Commentary

Secular stroke trends: early life factors and future prospects

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Summary

Stroke mortality rates have declined during the second half of the 20th century in developed countries. Possible reasons for this include preventive measures, recent environmental changes impacting on adult health risks, and more distant environmental influences on childhood health. Data from a number of populations in Europe and the USA suggest that a decrease in early life blood pressure, occurring since the beginning of the 20th century, may have been an important determinant of declining stroke incidence rates and cardiovascular disease mortality in general. Advances in stroke epidemiology are increasing the accuracy of case ascertainment, and neuroimaging refinements (particularly MRI) are improving the accuracy of stroke type and subtype diagnoses. Although some risk factors are common to ischaemic and haemorrhagic stroke, there is accumulating evidence of differing aetiology. There is also an increasing recognition that early life factors may influence stroke risk. Despite the encouraging decline in stroke incidence, there is evidence of a recent increase in mean blood pressure in young people observed in the USA and UK, prompting concern that favourable trends in stroke risk may not be maintained. Reducing early life blood pressure in a population and delaying the onset of hypertension, along with effective measures to combat obesity, are required to avoid a reversal in stroke incidence trends in developed countries, and to prevent the anticipated increase in the burden of stroke in developing countries.

Introduction

The aim of stroke epidemiology is to improve understanding of the aetiology of cerebrovascular disease and thus provide insights into public health measures that can reduce the burden of stroke. There is increased impetus to develop stroke research, because of the anticipated further increase in the elderly population in both the developed and developing world, making efforts to combat stroke of global importance. While the causes of stroke are broadly understood,¹ better knowledge of stroke aetiology will inform preventive interventions. Several developments are likely to lead to more comprehensive knowledge of the causes of stroke. Here we review recent epidemiological developments in stroke and changes in completeness of case ascertainment, and consider how risk exposure over the life course—in particular blood pressure—affects disease burden and informs our understanding of
incidence and secular trends in stroke. We also discuss how technological advances in neuroimaging can provide better classification of stroke and more information on the natural history of cerebrovascular disease.

**Improving stroke ascertainment**

Many factors may contribute to apparent or real changes in stroke incidence. However, only accurately measuring and monitoring complete population-based stroke case ascertainment will improve our understanding of the aetiology of stroke, and the subsequent planning of stroke services. As recently reported from the Oxford Vascular Study, despite increases in the proportions of stroke patients reaching hospital, 10% of stroke patients die before hospital assessment. Case ascertainment must therefore continue to rely on a prospective study design using multiple overlapping sources of information that go beyond the hospital setting.

In the Oxford Vascular Study, ascertainment methods included monthly searching of databases of general practitioners for all patients given a cerebrovascular diagnosis, daily reviewing of all patients admitted to hospital with an acute vascular problem, and the additional assessment of all patients undergoing any coronary, carotid, or peripheral vascular investigations or interventions. Although labour-intensive, improved case ascertainment was demonstrated and the study has therefore been described as the ‘first ideal population-based study’ in which the completeness of case ascertainment for stroke was validated. Such complete ascertainment lends credence to the finding that the 40% decrease in the age-specific incidence of major stroke from 1981 to 2004 reported in this study was a real effect. This marked decline in incidence attests to the opportunities for stroke prevention, and may provide clues to improve primary interventions. Only through the monitoring that is possible in community-based stroke registries can accurate data on stroke burden be acquired.

**More than one disease—neuroimaging and stroke types**

While stroke registries can provide stroke incidence data, further investigation is required to ensure accurate assessment of stroke type. Although many types and subtypes of stroke have broadly similar clinical presentations, the condition is pathologically heterogeneous. The basic classification of ischaemic infarction and intracerebral haemorrhage has had to await the arrival of neuroimaging, with computer tomography (CT) in the 1980s and magnetic resonance imaging (MRI) in the 1990s.

Initial use of CT scanning led to an apparent increase in the incidence rate of intracerebral haemorrhage. However, the underestimation of intracerebral haemorrhage has not been entirely eliminated in the CT era, because delays in CT scanning can lead to bleeds being misclassified as infarcts. The characteristic hyperdensity on a CT scan which distinguishes intracerebral haemorrhage from ischaemic stroke may disappear within 14 days. As this may be particularly true of small intracerebral haemorrhages, which may present late with minor symptoms and result in delayed investigation, misdiagnosis can still occur.

