Section 1 Chapter 1

Epidemiology, risk factors, pathophysiology and causes of transient ischemic attacks and stroke

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 cut-off 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 which 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 cut-off 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 infarction: brain imaging may be normal in clinically definite stroke,

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 which 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.

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 (Chs. 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 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 an a score on the National

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 >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

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 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 (Ch. 9).

The burden of transient ischemic attack and stroke

Each year there are about one million strokes in the European Union (Sudlow and Warlow 1997), making it by far the most common neurological disorder (MacDonald *et al.* 2000) (Table 1.3). Approximately 25% of men and 20% of women can expect to suffer a stroke if they live to be 85 years old (Bonita 1992) and stroke is the second most common cause of death worldwide (Murray and Lopez 1996). However, mortality data underestimate the true burden of stroke since, in contrast to coronary heart disease and cancer, the major burden

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)
Myaesthenia gravis	0.03 (0.008–0.070)	
Guillame–Barré	0.03 (0.01–0.06)	
Motor neurone disease	0.02 (0.003–0.050)	0.1 (0.01–0.30)

Notes:
CI, confidence interval; TIA, transient ischemic attack.
[a]Age- and sex-adjusted rates per 1000 population.
[b]Includes ischemic and hemorrhagic stroke.
[c]Two or more unprovoked seizures.
Source: From MacDonald *et al.* (2000).

of stroke is chronic disability rather than death (Wolfe 2000). Brain diseases, of which stroke forms a large proportion, cause 23% of healthy years lost and around 50% of years of life lived with disability in Europe (Olesen and Leonardi 2003).

Approximately a third of stroke survivors are functionally dependent at one year and stroke is the commonest cause of neurological disability in the developed world (Murray and Lopez 1996; MacDonald *et al.* 2000). Stroke also causes secondary medical problems, including dementia, depression, epilepsy, falls and fractures. In the UK, the costs of stroke are estimated to be nearly twice those of coronary heart disease (British Heart Foundation Statistics Database 1998; Rothwell 2001), accounting for about 6% of total National Health Service (NHS) and Social Services expenditure (Rothwell 2001). As the population ages over the coming two decades, the total stroke rate will probably increase unless there are substantial decreases in age- and sex-specific incidence (Rothwell *et al.* 2004a). Stroke deaths are projected to increase from 4.5 million worldwide in 1990 to 7.7 million in 2020, when stroke will account for 6.2% of the total burden of illness (Bonita 1992; Sudlow and Warlow 1997; Menken *et al.* 2000).

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).

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).

The age-standardized death rate attributed to stroke varies six-fold between developed countries while very little is known about the developing world (Inzitari *et al.* 1995; Connor *et al.* 2007). Particularly high reported rates of stroke occur in eastern Europe and Japan, and particularly low rates in certain parts of North America and some western European countries (Feigin *et al.* 2003). The reasons for these differences are unclear but one possibility is that the stroke subtypes more likely to be fatal, particularly intracranial hemorrhage or cardioembolic stroke, are more frequent in countries with high stroke mortality.

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 91 000 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 cut-off 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 2.3/1000 and the incidence of TIA was 0.5/1000 (Rothwell *et al.* 2005), with about a quarter of events occurring in those under the age of 65 and about a 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, 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

Table 1.4. Population- and hospital-based incidence studies

Study type	Description	Advantages	Disadvantages
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 hospital are included, particularly elderly, those with mild condition and fatal events occurring outside hospital	Time consuming and resource intensive
		Results of studies conducted in different populations and over different time periods can be directly compared (after statistical adjustment for age and sex)	Patients with the condition but who do not seek medical attention or who are misdiagnosed in primary care not included
		Representative of the requirements of an entire population	Mortality statistics are not collected reliably
Hospital based	Methods of case ascertainment used to identify all cases that are referred, admitted, managed or discharged from hospital setting from a predefined population	Less time consuming and less resource intensive	Prone to referral bias; outpatient attendance variably included and events managed only in the community not included
	Typically, hospital-based databases only searched.	Representative of the requirements for hospital services	Liable to inaccuracies of diagnostic coding
			Patients transferred between departments or hospitals either not identified or double counted
			Referral rates to hospital vary geographically and over time; comparison between studies, therefore, less reliable

