

Geographical and social class differentials in stroke mortality—the influence of early-life factors: comment on papers by Maheswaran and colleagues

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Marked and consistent geographical differences in stroke mortality are seen in many countries. In the United States the “stroke belt” in the south east has maintained its relative position, of considerably higher rates than the rest of the country, against a background of persistently declining stroke mortality rates.^{1,2} Rural areas within the US have consistently experienced higher stroke mortality rates over the past 60 years.³ Coronary heart disease (CHD) mortality, conversely, was lower in rural areas in the 1930s, with this advantage having been lost in recent years.³ In the UK, the north west and north Wales have continued to experience higher stroke mortality rates than the south east.^{4,5} This does not simply reflect differences in socioeconomic conditions and thus in all cause mortality. The geography of stroke is different to that of CHD, respiratory disease, and all cause mortality, but closely similar to that of stomach cancer mortality, which has also shown declining mortality rates this century.⁴ When stroke mortality is analysed by geographical region and social class, the geographical differences are seen within each social class grouping,⁶ and vice versa.

The stable geographic distribution of CHD mortality in Norway led Forsdahl to speculate that deprivation in early life, which could be indexed by the infant mortality rate earlier this century, increased susceptibility to CHD in adult life.⁷ This work was replicated and extended to other causes of death, including stroke and respiratory disease, and indicators of influences acting at particular stages of early development, including maternal mortality, neonatal mortality, and postneonatal mortality.⁸ Stroke mortality was strongly related to maternal and neonatal mortality, suggesting a particular influence of intrauterine development, whereas CHD mortality was related to all three past indicators, suggesting an influence of intrauterine and infant environment. Chronic bronchitis was associated mainly with postneonatal mortality, indicating an important contribution of environmental conditions in early infancy. There is also a strong correlation ($r=0.66$) between infant mortality rates in the 1930s and current stroke, across the countries included in the WHO Monica project, with no correlation ($r=0.10$) being seen with regard to CHD mortality.⁹

The hypothesis that early-life factors importantly determine stroke risk in adulthood is an exciting and attractive one. A problem is

clearly introduced by the persistence of socioeconomic disadvantage and other environmental influences, many of which have also remained geographically stable over many years. Areas with high rates of neonatal mortality earlier this century are the same areas with high levels of socioeconomic deprivation today. Thus, the strong correlations between current stroke mortality and infant mortality earlier this century ($r=0.68$ for women and $r=0.77$ for men) are greatly attenuated when present-day socioeconomic factors are taken into account ($r=0.24$ for women and $r=0.16$ for men).¹⁰ Prospective studies of individuals, associating low birth weight with elevated blood pressure and stroke mortality risk,^{11,12} offer more robust evidence of direct influences of poor development in early life on stroke risk in adulthood, although they do not entirely escape from possible confounding by environmental factors acting later in life.

A particularly striking geographical difference in stroke mortality, which has been taken to provide evidence for the importance of early life influences on stroke risk, is the lower mortality for Greater London than the rest of England and Wales.¹³ It has been suggested that young women who migrated to London to work in domestic service from rural areas were generally well nourished and thus had well developed offspring.¹³ Maheswaran *et al*¹⁴ have subjected this interpretation to critical scrutiny. They find that the London advantage has decreased over time and is now only seen for those aged 75 years and older, with younger cohorts experiencing higher stroke mortality in London than the surrounding South East Region. Separating cohort effects from period effects is notoriously difficult,¹⁵ but the cross-over in stroke mortality allowed the identification of cohorts born since about 1920 as having higher stroke mortality in London, whereas those born before this time had lower stroke mortality. This suggests some change in an influence favouring cohorts in London born before 1920 and favouring cohorts in the South East Region born after 1920.

The early-life influences which have been directly related to blood pressure and stroke occurrence in adult life have been birth weight and head circumference at birth.^{11,12} Reliable comparative data for London and the remainder of the south east are not available for the time period under consideration. Therefore Maheswaran and colleagues utilised the two

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proxy indicators of early life conditions – maternal mortality and neonatal mortality – which showed strongest associations with stroke mortality. The expectation would be that maternal and neonatal mortality would be higher in the rest of the south east than in London up until around 1920, with the reverse being seen after this date. These patterns, which would be congruent with an explanation of the cohort changes in relative stroke risks in London and the rest of the south east, were not seen. Indeed, neonatal mortality showed the opposite pattern to that expected, being higher in London until the early 1920s after which it was lower in London than the surrounding South East Region.

There are clearly problems with utilising these indicators of intrauterine environment, especially in the later period when rates had declined to low levels, and they may cease to serve as sensitive proxy measures. The findings do encourage the investigation of alternative hypotheses, however. While adult behaviours, such as smoking, physical activity, fruit, vegetable, salt, and alcohol consumption, or medical treatment differences could show changes between London and the surrounding South East Region in such a way as to produce effects in successive cohorts in a differential manner, this would appear unlikely.

