Prenatal Influences on Stroke Mortality in England and Wales

David J.P. Barker, FRS; Daniel T. Lackland, MD

Background and Purpose—Within Britain and the United States there are geographic variations in mortality from stroke that are not explained by differences in adult lifestyle. We report on the geographic distribution of stroke mortality in England and Wales and compare it with that in the United States.

Methods—Data from 4 studies are presented. The geographic distribution of stroke deaths in England and Wales during 1968–1978 is compared with the distribution of (1) other causes of death during the same years, (2) neonatal and maternal mortality during 1911–1925, (3) average adult height, and (4) place of birth.

Results—Areas of England and Wales with high stroke mortality were characterized in the past by poor living standards, demonstrated by high infant and maternal mortality rates and short stature in the adult population. People who were born in areas of high stroke mortality rather than migrating into them are at high risk. Stroke mortality is not geographically correlated with past postneonatal mortality independently of neonatal or maternal mortality. The geographic distribution of stroke mortality in the United States and England and Wales has features in common.

Conclusions—Stroke may originate through maternal influences associated with poverty. This conclusion is supported by recent findings that rates of stroke in adult life are higher among people who had low birth weight. (Stroke. 2003;34:1598-1603.)

Key Words: birth weight • epidemiology • mortality • stroke

For many years there has been a definitive geographic pattern of cerebrovascular disease within the United States, with the highest disease rates being in the Southeast. The so-called Stroke Belt comprises a contiguous cluster of states in the Southeast, with Indiana jutting upward from it.1 Mortality rates from stroke in each of these states are ≥10% above the average for the country. These high death rates from stroke affect men and women and blacks and whites,2 and they are associated with especially high rates in young black people.3 They are not explained by differences in the quality of medical care.4 Stroke incidence rates are also higher in the Southeast, and the onset of disease may be at an earlier age than is usual.5 The prevalence of hypertension, the main biological risk factor for stroke, has also been shown to be higher in the Southeast,6 and the geographic pattern of coronary heart disease in the southeastern United States is similar to that of stroke.7 Despite intensive investigation, there is no agreement regarding an explanation for the existence of the Stroke Belt, and the reasons for the differences in stroke rates and patterns of stroke are not understood.8

Mortality and incidence of stroke are also unevenly distributed within England and Wales. High rates are concentrated in the northern towns, which expanded rapidly during the industrial revolution in the 19th century, and in poor rural areas in the north and in Wales.9 The high rates affect men and women, and areas with high stroke mortality also have high mortality from coronary heart disease and higher blood pressure levels among adults.10 In this report we present analyses that relate the distribution of stroke to average adult stature and to the distributions of maternal and neonatal deaths in the past. The findings, taken together with an analysis of the effect of place of birth on stroke mortality, develop the hypothesis that the distribution of stroke in England and Wales is determined by influences acting prenatally. We propose that this could similarly explain the Stroke Belt within the United States.

Methods

We use data from 4 studies. We first examined the geographic distribution of death rates from stroke (International Classification of Diseases, Eighth Revision codes 431 to 438) at ages 55 to 74 years in England and Wales during 1968–1978.11 These years were selected because the computerized data were readily available, having been used in the preparation of a national atlas of disease published in 1984.12 Deaths over the age of 75 years were excluded because of the known inaccuracy of certified cause of death in old

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age. Death from stroke under the age of 55 years is rare in Britain. Death rates were expressed as standardized mortality ratios in which the rates in each area were related to the national average, taking account of the age and sex composition of the area's population. The average for the country was set at 100. During the time period of the study, there were 142,975 deaths from stroke in men and 134,503 deaths in women. The distribution of stroke deaths was compared with that of deaths from 4 other disorders: coronary heart disease and lung cancer during 1968–1978 and neonatal deaths (deaths in the first month after birth) and maternal mortality during 1911–1914. These are the earliest years for which neonatal mortality rates were published and include the years of birth and dying of stroke at ages 55 to 74 years during 1968–1978. The analysis of maternal mortality was restricted to deaths from causes other than puerperal fever. The geographic distribution of deaths from puerperal fever differed from that of maternal deaths from other causes and was thought to be largely determined by midwifery practices.13 The analysis was performed in the 154 local authority areas of the country used by the registrar general since 1911, that is, 80 large towns, 15 London boroughs, and 59 administrative counties, which are aggregates of small towns and rural areas. Details of these analyses have been published.11

