NEUROEPIDEMIOLOGY

Epidemiology of stroke

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Stroke accounts for about 10% of all deaths in industrialised countries and is responsible for a vast burden of disability in the community. Once a stroke has occurred, treatment is largely focused on care and rehabilitation. However, there is evidence to suggest that stroke is potentially preventable. Firstly, there are large international variations in mortality from stroke and migrants between areas where the rates of stroke are different generally experience a change in risk; this implies that environmental factors may be more important than genetic susceptibility in determining risk. Secondly, many countries have experienced a steep decline in mortality from stroke in recent decades; although alterations in diagnostic fashion or certification practice might account for a small proportion of this decline, the most likely explanation seems to be changes in risk factor levels over time. Thirdly, epidemiological studies on causes of stroke have indicated that some of these are avoidable.

Stroke is often grouped together with coronary heart disease as cardiovascular diseases but there are substantial differences in the epidemiology of stroke and coronary heart disease. The most notable of these are the differences in time trends and the fact that the pronounced male excess found for coronary heart disease is not seen in stroke.

Definitions

The World Health Organisation defines stroke as "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 vascular origin".[1][2] Thus subarachnoid haemorrhages are included but not transient ischaemic attacks, subdural haematoma, and tumour or infection causing haemorrhage or infarction. Clinical diagnoses have been shown to be reliable.[3]

Most comparisons of stroke using routinely collected vital statistics rely on mortality rates. These have disadvantages including issues of diagnostic reliability, and variable case fatality which have been fully discussed elsewhere.[4][5] It is also not possible in mortality data to make accurate distinctions between the various stroke subtypes, in particular between haemorrhagic and thrombotic strokes. Morbidity

and disability due to stroke are also of major concern, but few routine sources are likely to provide satisfactory data. A substantial proportion of people having a stroke die suddenly before reaching hospital or are cared for at home; hospital admission or discharge statistics depend on admission policies and accessibility and these vary enormously from country to country and over time. Most studies on incidence of stroke have methodological problems. When community stroke registers have been specially set up, as in the World Health Organisation (WHO) MONICA Project[4] the evidence suggests that, for the purposes of international comparisons, there is good agreement between mortality rates in official statistics and stroke incidence registers. Time trends also need to be viewed with caution because of changing coding practices but again, many comparative studies have been conducted to examine the impact of these.

Case fatality

In the MONICA study, case fatality rates (defined as the proportion of events that are fatal within 28 days of onset) averaged about 30%, although they ranged from 15%–50%, with the lowest case fatalities in the Nordic countries and the highest in most of the Eastern European populations; there was no substantial sex difference in case fatality.[3]

Mortality by age and sex

Table 1 shows the mortality rates for stroke by age and sex in the United Kingdom. Rates rise sharply with increasing age. In marked contrast with coronary heart disease, in which there is a 5:1 male:female ratio at younger ages, there is no consistent sex differential in stroke mortality rates.

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Table 1 *Mortality rates/100 000 for stroke, United Kingdom 1992 (from WHO[6])*

	Stroke mortality rate/100 000/age group				
	35–44	*45–54*	*55–64*	*65–74*	*≥ 75*
Men	7	19	79	291	1351
Women	7	17	55	230	1438