conditions. Thus consequently, although the annual incidence of definite, first-ever-in-a-lifetime TIA in OXVASC was 0.5/1000, the rate of definite or possible, incident or recurrent TIA was 1.1/1000, and the rate of all referrals to a TIA clinic including all TIAs, suspected events with non-vascular causes and minor strokes was 3.0/1000 (Giles and Rothwell 2007) (Table 1.5).

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, stroke prevalence is approximately 5/1000 population and in 65 to 74 year olds is approximately 50/1000 in men and 25/1000 in

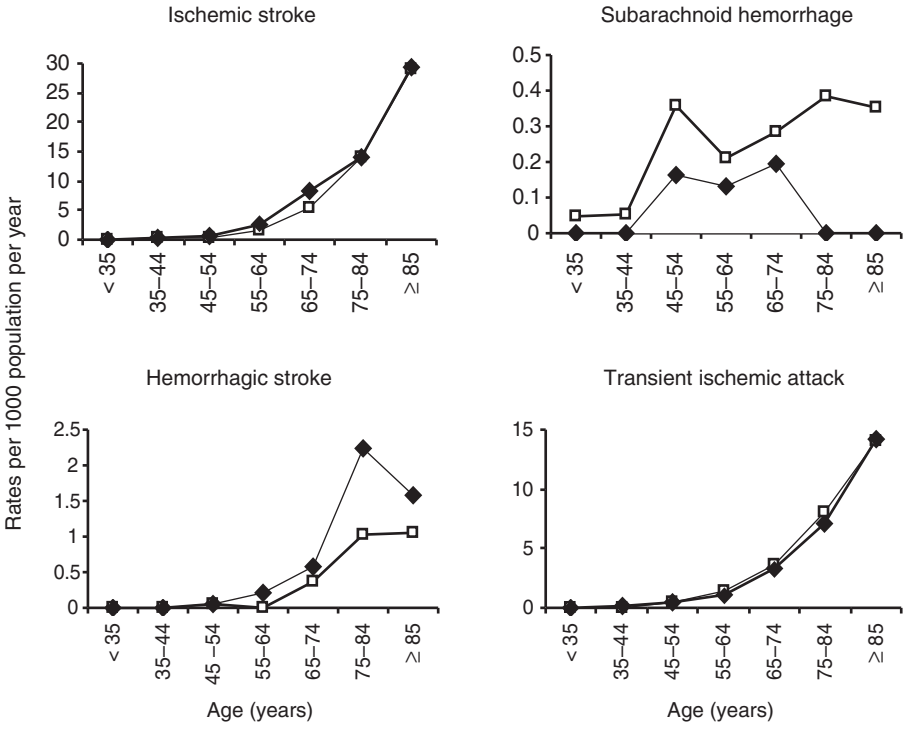

Fig. 1.1. Age-specific rates of all events for different types of acute cerebrovascular event in men (diamonds) and women (open squares) in Oxfordshire from 2002 to 2005 (Rothwell *et al.* 2005).

