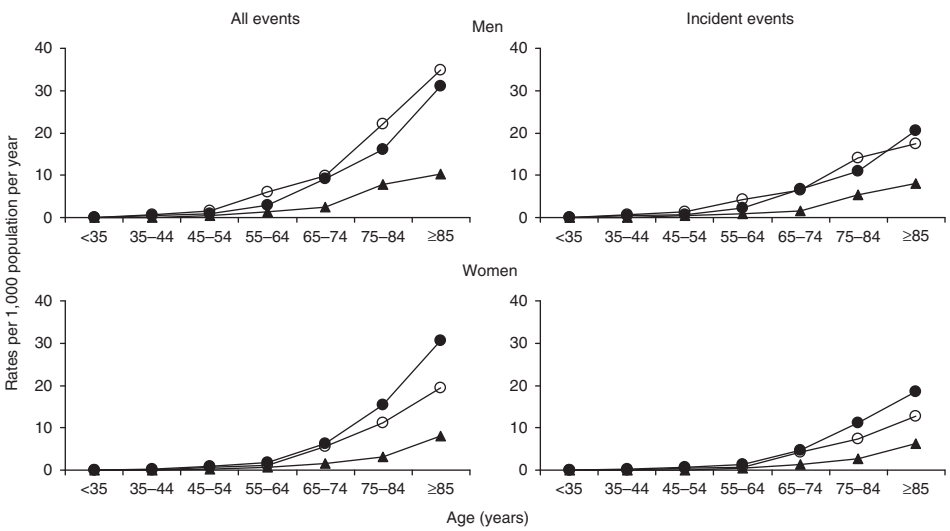

Fig. 1.2 Age-specific rates of all events and of incident events for stroke (i.e., not including transient ischemic attack; closed circles), myocardial infarction and sudden cardiac death combined (i.e., not including unstable angina; open circles), and acute peripheral vascular events (triangles) in men and women in Oxfordshire from 2002 to 2005 (Rothwell *et al.* 2005).

Table 1.5 Incidence rates of transient ischemic attack and stroke according to stringency of definition applied and previous cerebrovascular disease measured in OXVASC (2002–2005)

Category of event	Incidence rate (95% CI)[a]
TIA, incident only	
Definite	0.47 (0.39–0.56)
Definite and probable[b]	0.59 (0.5–0.68)
TIA, incident and recurrent	
Definite	0.82 (0.72–0.94)
Definite and probable[b]	0.95 (0.84–1.07)
All definite, probable, and suspected TIA (including all referrals to a TIA service with an eventual non-neurovascular diagnosis)	2.06 (1.89–2.23)
Stroke,[c] incident only	
Definite and probable	1.39 (1.25–1.54)
Stroke,[c] incident and recurrent	
Definite and probable	1.85 (1.70–2.02)
All definite, probable and suspected (including all referrals to the hospital of suspected stroke with an eventual non-neurovascular diagnosis)	2.29 (1.89–2.23)

Notes: CI, confidence interval; TIA, transient ischemic attack.
[a] Unadjusted rate per 1,000 population.
[b] Probable TIA defined as any transient symptoms lasting less than 24 hours of likely (but not certain) vascular etiology that was felt to justify secondary prevention treatment.
[c] Stroke includes ischemic and primary intracerebral hemorrhage but not subarachnoid hemorrhage.
Source: From Giles and Rothwell (2007).

Stroke prevalence is the total number of people with stroke in a population at a given time and is usually measured by cross-sectional surveys (Box 1.2). It is a function of stroke incidence and survival and, therefore, varies over time and between populations with differing age and sex structures. In the UK, the point prevalence of stroke was 507 (95% confidence interval [CI], 302–781) per 100,000 people in 1990 and 573 (95% CI, 339–899) per 100,000 people in 2010 (Feigin *et al.* 2014). Measuring TIA prevalence is methodologically more challenging because it is difficult to confirm, without direct patient assessment, whether transient neurological symptoms reported in a population survey are of vascular origin. Accurate data are, therefore, lacking, but a large telephone survey of randomly selected households in the USA reported a prevalence of physician-diagnosed TIA of 23/1,000 while a further 32/1,000 recalled symptoms consistent with TIA that had not been reported to medical attention (Johnston *et al.* 2003).