*Figure 1   Age standard-
ised stroke mortality rates
100 000 by sex 1990–2
(from WHO[6]).*
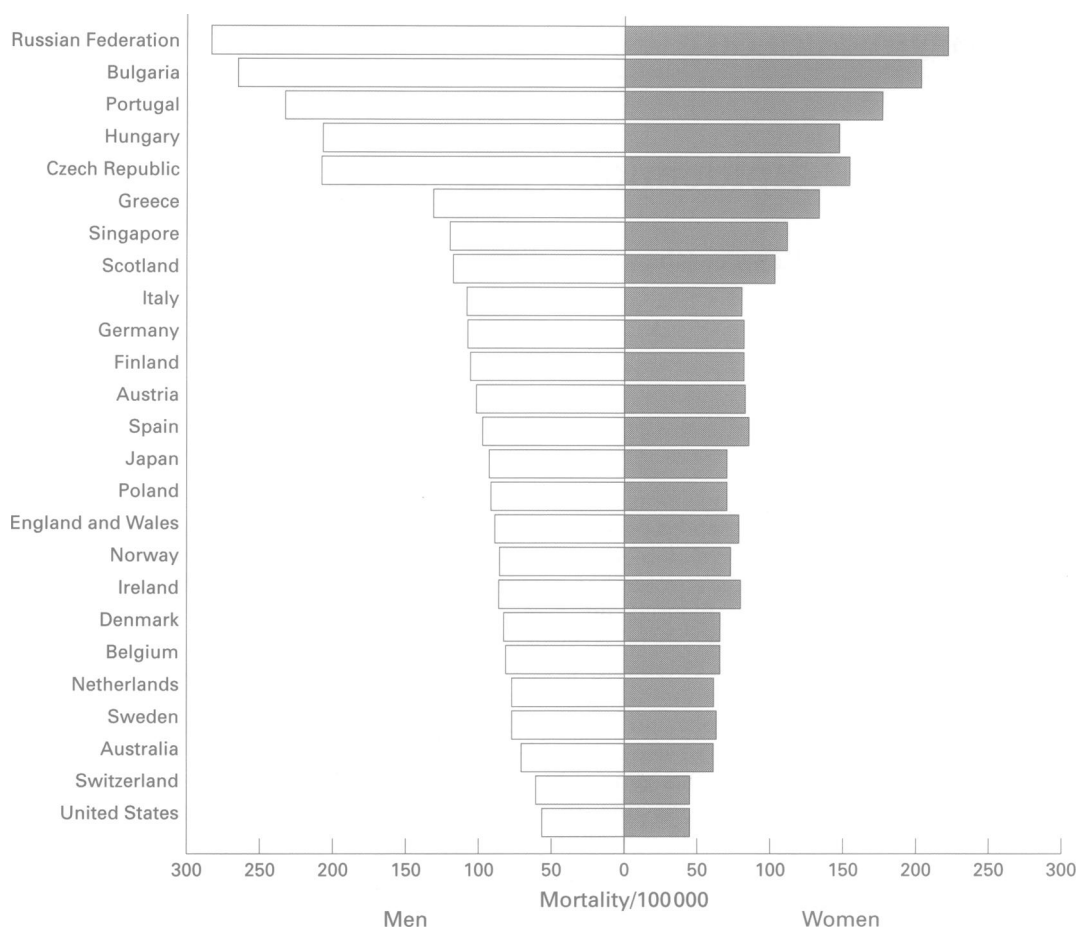
International comparisons

Figure 1 shows age-standardised stroke mortality rates in men and women for selected countries between 1991–2.[6] The highest documented rates are now seen in the countries of Eastern Europe and the former USSR. There is substantial international variation with men and women in the highest rate countries having about fivefold the rates in the lowest rate countries. Whereas men tend to have slightly higher rates than women, the sex differential does not compare with the pronounced male excess for coronary heart disease noted elsewhere. Figure 2 shows age specific rates for the United Kingdom, United States, and Russian Federation and indicates that the age standardised mortality comparisons reflect consistent differences over all age groups.

Time trends

Figure 3 shows time trends in stroke mortality from 1950 to 1989[6] and illustrates how these differ between selected countries. Japan, which had the highest rates in 1950–4, had an increase in mortality during the 1960s but then experienced a substantial decline; this trend was similar in men and women, although greater in men. Most other countries experienced a decline in mortality from stroke although others, particularly in Eastern Europe—of which Hungary is an example—had an increase in rates and only from the 1980s was there a decline. The reason for these trends is unclear. It has often been noted that the decline in stroke mortality in the western countries preceded, and hence cannot be explained by, the use of antihypertensive medication.[7]
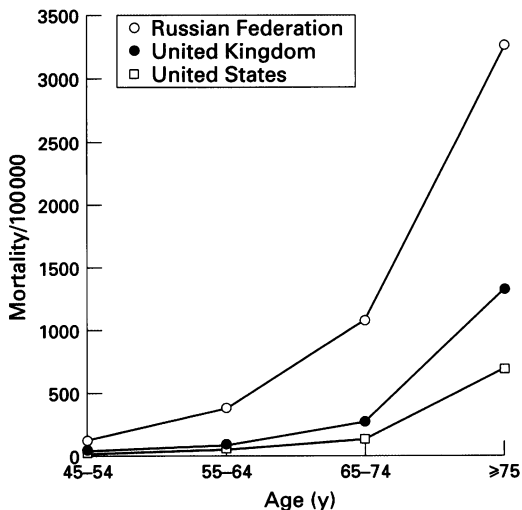
Figure 4 shows changes in stroke mortality rates between 1960–4 and 1985–9 in various countries. During this period many countries experienced substantial declines, more than halving stroke mortality; however, in some countries, notably those in eastern Europe, there was an increase in death rates. These trends suggest that the major determinants of mortality rates from stroke are likely to be potentially modifiable factors rather than

*Figure 2   Stroke mortality
rates per 100 000 by age
for men in three countries.*