women (Wyller *et al.* 1994; Geddes *et al.* 1996; Bots *et al.* 1996). 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 23/1000 while a further 32/1000 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. Indeed, it has been estimated that full implementation of currently available preventive strategies could reduce stroke incidence by as much as 50–80% (Murray *et al.* 2003; Wald and Law 2003). Stroke mortality rates certainly declined from the 1950s to the 1980s in North America and western Europe (Bonita *et al.* 1990; Thom 1993), but this decline has since levelled off. Although apparent trends in stroke mortality are very difficult to interpret because of changes over time in death certification practices and case-fatality, stroke incidence also appeared to decline in the 1960s and 1970s in the USA, Asia and Europe (McGowern *et al.* 1992; Kodama 1993; Tunstall-Pedoe *et al.* 1994; Numminen *et al.* 1996). However, the majority of subsequent studies during the 1980s and 1990s, when effective preventive treatments had become more widely available, have shown either no change (Wolf *et al.* 1992; Bonita *et al.* 1993; Stegmayr *et al.* 1994) or, more commonly, an increase in age- and sex-adjusted incidence (Johansson *et al.* 2000; Medin *et al.* 2004).

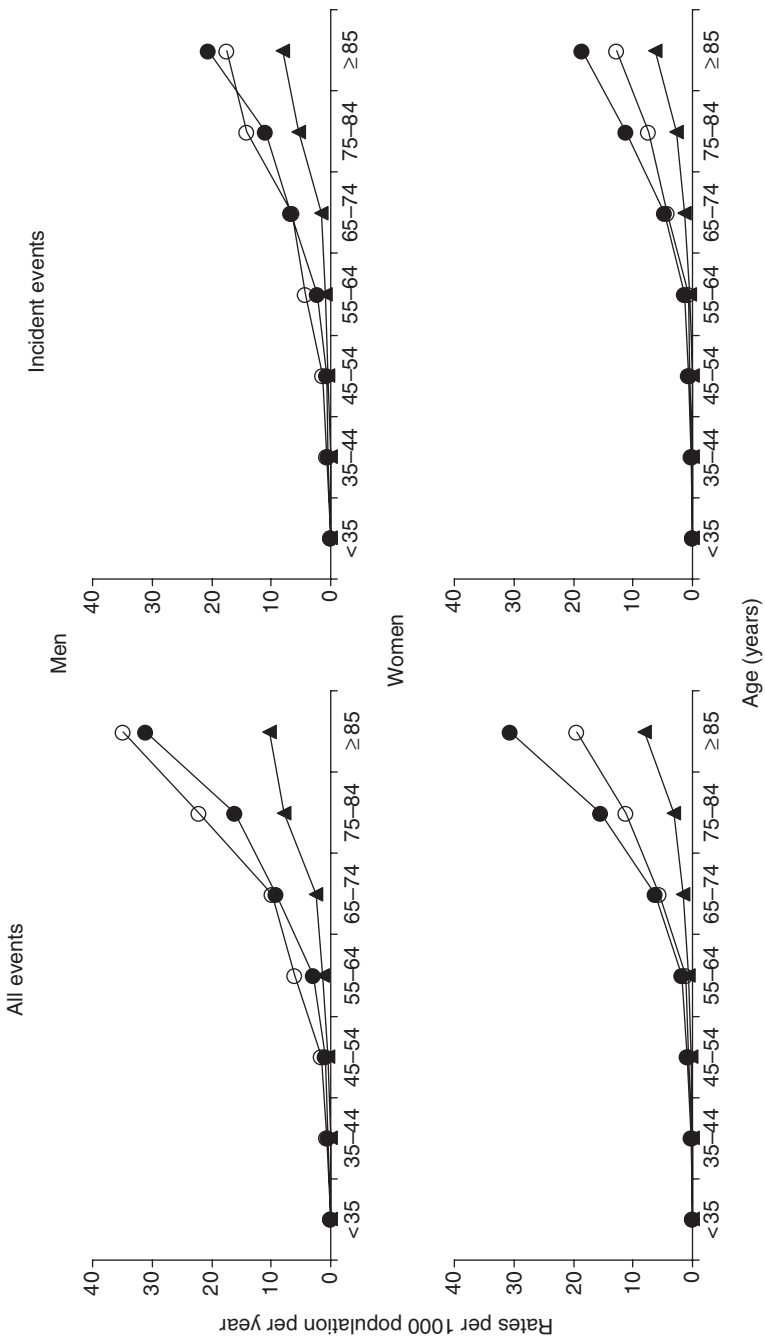

Fig. 1.2. Age-specific rates of all events and of incident events for stroke (i.e. not including transient ischemic attack; closed circles), myocardial infarction and sudden cardiac death combined (i.e. not including unstable angina; open circles), and acute peripheral vascular events (triangles) in 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 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 1000 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).