A reduction in stroke and TIA incidence since the late 1980s would be expected, given that randomized trials have shown several interventions to be effective in the primary and secondary prevention of stroke. The most recent studies of time trends in stroke incidence from GBD 2010 showed that from 1990 to 2010, the age-standardized incidence of stroke significantly decreased by 12% (95% CI, 6–17) in high-income countries but increased by

BOX 1.2 Definitions of Incidence and Prevalence

Incidence Rate The number of new cases of a condition per unit time per unit of population at risk. Usually expressed as the number of new cases per 1,000 or 100,000 population at risk per year.

Adjusted/Standardized Incidence Rates Overall incidence rates depend critically on the age and sex structure of the population studied. For example, a relatively old population may have a higher mortality rate than a younger population even if, age for age, the rates are similar. Incidence rates from different populations are, therefore, often compared following adjustment or standardization by applying age- and sex-specific rates to a "standard" population.

Prevalence Rate The total number of cases of a condition per unit of population at risk at a given time. Usually expressed as a percentage or the total number of cases per 1,000 or 100,000 population at risk.

12% (95% CI, –3 to 22%) in low- and middle-income countries (Feigin *et al.* 2014). When analyses were stratified by stroke subtype, incidence of ischemic and hemorrhagic stroke reduced by 13% (95% CI, 6–18%) and 19% (95% CI, 1–15%) respectively in high-income countries. In contrast, in low- and middle-income countries, ischemic stroke incidence increased non-significantly by 6% (95% CI, –7 to 32%) while hemorrhagic stroke incidence increased by 22% (95% CI, 5–30%) (Krishnamurthi *et al.* 2013). Similarly, between the periods 1981–1984 and 2002–2004, a 40% reduction in the incidence of fatal and disabling stroke was found in Oxfordshire, UK (Rothwell *et al.* 2004), although this reduction was less marked in the oldest old (Fig. 1.3). High-quality population-based studies of time trends in TIA and minor stroke are lacking. However, moderate rises in TIA incidence were reported in Oxfordshire, UK, between the periods 1981–1984 and 2002–2004 (Fig. 1.3) (Rothwell *et al.* 2004) and in Novosibirsk, Russia, between the periods 1987–1988 and 1996–1997 (Feigin *et al.* 2000), but no significant change in TIA incidence was found in Dijon, France, between 1985 and 1994 (Lemesle *et al.* 1999).

It is difficult to find a single explanation for the differences in change in incidence of major stroke in recent years in countries of different income levels and a contemporaneous stabilization or increase in the rates of TIA. Reductions in stroke incidence and mortality in high-income countries are likely related to better preventive strategies leading to a decline in the prevalence of causative risk factors, increased recognition of stroke symptoms leading to earlier medical advice sought, and better acute treatment and rehabilitation strategies (Murray *et al.* 2003; Wald and Law 2003). Increases in stroke incidence in low- and middle-income countries are likely to be more complex and may be related to a number of factors. Childhood mortality has substantially reduced and diseases related to infection and malnutrition have been replaced by non-communicable diseases such as stroke. Industrialization and urbanization have also led to an increase in smoking rates, and changes in nutritional quality of foods with increasing use of processed foods have resulted in an increased intake of salt and fat. Rises in TIA incidence are likely to reflect changes in public health awareness and behavior, with people now being more likely to seek medical attention for transient neurological symptoms.

Racial and Social Factors

There are racial and social differences in susceptibility to stroke and TIA (Forouhi and Satter 2006) and in the incidence of the various stroke subtypes (Fig. 1.4). Some of these