The second study compared standardized mortality ratios for stroke during 1968–1978 with past mortality in the neonatal and postneonatal (1 month to 1 year) periods. In this analysis the small towns and rural areas within each county were examined separately to give 212 local authority areas. Infant mortality ratios were calculated for an extended period of 1911–1925 to give adequate numbers of deaths in each area.

The third study compared the distribution of standardized mortality ratios for stroke with that of average adult height.16 The analyses were performed within the 59 counties, including the 80 large towns within them, and London. Data on height came from national samples of people born between 1920 and 1970. Although height increased over this 50-year period, the differences between counties persisted.

In England and Wales, place of birth is recorded on death certificates but is not routinely coded. For a trial period, however, during 1969–1972, place of birth was coded. There were 251,565 deaths from stroke during this period, and the fourth study examined the separate effects of place of birth and place of death on stroke mortality.17 Proportions of all deaths that were due to stroke were calculated and related to place of birth and place of death with the use of log linear regression and with adjustment for age, sex, and social class group. For each area, 2 numbers were generated, one denoting the risk of stroke associated with being born there and the other the risk associated with being there at the time of death. The average value of these numbers was 1.0, and a value of 2.0 denoted a doubling of risk. A $\chi^2$ statistic was used to calculate the strength of effects of place of birth across all areas. Another value was calculated for place of death. Values $>189$ were significant at the 5% level.

**Statistical Significance**

The number of stroke deaths in these analyses is very large, and with these numbers consideration of statistical significance is no longer helpful. All the correlations and trends presented in the tables are strongly statistically significant. Details of the analyses used have been reported previously.11,14,16,17

**Results**

Table 1 shows that the geographic distribution of standardized mortality ratios for stroke was strongly correlated with the distribution of coronary heart disease in both sexes and within each kind of geographic area. The distribution of stroke was also consistently correlated with the past distribution of neonatal and maternal mortality. The statistical dependence of stroke on maternal mortality was such that an increase of 1 maternal death per 1000 births corresponded to an increase of 12 in the standardized mortality ratio for stroke. Stroke mortality was not consistently correlated with mortality from lung cancer, and the coefficients were mostly negative.

To derive Table 2, the 212 areas of England and Wales were ordered according to neonatal mortality, and 5 groups, each comprising 42 or 43 areas, with increasing mortality were derived. Five groups with increasing postneonatal mortality were derived similarly. Table 2 shows death rates from stroke within each neonatal and postneonatal mortality group. Two cells of Table 2 are blank because of insufficient numbers. Although it would be possible to formally examine the separate effects of neonatal and postneonatal mortality with a log-linear model (Poisson variation for the counts), there are such large numbers of stroke deaths that even shallow trends are statistically significant. Each standardized mortality ratio is closely estimated. The overall effect size can be inferred by direct observation. The same argument applies to Table 3. Within any band of postneonatal mortality in

<table>
<thead>
<tr>
<th>TABLE 1. Correlations Between Standardized Mortality Ratios for Stroke in Both Sexes During 1968–1978 and Death Rates From Other Disorders Within the Local Authority Areas of England and Wales</th>
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</thead>
<tbody>
<tr>
<td>London Boroughs and Large Towns</td>
</tr>
<tr>
<td>Men</td>
</tr>
<tr>
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</tr>
<tr>
<td>Coronary heart disease 1968–1978*</td>
</tr>
<tr>
<td>Lung cancer 1968–1978*</td>
</tr>
<tr>
<td>Neonatal mortality, 1911–1914†</td>
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<tr>
<td>Maternal mortality, 1911–1914†</td>
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| *Standardized mortality ratios. †Rates per 1000 births.

