REVIEW ARTICLES

Editorial Comment

Review articles childhood origins of disease

The editorial board commissioned a review by Dr Elford and colleagues on the subject of "The influence of early childhood health on morbidity of adults" which is published below. Dr Elford and colleagues, for the purposes of this review, have restricted their comments to data derived from ecological studies. Data derived from analytical studies, from which they reach broadly similar conclusions, have been reviewed by them and have been published elsewhere. It is apparent that the conclusions reached by these authors are at variance with those of others and the Editorial Board therefore invited Professor Barker and colleagues from the MRC Environmental Epidemiology Unit in Southampton to reply to the review by Elford *et al*, incorporating their own conclusions. Their review is also published in this issue.

Review article

Early life experience and cardiovascular disease—ecological studies

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The possibility that experiences early in life influence the subsequent risk of adult cardiovascular disease excites the imagination. Such a relationship, if it exists, raises questions of vital importance for the aetiology of cardiovascular disease. What effect does early infant diet have on the subsequent risk of cardiovascular disease? Does the quality of the intrauterine environment reveal itself four or five decades later through the risk of cardiovascular disease in adult life? Clearly such a relationship, if it exists, has profound implications for public health policy. Instead of focusing on adults who are believed to be at risk, perhaps we should be concentrating on a new generation of infants and their mothers.

Several published papers have explicitly examined the relationship between circumstances early in life and adult cardiovascular disease. Others have been cited as providing supporting evidence. They have drawn upon different methodologies, have been conducted in a variety of settings, and have employed a wide range of early life indices and adult outcomes. This review considers these papers in order to establish whether they provide sufficient evidence to support a causal relationship between early life experience and adult cardiovascular disease.

Several features of an association allow causal relationships to be distinguished from those that are non-causal.¹ An association which is strong, specific, dose related, independent of recognised confounding factors, and consistently found in

different studies supports a causal relationship. The conjectured cause must precede the effect in time. For the hypothesis under scrutiny in this review, the suspected cause is situated early in the life cycle, long before the development of the cardiovascular outcome. Biological plausibility and experimental evidence provide additional support for causality, but very often such knowledge or evidence are not available. How well do the papers reviewed here satisfy the first five of these criteria—strength, specificity, dose-response, consistency, and independence from confounding factors?

The papers reviewed fall into three methodological groups: ecological, case-control, and longitudinal studies. In this, the first part of the review, we consider the 10 ecological studies.²⁻¹¹

The ecological studies

In ecological studies the group, rather than the individual, is the unit of comparison¹²; disease rates in various groups, usually living within specific geographical areas, are compared. The variation in rates from one area to another may be explained by other factors that also differ between the localities. For example geographical differences in lung cancer mortality may be correlated with the geographical distribution of petrochemical plants. In such studies data on individual behaviour that may influence risk are not always available. Thus the correlation

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between lung cancer and petrochemical industries may be confounded by a higher prevalence of smoking in areas with those industries. This is the “ecological fallacy”.¹³ Ecological studies are therefore valuable for generating rather than testing hypotheses.

Several ecological studies have explored the relation between early life experience and geographical variations in adult cardiovascular

disease. These have been conducted in a variety of settings: Norwegian counties,² registration states in the USA,⁴ counties^{3 8 9} and local authorities^{5-7 11} in England and Wales, and British towns.¹⁰ Of the 10 studies reviewed here, two were concerned with the relation between children’s blood pressure and adult cardiovascular mortality^{10 11} (table I). These are discussed separately at the end of this section.