T2*-gradient-echo MRI has demonstrated that an apparent infarct on CT may in fact be a haemorrhage. In routine clinical practice, for every 1000 patients with a mild stroke, CT scanning may miss 24 patients with intracerebral haemorrhage. Better designed epidemiological studies such as the Oxford Community Stroke Project and the Oxford Vascular study have tried to address the basic haemorrhagic/ischaemic classification issue, but even in these settings, delays in presentation may have resulted in some cases of intracerebral haemorrhage being misclassified as ischaemic stroke.

Even after distinguishing between the two major types of stroke (haemorrhagic and ischaemic stroke), much heterogeneity remains. For example, scrutiny of primary intracerebral haemorrhage data indicates that these can be further subtyped into lobar and deep haemorrhagic strokes. Lobar haemorrhages associated with cerebral amyloid angiopathy do not appear to be influenced by hypertension and comprise 10–15% of the total intracerebral haemorrhage burden. Specific examination of the commoner, deep, hypertensive intracerebral haemorrhages may thus reveal an even more pronounced effect of lowering blood pressure.

**Secular stroke trends: what do they show?**

Use of the term stroke to refer to ischaemic and haemorrhagic cerebrovascular events tends to suggest that the two conditions are similar, but, while having similar symptomatology, it is clear from radiological (as indicated above) and pathological findings that they are distinct entities. Consistent with this notion are findings from recent research indicating that rates of ischaemic and haemorrhagic stroke have different secular patterns.
Although somewhat limited, the evidence suggests that trends in the incidence and mortality patterns of ischaemic and haemorrhagic strokes differed markedly over the last century. Whereas cerebral infarction mortality remained stable in the early years of the 20th century before rising to a peak in the 1970s and then declining, intracerebral haemorrhage mortality fell throughout the century (Figure 1). Thus, ischaemic stroke mortality trends appear to mirror that of coronary heart disease, as is clear from the closely parallel curves for these two disorders, suggesting that their aetiology is similar. By contrast, the secular changes in intracerebral haemorrhage mortality suggest that haemorrhagic stroke may have a different aetiology or at least different attributable effects from changes in common risk factors. The cause of divergent secular stroke trends merits further study.

Risk factor profiles—explaining different trends

Investigation of the association between classical cardiovascular risk factors and stroke serves to further highlight aetiological distinctions between intracerebral haemorrhage and ischaemic stroke. In recent years, large studies have shown different associations for cholesterol level, body mass index and blood pressure, with findings broadly indicating that ischaemic stroke has a risk profile closer to that of coronary heart disease than haemorrhagic stroke. Table 1 shows typical values for the association between several risk factors and ischaemic and haemorrhagic stroke.

Observational studies have hinted that blood pressure may be a stronger risk factor for haemorrhagic stroke than ischaemic stroke, because systolic blood pressure gradients may have a stronger association with haemorrhagic stroke than ischaemic stroke. However, this has not been a consistent finding in all observational studies. In a secondary prevention trial, the Perindopril Protection Against Recurrent Stroke Study (PROGRESS), which distinguished between ischaemic and haemorrhagic stroke, blood pressure lowering diminished the risk of stroke recurrence, which was also confirmed in a systematic review. The blood-pressure-lowering regimen had a more dramatic effect on outcome from haemorrhagic stroke (50% relative risk reduction, 95%CI 26–67) than ischaemic stroke (24% relative risk reduction, 95%CI 10–35). However, in view of the overlapping confidence intervals, it cannot be concluded that blood pressure is more strongly related to haemorrhagic risk. The insufficient data in PROGRESS and primary prevention trials such as the Heart Outcomes Prevention Evaluation study mean that confirmation of this hypothesis is still awaited. Thus, in addition to the need for complete ascertainment of strokes, typing of stroke is also essential, not least for conducting outcome studies. It is likely that determining different attributable risk profiles of common risk factors will remain an area of active research, as any

![Figure 1. Secular stroke trends in the later 20th century.](image)

**Table 1** Strength of association between selected risk factors* and mortality from ischaemic stroke and intracerebral haemorrhage