Figure 3 (A) Age standardised mortality rates 100 000 from stroke in men 1950–89. (B) Age standardised mortality rates 100 000 from stroke in women 1950–89.
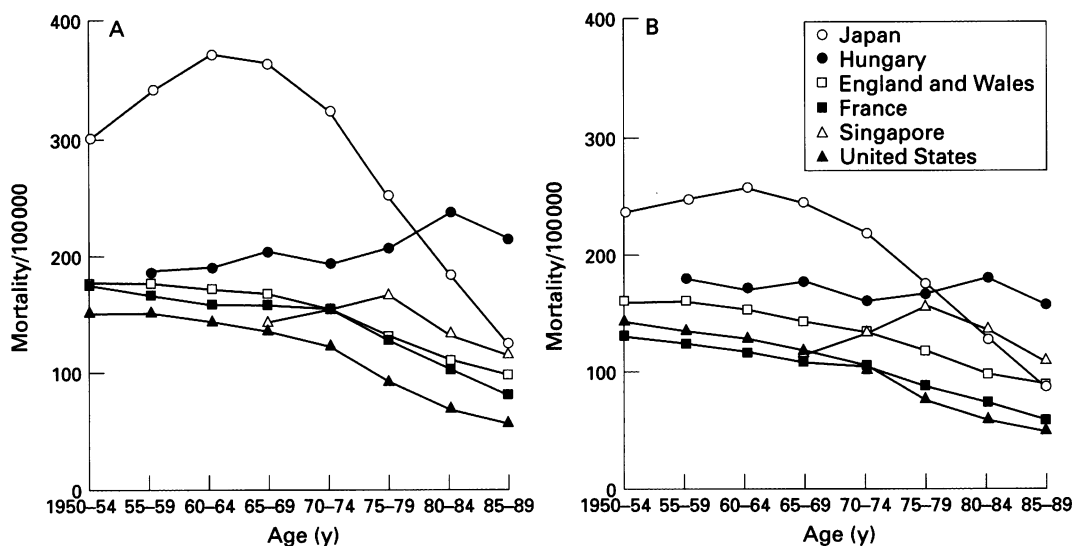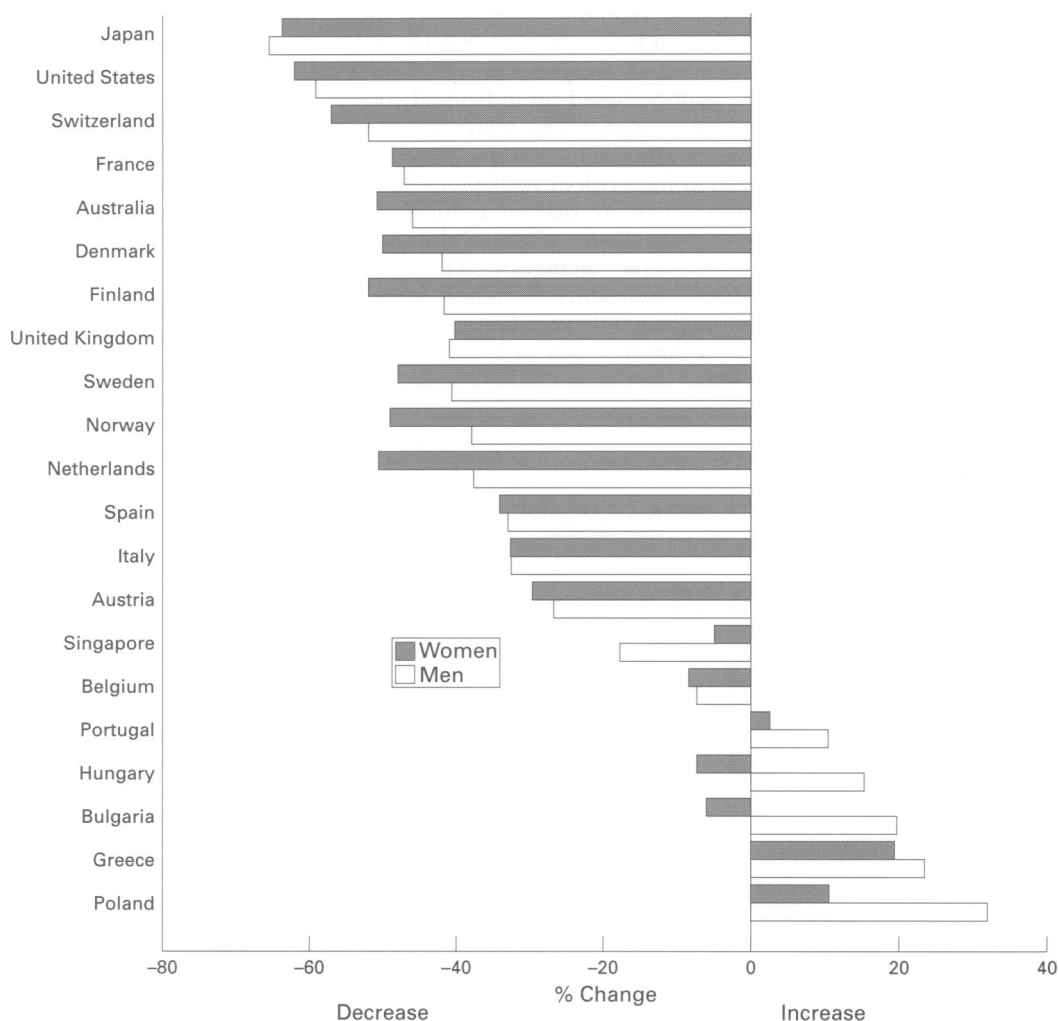