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 1000 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 1000 or 100 000 population at risk.

The most recent studies of time trends in stroke incidence do suggest that age-specific incidence is now falling (Sarti *et al.* 2003; Rothwell *et al.* 2004; Anderson *et al.* 2005; Hardie *et al.* 2005). 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

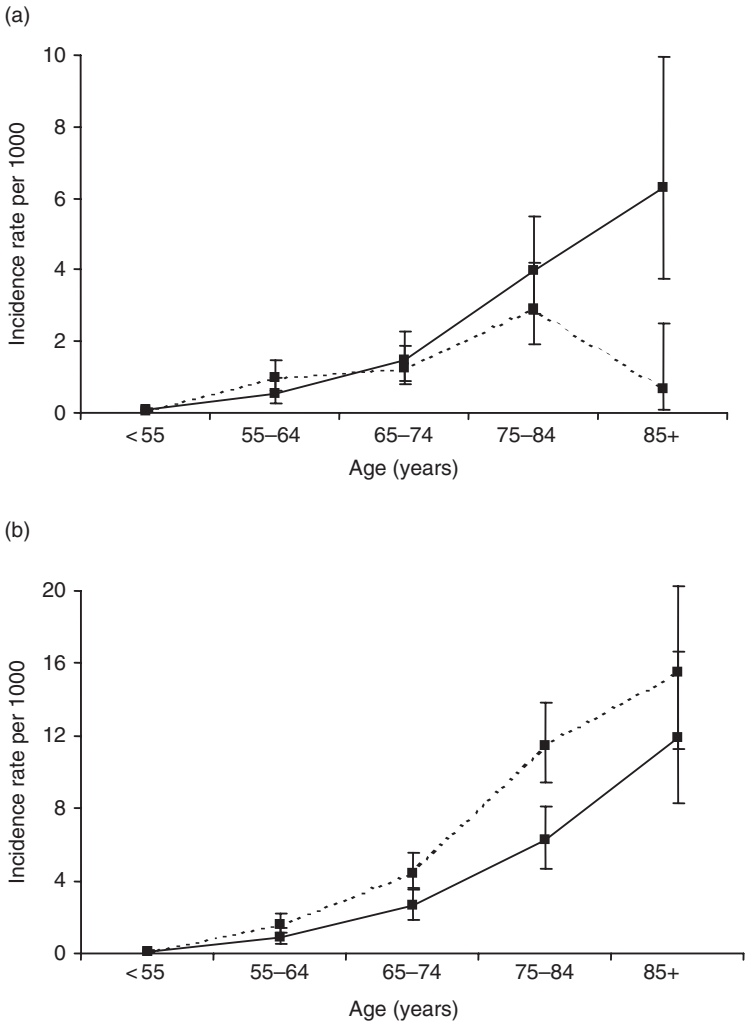

Fig. 1.3. The age-specific incidence of transient ischemic attack (a) and major disabling stroke (b) in Oxfordshire in 1981–1984 (the Oxford Community Stroke Project [OCSP], - - -) and 2002–2004 (the Oxford Vascular Study [OXVASC] —) (Rothwell *et al.* 2004).

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. It is difficult to find a single explanation for the decline in incidence of major stroke in recent years and a contemporaneous stabilization or increase in the rates of TIA. The former may be related to a decline in the prevalence of causative risk factors or to treatment of risk factors such as hypertension and elevated cholesterol, while the latter is 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 racial differences are partly caused by differences in risk factor prevalence: hypertension