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Ischaemic stroke</th>
<th>Intracerebral haemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure: per 10 mmHg increase</td>
<td>1.49 (1.47–1.52)</td>
<td>1.78 (1.75–1.82)</td>
</tr>
<tr>
<td>Diastolic blood pressure: per 10 mmHg increase</td>
<td>2.69 (2.30–3.08)</td>
<td>3.43 (2.97–4.00)</td>
</tr>
<tr>
<td>Cholesterol: per 1 mM increase</td>
<td>1.25 (1.13–1.40)</td>
<td>0.8 (0.70–0.92)</td>
</tr>
<tr>
<td>BMI: per 1 kg/m² increase in BMI</td>
<td>1.06 (1.04–1.07)</td>
<td>1.02 (1.00–1.04)</td>
</tr>
<tr>
<td>Height: per 10 cm shorter</td>
<td>1.14 (0.93–1.39)</td>
<td>1.39 (1.00–1.92)</td>
</tr>
<tr>
<td>Siblings: per sibling</td>
<td>1.01 (0.93–1.09)</td>
<td>1.11 (1.00–1.23)</td>
</tr>
<tr>
<td>Father’s social class: manual vs. non-manual</td>
<td>3.22 (1.15–9.03)</td>
<td>0.92 (0.53–1.61)</td>
</tr>
</tbody>
</table>

Date are relative risks (RR) (95%CI). *RR quoted with respect to worsening level of risk factor. BMI, body mass index (BMI). Recalculated RR: published results were per 20 mmHg increase. Recalculated RR: published results were per 5 mmHg decrease. Recalculated RR: published results were per 10 cm increase.
change in exposure to one such risk factor may explain secular stroke trends. Table 1, which summarizes the strength of associations between selected risk factors and types of stroke, highlights the difference in risk factor profiles, and in likely aetiology, for ischaemic and haemorrhagic stroke.

**Early life exposures**

The last two decades have established the importance of early life exposures in disease causation. While mid-life blood pressure is clearly important in determining the risk of (untyped) stroke, its importance in early life has also been recently recognized; higher blood pressure in young adult men is associated with increased cardiovascular disease mortality in later life. In addition, in many developed countries, blood pressure in children and young adults has been declining for at least 50 years, and there is evidence from the USA of a downward trend starting in the early part of the 20th century or even earlier. These changes in young healthy populations occurred without any real influence from disease, medication or behavioural changes subsequent to morbidity. Increased blood pressure levels in childhood strongly predict hypertension in young adulthood. Since blood pressure in general tracks into adulthood, the consistent decline in blood pressure in young people may have contributed to the observed declines in later-life cardiovascular disease. Further, the fact that these changes were occurring in young individuals indicates that several important factors that set blood pressure in train are already acting at this early stage of life.

It is also plausible that declining blood pressure in the 20th century may have partially contributed to the divergent trends in haemorrhagic and ischaemic stroke. Potential explanations for the declines observed in early life blood pressure include prenatal influences, a decline in salt intake in infancy, and an increase in fruit and vegetable consumption. Identifying the reason(s) for the decline in blood pressure should become an important public health research area, with the goal of improving and maintaining this substantial downward trend. Better understanding is particularly important currently, in view of the emerging evidence from the USA and UK (A. Black, personal communication) that over the last decade blood pressure trends in children and adolescents have started to rise, an indication that recent favourable trends in stroke risk may not be maintained in the future.

**Improving prevention: harnessing clues from secular trends**

The lowering of stroke mortality throughout the 20th century is a medical success, and well-conducted population-based studies have shown that morbidity (incidence) has also fallen. Such surveys are vital for better understanding of stroke and planning of both primary and secondary preventive interventions. At the same time, better diagnosis of stroke type and subtype will improve the scope for unravelling the natural history of the different forms of stroke. Epidemiologists have recognized for some time that modest lowering of an entire population’s blood pressure may be a more effective primary preventive strategy than just targeting individuals at higher risk with an arbitrary definition of hypertension. Reducing blood pressure throughout life rather than just treating hypertension in middle age and beyond may therefore yield very worthwhile public health gains. Only by identifying the determinants of early life blood pressure can the potential impact of primary prevention be realised. The advances in neuroimaging and case ascertainment may provide a better understanding of the effect of lifelong blood pressure in different types and subtypes of stroke.
To date, the focus for cardiovascular aetiological and preventive studies has been the industrialized world. However, three-quarters of all strokes occur in less developed countries, where there is very little population-based study of stroke and little chance of applying the advances in case ascertainment and neuroimaging. Accurate secular trends in developed countries could provide useful information to improve primary prevention measures throughout the world, an aspiration of the Global Stroke Initiative. Timely primary prevention of stroke, even with a firm evidence base, has a lag period in decades before benefits are apparent and measurable. The impetus of primary prevention can be lost amongst acute and secondary stroke interventions. As early life factors may contribute to secular stroke trends, identification of simple intervention measures for primary prevention may lead to long-lasting favourable global secular trends in stroke.

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References