Other evidence points to a lasting influence of early-life factors on stroke risk and encourages the search for influences beyond those of adult behaviours. In the US, the influence of State of birth on cardiovascular mortality in adulthood, independent of State of residence in later life, has long been noted.¹⁶ In New York City blacks born in the south (in the “stroke belt”) or the Caribbean have higher rates of stroke mortality than blacks born in the north east of the US (mainly in New York City itself).¹⁷ In the UK, place of birth and place of death both contribute to cardiovascular disease mortality risk, although the effect of place of birth is greater for coronary heart disease than for stroke mortality.¹⁸

Early-life factors acting after birth may be influenced by place of residence in childhood and in turn contribute to stroke risk in adulthood. These have been less well studied with respect to blood pressure and stroke occurrence in adulthood. Better growth in childhood has been associated with lower cardiovascular disease mortality in a follow up of children examined in the 1930s.¹⁹ Currently, height in childhood is correlated with coronary heart disease mortality in areas across Britain, while birth weight shows less consistent ecological correlations.^{19,20} Height in adulthood, which will partly reflect nutrition and growth in child-

hood, is inversely associated with stroke mortality across the regions of England and Wales, and at an individual level height is inversely related to stroke risk in men and women.^{22,23} While one cross sectional and one prospective study have failed to find an association between childhood socioeconomic circumstances and stroke,^{24,25} a prospective study with data on both childhood and adulthood social class²⁶ and long follow up found the former to be a particularly strong indicator of stroke mortality risk, with little contribution of adulthood social class being seen once childhood social class had been taken into account (Davey Smith and Hart, unpublished observations).

Heights of males and females aged 16–64 are 1 cm lower in Greater London than in the rest of the south east.²⁷ In the first decade of this century heights of school children in London seemed to be about the same as those in the rest of the south east,²⁸ with the same being true for heights of young adult males in 1939,²⁹ although the representativeness of the samples and the degree to which the data can be desegregated render comparisons problematic. It is possible that an increasing disparity in height between London and the rest of the south east is reflected in the changing relative stroke mortalities. Further investigation of the contribution of childhood socioeconomic and nutritional status is merited in this regard.

Socioeconomic differentials in stroke mortality are substantial.²³ In the United States the available data, while imperfect, suggest that poorer folk have experienced higher stroke risk over the whole century.^{30,31,32} Maheswaran and colleagues³³ tabulate data from the *Decennial Supplements* for England and Wales which suggest higher stroke rates in the higher social classes for the years surrounding the 1931 and 1951 census. These data are problematic, however, since classification of stroke changed and the full range of possible categories are not presented in the *Decennial Supplements*. For the 1911³⁴ and 1921³⁵ analyses, the available data show lower stroke rates amongst the non-manual than the manual occupational social class groups. For the 1931 and 1951 *Decennial Supplements*^{36,37} the data are only presented for a category which includes arteriosclerosis, a classification which was probably over-assigned in a biased fashion to non-manual groups,³⁸ an interpretation consonant with the social class distribution of this cause of death in the 1921 *Decennial Supplement*.³⁵ For the 1951 *Decennial Supplement*, all cause mortality showed unexpectedly high rates for social class I and unexpectedly low rates for social class IV, mirroring the pattern seen for stroke.

The Chief Medical Statistician responsible for the 1951 *Decennial Supplement* considered that misclassification of occupation had caused numerator-denominator bias and later corrected the all cause data for this³⁹ (table 1). Corrected data for cause specific mortality are not available, but it is clear the general pattern of high mortality in social class I and low mortality in social class IV, seen to be erroneous with respect to all cause mortality, is the pattern

Table 1 Male mortality in the group 15–64 in relation to social class, before and after correction, 1949–53.

	Social classes				
	I	II	III	IV	V
SMR, males 20–64 (published)	98	86	101	94	118
SMR, males 20–64 (adjusted)	86	92	101	104	118

SMR = Standardised mortality rate.

seen in the uncorrected data with regard to stroke mortality.

In general stroke appears to be a disease of those in unfavourable socioeconomic circumstances. Unlike coronary heart disease, stroke rates can be high in countries, such as China, where most people are poor throughout their lives.⁴⁰ Stroke rates have consistently declined with improving economic circumstances in the US and UK.^{41,42} The “two-stage” hypotheses⁴² regarding a necessary adulthood factor (such as a high energy “western” diet in the case of coronary heart disease) is not essential with respect to stroke.