Figure 4 Changes in age standardised mortality rates from stroke in men and women 1960–4 and 1985–9 in selected countries.

genetic differences in stroke susceptibility. The results of migrant studies also emphasise this point; Japanese populations in the United States experience rates of stroke that are closer to those of American white populations than to those of Japanese populations in Japan.[8] Whereas some of the decline in stroke mortality may be due to a reduction in case fatality,[9] possibly due to better medical care or changing severity of disease, the magnitude of the declines suggest mortality rates also reflect changing incidence.

Regional and social class differences
Within any country, rates of mortality from stroke vary by social class and geographic region.[10] In Britain, rates vary over threefold between different regions, with the lowest mortality in the south and the highest in the

north. Men in social class V have a risk of death from stroke nearly three times as high as men in social class 1; a similar pattern is seen in women.

Preventive strategies

There are two dimensions to the problem of stroke in the community: treatment, rehabilitation, and care of those who have had a stroke; and prevention of the occurrence of stroke. The large geographic variations, results of migrant studies, and changes over time in stroke mortality and incidence indicate the potential for prevention. Major challenges are to identify aetiological factors, and to quantify their potential impact on stroke burden. Laboratory, clinical, and epidemiological studies all contribute to our understanding of aetiology; this review focuses on the epidemiological evidence. Many biological and environmental factors have been implicated in the aetiology of stroke. Of these, the role of raised blood pressure has been the best documented. Strategies aimed at preventing stroke may be based on individual subjects or population based.[11] The high risk, or individual based approach aims to identify specific subjects at high risk of stroke for clinical interventions (such as that of reduction of high blood pressure using pharmacological therapy or behavioural changes). The population based approach aims to change levels of risk factors in the whole population to a more optimal distribution (such as by changing dietary patterns).

Table 2   Risk factors for stroke

Major risk factors	Prospective studies predictive of stroke	Intervention trial with stroke end point
Blood pressure	+	+
Cigarette smoking	+	−
Diabetes	+	−
Fibrinogen level	+	−
Obesity	+	−
Blood homocysteine level	+	−
Respiratory function	+	−
White cell count	+	−

Table 3   Lifestyle factors implicated in stroke

	Relation with blood pressure reported	Predictive of stroke in prospective studies
Diet:		
Adverse		
Sodium	+	−
Saturated fat	+	−
Alcohol	+	+
Protective		
Potassium	+	+
Vitamin C	+	+
Total calories	−	+
Fruit and vegetables	−	+
ω-3-fatty acids	+	−
Fibre	+	−
Cigarette smoking (adverse)	−	+
Physical activity (protective)	+	+
Obesity (adverse)	+	+

Biological risk factors

BLOOD PRESSURE

The evidence for the aetiological role of raised blood pressure in stroke is overwhelming. Numerous prospective studies, recently reviewed,[12] have shown that systolic and diastolic blood pressure both independently predict stroke; the risk increases steeply and continuously with increasing blood pressure, with no threshold: the higher the blood pressure, the higher the stroke risk over the whole distribution of blood pressure, with relative risks increasing by nearly twofold for every 10 mm increase in diastolic blood pressure. Treatment trials of reduction of blood pressure have shown that a 5–6 mm Hg reduction in diastolic blood pressure reduces stroke risk by about 33–50%.[13]

CHOLESTEROL

By contrast, the evidence that raised blood cholesterol, which is a powerful risk factor for coronary heart disease, has an effect on stroke is much more equivocal.[12] It has been postulated that the apparent lack of any consistent relation might be due to a positive association with ischaemic stroke and a negative association with haemorrhagic stroke; trials of cholesterol reduction to date have not had sufficient power to examine significant effects on stroke one way or another.