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<tr>
<td>Neonatal Mortality</td>
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<tr>
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<tr>
<td>1 Lowest</td>
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<tr>
<td>1 Lowest</td>
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<td>2</td>
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<td>4</td>
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<tr>
<td>5 Highest</td>
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Table 2, standardized mortality ratios for stroke increased sharply with increasing neonatal mortality. There was no independent trend in stroke mortality with postneonatal mortality.

To derive Table 3, the counties of England and Wales were ordered according to the average heights of men and women in them and divided into 5 groups such that the numbers of people in each group were as similar as possible. Table 3 shows that standardized mortality ratios for stroke fell progressively from the shortest to the tallest group of counties.

Table 3. Standardized Mortality Ratios for Stroke in Both Sexes During 1968–1978 Within the Counties of England and Wales Grouped by Average Adult Height

<table>
<thead>
<tr>
<th>Group of Counties</th>
<th>1 Short</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5 Tall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td></td>
<td></td>
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<tr>
<td>121</td>
<td>113</td>
<td>96</td>
<td>89</td>
<td>84</td>
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<td>Women</td>
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<td>117</td>
<td>110</td>
<td>93</td>
<td>93</td>
<td>88</td>
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</table>

Discussion

Stroke mortality is unevenly distributed within England and Wales. In a manner similar to that in the United States, this geographic distribution cannot be explained by current differences in adult lifestyle, although lifestyles are known to contribute to the occurrence of the disease. The distribution differs markedly from the distribution of the main smoking-related disease, lung cancer (Table 1), especially among women. When smoking became common among women, lung cancer rates became high in many prosperous areas, whereas stroke rates are higher in less affluent places.

Death from stroke is influenced by many factors, such as severity, whether hemorrhagic or thrombotic in origin, and medical care. Although these may vary from one area to another, there is evidence from both the United States and Britain that the geographic variations in mortality reflect similar variations in incidence. Although there is nothing that today characterizes places in England and Wales with high rates of stroke, they were characterized by poor living standards in the past. The geographic association between stroke and poor past living standards is shown by the relation between high stroke rates and short adult stature (Table 3), a known biological marker of poor growth in utero and poor living standards in childhood. The people who were born in the high mortality areas rather than those who migrated into them in adult life are at high risk. Part of the increased risk of people born in areas of high mortality persisted whether or not they had moved to other areas of the country.

At around the time of birth of people now dying from stroke, areas with high stroke mortality had high death rates among mothers and newborn babies (Table 1). The immediate causes of these high death rates were closely documented at the time. Mothers in these areas were poor, were badly nourished, and had poor physiques and health; their babies had low birth weights. Many of the areas also had high postneonatal mortality. There is, however, no geographic correlation between stroke and postneonatal mortality, independently of neonatal mortality (Table 2). Analyses at the time showed that the causes of high postneonatal mortality differed from those of high maternal and neonatal mortality. Postneonatal deaths were the result of overcrowding; large numbers of persons per room, high population density, and large family size. The discontinuity between the causes of neonatal and postneonatal deaths was illustrated by London in those times. Mothers there were well nourished, and neonatal death rates were exceptionally low: overcrowding was intense, and postneonatal death rates were high. The absence of an association between stroke and postneonatal mortality suggests that geographic variations in stroke mortality may originate through maternal influences associated with poverty rather than through the effects of poor living standards in childhood.

The poor nutrition of the mothers in areas of high stroke mortality within England and Wales reflected either the generally poor nutrition of people living in rural areas, where the agricultural land was of poor quality, or the poor living standards in towns and cities, which grew rapidly during the 19th century and which were the cradle of the industrial revolution. Some of the industries, such as cotton weaving and pottery, selectively employed women and adolescent girls who worked long hours in poor conditions.