While problems with classification of both cause of death and social class create difficulties with interpreting trends, as mentioned above, it is clear that social class differentials in stroke mortality have increased over the past 30 years. Infant mortality rates showed large social class differences earlier this century,⁴³ which is compatible with the current social class differentials in stroke mortality.⁴⁴ Despite problems with the classification of stroke mortality and social class in earlier *Decennial Supplements* it is clear that socioeconomic differentials in stroke mortality have been increasing over the past 40 years, and this increase has been most marked at younger ages.⁴⁵

Increasing social class differences in infant mortality during an identified earlier period could account for the time trends in social class differences in stroke mortality only if a steadily accelerating increase in differentials since the 1870s is observed. This is not what the, admittedly imperfect, data suggest. While social class differentials in infant mortality seem to have increased from 1895 to 1911,⁴⁶ there was then a stabilisation or possibly a decrease in the relative magnitude of the social class differentials, even when the changing size of social class groups is taken into account.⁴⁷ These trends are not compatible with the observed recent parallel widening of social class differences in stroke mortality among both sexes, which is more marked for the younger age groups.

Maternal mortality was higher in the more affluent social groups earlier this century,⁴⁸ which is not congruent with the socioeconomic distribution of cardiovascular disease mortality seen for people born prior to the second world war and dying in the 1960s to 1980s. The complex causes of maternal mortality make it a problematic ecological indicator of influences which may be detrimental to the intrauterine development of children and relatively little can be made of this discrepancy.⁴⁸

Height has increased for men and women over this century,⁴⁹ in keeping with the declines in stroke mortality. Indeed it has been argued that trends in height over a longer period underlie changes in life expectancy.⁵⁰ The limited data available suggest persistent social class differences in height for people born between the turn of the century and the late 1950s. These differences may have increased slightly in women and decreased slightly in men.⁴⁹ Childhood height shows greater relative and absolute social class differentials. This reflects the

ability of catch-up growth to compensate for restricted earlier growth, partly through an extension of the growing period. Whilst social class differences in the height of children have persisted through the century,⁵¹ they did not appear to have greatly increased or decreased from the turn of the century to the mid-1950s,⁵² although only limited data are available.

Parallelism with trends in socioeconomic differentials in stroke mortality is difficult to substantiate for the indicators of early life environment which are available. Infant mortality and height, but not maternal mortality, demonstrated social class differences earlier this century which are congruent with present day social class differences in cardiovascular disease mortality. Trends in the socioeconomic differentials of these indicators do not parallel trends in coronary disease differentials, however, except in the case of maternal mortality where the crossover of social class differences in maternal mortality in the mid-1930s can be considered to be consistent with the widening social class differentials in stroke mortality which are currently seen.

Conclusions

One of the paradoxes regarding the epidemiology of stroke is that many of the conventional adult risk factors, such as hypertension, smoking, and obesity, are common to both stroke and CHD. Yet we continually observe discordant patterns for these two diseases, in relation to geography (see above) and ethnicity. Both the Japanese and African-Caribbeans in the US and UK show higher rates of stroke but lower rates of CHD than their indigenous or white counterparts.^{17,53,54} Reed tried to explain the Japanese paradox of high stroke and low CHD mortality by differentiating risk factors which predicted autopsy-proven atherosclerosis in large vessels, such as the coronary arteries, as compared to the small cerebral vessels. He noted that certain risk factors, such as cholesterol, alcohol and certain aspects of an oriental diet, could account for the differences seen between the Japanese and western populations. These factors, however, are unlikely on their own to explain either rural-urban differences or those seen for African-Caribbean populations living in the US or UK.

An alternative explanation is that important interactions between influences acting at different stages of the lifecourse may occur. Thus adult hypertension might have a greater influence in increasing the risk of stroke if combined with the long term influence of early-life exposures, which might effect the structure of the arterial walls of smaller vessels. Whilst we have little empirical evidence, as yet, to test this suggestion, there is evidence of interactive effects for other adult risk factors and outcomes. A Swedish study demonstrated that low birth weight was associated with higher blood pressure and insulin resistance when coupled with obesity in adulthood. There also appeared to be an interaction between low birth weight and stature in adulthood, such that people who ended up tall but had low birth weights –

interpreted to reflect low birth weights in relation to genetic potential – had increased blood pressure.⁵⁵ With regard to coronary heart disease incidence, low birth weight in combination with adulthood obesity is the important exposure combination, with birth weight is not related to coronary heart disease incidence among those who were of average or low weight in adulthood.⁵⁶

Despite the decline in infant and maternal mortality, the increasing trend in obesity would be expected to increase the risk of stroke. Contrasting trends in factors which interact to elevate risk could lead to expectations in any direction. Since exposures acting across the lifecourse, together with interactions between exposures acting at different times, contribute to disease risk, studies which only have data concerning one period of the life course are inadequate for further advancing our understanding of both disease aetiology and the production of geographic, socioeconomic, and ethnic differentials in health.

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