Other biological risk factors

Many other biological factors have been implicated as predictive of stroke. They provide intriguing evidence for the mechanisms underlying stroke and raise the possibility of preventive interventions. However, for these risk factors, there is as yet no evidence from intervention trials that changes in exposure will reduce risk of stroke. Raised fibrinogen,[14] raised homocysteine[15] and lower albumin concentrations,[16] raised white cell count,[17] infection,[18] poor respiratory function,[19] diabetes or impaired glucose tolerance,[20] and obesity, mainly central adiposity[21 22] have all been linked with increased risk of stroke. These factors may have independent effects, may interact, or may simply be markers of underlying processes. For example, white cell count or poor respiratory function may be a marker of chronic infection or inflammation, which may raise stroke risk by increasing the likelihood of thrombosis. Alternatively, white cell count might be a marker for cigarette smoking. Table 2 summarises these factors.

Lifestyle risk factors

Many lifestyle factors have been linked with stroke (table 3). These include cigarette smoking, physical activity, and diet. Some prospective studies have reported direct associations between these factors and stroke mortality or incidence; the results of other studies suggest that dietary factors may influence risk of stroke by their effect on blood pressure.

SMOKING

Cigarette smoking is now well documented as

increasing stroke risk; one study reported an approximate threefold risk in current compared with non-smokers.[23] It is not clear how smoking affects risk of stroke but it may be through thrombotic mechanisms.

PHYSICAL ACTIVITY

Several studies have reported that physical activity is protective against stroke in both men and women[24-26]; this may be through influencing blood pressure, or through other mechanisms such as platelet aggregation.

DIET

Much interest and debate has focused on the role of dietary factors.[26-28] The evidence has been along two lines: dietary factors which may influence blood pressure, and thereby stroke, and dietary factors which may affect risk of stroke through other mechanisms, such as haemostasis or homocysteine concentrations. Of these, sodium has figured most prominently. The hypothesis that sodium might have an aetiological role in hypertension and stroke is not at all new but the debate is periodically revived.[29-33] There is little doubt from a wealth of intervention trials and observational studies that sodium has an effect on blood pressure; the debate is largely over the clinical and public health importance of the effect. Ecological studies have found that populations with a high sodium intake have an increased risk of stroke, but this association has not been convincingly demonstrated in prospective studies, perhaps due to the difficulty of measuring sodium intake. On balance, there is considerable circumstantial evidence that sodium is important in influencing hypertension and stroke risk. The magnitude of effect applied to the population has been estimated at about 10 mm Hg blood pressure difference for a 100 mmol difference in sodium intake, or about 34% difference in risk of stroke.[34]

Other dietary factors which have been related to blood pressure include potassium, magnesium, calcium, dietary fibre, ω-3 fatty acids, saturated fat, vitamin C, protein, and alcohol,[26 35-42] but again the relation with stroke is more uncertain. Several prospective studies have suggested that high intakes of potassium or vitamin C may be protective for stroke[43 44] and others that high alcohol intake may have an adverse effect, particularly as regards risk of haemorrhagic stroke.[45] Dietary factors may have effects other than on blood pressure. Antioxidant vitamins, for example, may influence haemostasis or endothelial function by protecting against free radical damage.[46] Folate may reduce stroke risk by influencing homocysteine concentrations. Fruit and vegetables are a rich source of vitamin C, potassium, and folate. Several studies have reported that a high fruit and vegetable intake seems to protect against stroke.[43 47-49] The magnitude of the effect was considerable with an estimated 25%–40% reduction in risk of stroke for an increase of two to three servings of fruit or vegetables daily.

Conclusions

Stroke is a devastating condition. However, the evidence from epidemiological and other studies suggests that stroke is eminently preventable; the challenge is to identify effective methods of prevention. We already have ample evidence that measures to reduce blood pressure in individual subjects and populations have a substantial impact on stroke rates. Because there is no threshold for the association with blood pressure, reduction of blood pressure in the population as a whole by altering lifestyle may be the most effective way to reduce the incidence of stroke. While the mechanisms remain to be clarified, intervention trials of vitamin supplements and other dietary modifications would be worthwhile. Such trials are already in progress in the USA. There is circumstantial evidence that lifestyle factors influence stroke risk in individual subjects and stroke rates in the community. Current health recommendations to increase fruit and vegetable intake, to reduce sodium intake, to increase physical activity, and to reduce cigarette smoking are likely to reduce risk of stroke and benefit health in general.

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