The geographic associations described do not imply causation; evidence for this comes from observational epidemiological studies and experiments in animals. The fetal origins hypothesis proposes that coronary heart disease and stroke, and the disorders related to them, hypertension and type 2 diabetes, originate through responses to undernutrition during fetal life and infancy. These responses permanently change the body's structure and function in ways that lead to disease in later life. Numerous experimental studies have shown that manipulation of the diets of pregnant animals leads to life-long alterations in the blood pressure and metabolism of their offspring. Studies on both sides of the Atlantic have shown that people who had low birth weight have higher rates of stroke. In 2 studies in which detailed measures of body size at birth were available, stroke was specifically associated with small body size in relation to head circumference, reflecting a pattern of reduced fetal growth in which brain growth is spared. One “brain-sparing” process is diversion of cardiac output away from the trunk to favor the brain, and as this changes the flow patterns in developing arteries it leads to persisting changes in vascular structure. The pattern of brain-sparing growth that leads to small body size in relation to head circumference is more common among babies born to mothers who are short in stature, reflecting poor early growth, or who have a “flat” pelvis, a deformity that originates through malnutrition in early childhood.

Under the fetal origins hypothesis, the areas of high stroke mortality in Britain may be viewed as a legacy of the effects of rural poverty and industrial slums on the growth and nutrition of girls and young women. We propose that the Stroke Belt in the United States is similarly a legacy of rural
poverty. In the areas of high stroke mortality within the United States, malnutrition was common around the turn of the last century as a result of the social changes that began in the Civil War and continued until the Depression. Diseases such as pellagra were widespread, and a high rate of low birth weight persists until this day. Within the Stroke Belt the patterns of stroke mortality change. During the period 1962–1988, the areas with the highest rates moved from the Piedmont region toward the Mississippi. It has been suggested that this change is linked to trends in socioeconomic influences.28 We suggest that these influences acted on mothers and babies in the early years of the last century. Data with which to explore this hypothesis, however, are scarce.

Some evidence links the Stroke Belt to poor living conditions and to events in early life. In the Stroke Belt, stroke mortality is highest in people with poor education, low income, and low occupational level.29 Indeed, in 1960 there was no excess of stroke mortality in the Southeast among residents of areas with the highest educational levels. Therefore, the pattern of disease is not so much a “belt” of increased stroke across the whole region but a “necklace” of different levels of risk.5

Within the Southeast, the highest rates of stroke occur among people who were born there. Deaths from stroke in South Carolina during 1980–1996 were analyzed according to place of birth.30 South Carolina has had the highest stroke mortality in the United States for many years, with rates 50% to 60% above the national average. The analysis showed that proportional mortality from stroke was greatest among people born in South Carolina, somewhat lower in those born elsewhere in the Southeast, and lowest in those born outside the Southeast. The increased risk associated with being born in South Carolina was greater for blacks than whites and for men than women. These findings are supported by an analysis of deaths in New York City. The higher rates of stroke among blacks in the city were largely explained by high rates among blacks who were born in the southern states but migrated to the Northeast.31 These findings suggest that events in early life may play a role in determining death from stroke.

In both the United States and Britain, stroke mortality has declined over many years and, as would be expected from the improvements in nutrition during the 20th century, the legacy of poor nutrition is dwindling. That it nevertheless persists and is a major public health problem reflects persisting poor nutrition. It seems that part of a mother’s ability to nourish her baby in utero was established when she was herself in utero. As Mellanby32 wrote long ago, “It is certain that the significance of correct nutrition in childbearing does not begin in pregnancy itself or even in the adult female before pregnancy. It looms large as soon as a female child is born or indeed in its intrauterine life.” It will therefore take more than 1 generation before improved nutrition has its full impact in reducing stroke mortality.

A recent study of chronic renal failure in South Carolina further encourages the view that the fetal origins hypothesis is relevant to the Stroke Belt in the United States.33 The highest rates of end-stage renal failure, occurring mostly as a result of hypertension and type 2 diabetes, occurs within the Stroke Belt, where rates are especially high among young blacks. An analysis of 1230 patients who were born in South Carolina and required chronic renal dialysis showed that, in comparison with controls from the general population in the state, they tended to have low birth weight. This association was found among men and women and among blacks and whites. Since low birth weight was associated with renal failure from a number of causes, an explanation for the observation is that reduced fetal growth is associated with defects in the development of the kidney that make it more vulnerable to a number of pathological processes. Low birth weight is known to be associated with reduced numbers of nephrons, and Brenner and Chertow34 have proposed that this underlies the association between low birth weight and hypertension. They suggest that reduction in the number of nephrons leads to hyperperfusion of each nephron and resulting glomerular sclerosis, further nephron death, and a cycle of increasing blood pressure and nephron death. This hypothesis links the Stroke Belt to impaired renal development in utero and consequent hypertension and increased risk of stroke.

In an aging population, the economic burden of stroke is considerable. These observations from both sides of the Atlantic suggest that the burden may be reduced in future generations if we do more to protect the growth and nutrition of girls, young women, and their babies. This may also be important in other parts of the world, including China, where marked geographic variations in stroke incidence and mortality are also associated with variations in the occurrence of raised blood pressure, pointing to a possible role of impaired intrauterine development.35,36

References

Editorial Comment

Prenatal Influences on Stroke Mortality in England and Wales

Genetic and environmental factors may interact in complex ways to alter an individual’s susceptibility to a variety of diseases, including stroke. Analysis of epidemiological data in the present study shows that people who were born in areas of high stroke mortality in England and Wales were at higher risk of stroke-related mortality than those migrating into these localities. The same may be true in the United States. South Carolina has one of the highest stroke mortality rates in the southeastern “stroke belt” region of the country, the existence of which is not fully understood. Those born and residing in South Carolina have higher stroke mortality rates than those who were born outside of the stroke belt and then moved to the state. Those residing in South Carolina who were born in other areas of the stroke belt have intermediate rates.

Why would place of birth affect stroke, a disease occurring decades later? The present study also finds that stroke mortality rates among adults in England and Wales are higher among persons who had lower birth weights. By analogy to their present results, the authors hypothesize that lower birth weights might at least partially underlie the US stroke belt as well. An abstract presented at the 2003 International Stroke Conference supports this view. This study compared a group of South Carolina Medicaid Beneficiaries having stroke under 50 years of age to population controls. The odds of stroke were more than double for those with birth weights <2500 g as compared with those weighing ≥4000 g (with a significant linear trend for intermediate birth weights). As in the present study, geographic variation in birth weight was further associated with geographic variation in deaths due to stroke.

Birth weight may be influenced by a variety of factors, including the mother’s socioeconomic status. However, present local socioeconomic conditions explain <16% of the geographic variation in excess stroke-related mortality in the United States. The areas of England and Wales with current high stroke mortality rates were characterized by poor living standards when present-day 60- , 70- , and 80-year-olds were born. However, this does not address whether the impact of poorer socioeconomic status is exerted during the prenatal period or during infancy. An additional important observation in the present study is that stroke mortality was not independently correlated with past postneonatal infant mortality, suggesting that prenatal or perinatal events initiate processes that lead to an increase risk of stroke decades later. On the basis on this and other work, the authors hypothesize that relatively poorer maternal nutrition during pregnancy may underlie
their children’s relatively higher stroke-related mortality (and likely incidence) in later life.

Although Barker and Lackland provide a reasonable argument linking low birth weight with increases in stroke-related mortality in adults, they appropriately caution that their analyses reflect associations and not causality. Despite this inherent limitation of epidemiologically based observations, the data provide another compelling argument to ensure adequate prenatal care and maternal nutrition. Investment in programs aimed at optimizing maternal health and nutrition may pay dividends in reducing the incidence of stroke in their unborn babies when they reach adulthood. It is an investment in the future that may prove both effective and cost-effective.

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References
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