Table I Ecological studies

Authors	Setting	Indicator of early life experience	Outcome in adult life	Main result
Forsdahl (1977) ²	Norwegian counties (n = 20)	Infant mortality rates 1896–1925	Mortality rates (40–69 years) 1964–67	Correlation between arteriosclerotic mortality (1964–67) and IMR (1896–1925) Males: r = 0.79 Females: r = 0.61
Williams <i>et al</i> (1979) ³	Counties in England and Wales (n = 53)	Infant mortality rates 1885–1948	Mortality rates for IHD (age specific) 1968–73	Correlation between age specific IHD mortality (1968–73) and county IMR (1885–1948) for each cohort eg, at age 55–64 years Males: r = 0.72 Females: r = 0.69
Buck and Simpson (1982) ⁴	Registration States in the USA (n = 17)	Infant mortality rates (diarrhoea and enteritis) 1917–21	Mortality rates (40–44 years) 1961 (50–54 years) 1971	Correlation between arteriosclerotic mortality in 1971 and infant mortality (D and E) in 1917–21 Males: r = 0.69 Females: r = 0.69
Barker and Osmond (1986) ⁵	Local authorities in England and Wales (n = 212)	Infant mortality rates 1921–25	Mortality rates (35–74 years) 1968–78	Correlation between IHD mortality (1968–78) and IMR (1921–25) Males: r = 0.69 Females: r = 0.73
Barker and Osmond (1987) ⁶	Local authorities in England and Wales (n = 154)	Maternal mortality rates 1911–14	Mortality rates (55–74 years) 1968–78	Correlation between stroke mortality (1968–78) and maternal mortality (1911–14) Males: r = 0.61 Females: r = 0.63
Barker <i>et al</i> (1989) ⁷	Local authorities in England and Wales (n = 212)	Neonatal and postneonatal mortality rates 1911–25	Mortality rates (35–74 years) 1968–78	Adult stroke mortality (1968–78) related to neonatal mortality (1911–25); adult chronic bronchitis mortality related to postneonatal mortality; adult IHD mortality related to both.
Barker <i>et al</i> (1990) ⁸	Counties in England and Wales (n = 60)	Height of adults born 1920–45	Mortality rates (35–74 years) 1968–78	Inverse relation between mean height and death from adult chronic bronchitis and IHD (1968–78).
Ben-Shlomo and Davey Smith (1991) ⁹	Counties in England and Wales (n = 43)	Infant mortality rates 1895–1908	Mortality rates (65–74 years) 1968–78	Correlation between IHD mortality (1969–73) and IMR (1895–1908) (Value in brackets is adjusted for current deprivation) Males: r = 0.72 (0.19) Females: r = 0.73 (0.15)
Blood pressure in childhood				
Whincup <i>et al</i> (1988) ¹⁰	British towns (n = 9)	Mean systolic blood pressure at ages 5–7 years 1987–88	Cardiovascular mortality (35–64 years) in each town 1979–83	Correlation between mean SBP in children (1987–88) and adult cardiovascular mortality (1979–83) r = 0.66
Barker DJP <i>et al</i> (1989) ¹¹	Local authorities in England and Wales ranked into areas of high and low mortality (n = 5)	Birthweight (1970); blood pressure, pulse rate, and height at age 10 (1980); maternal blood pressure and height	Cardiovascular mortality rates (35–74 years) 1968–78	No relation between either birthweight (1970) or systolic blood pressure at age 10 (1980) and adult mortality (1968–78). Inverse relation between height and adult mortality. Positive association between both pulse rate at age 10 and maternal BP and adult mortality.

IMR = infant mortality rate; IHD = ischaemic heart disease; D and E = diarrhoea and enteritis; SBP = systolic blood pressure

NORWEGIAN COUNTIES

For a long time conventional wisdom argued that geographical differences in cardiovascular mortality probably reflected corresponding differences in the physical and social environment. In 1977, however, Forsdahl observed that “in Norway, there are still considerable variations in mortality among counties which cannot easily be explained by current living conditions”.² At the beginning of this century there had been sizeable variations in infant mortality between Norwegian counties but by the 1960s these differences had practically disappeared. Infant mortality has long been considered to be a reliable index of the standard of living. Consequently, Forsdahl assumed that earlier differences in the standard of living between counties had also disappeared by the 1960s. Nevertheless, pronounced geographical variations in middle age mortality persisted. How could the county differences in adult mortality be accounted for, if, according to Forsdahl’s assumption, all counties now enjoyed a similar standard of living? Seeking an answer to this question, Forsdahl went back to the beginning of the life cycle. His objective was to “explain the hypothesis that poverty during adolescence is positively correlated with the risk of dying from arteriosclerotic disease”.

Using data from 20 Norwegian counties, he found a strong correlation between county infant mortality rates during 1896–1925 and adult mortality in the same area between 1964–67. The relationship held for all cause, arteriosclerotic, and cancer mortality for both men and women aged 40–69 years (table I). County infant mortality rates also correlated with cerebrovascular disease and lung cancer death rates for men, but *not* for women.

Forsdahl argued that counties which experienced poverty at the turn of the century, as indicated by their high infant mortality, and which had subsequently been “exposed to affluence”, experienced an excess mortality risk, particularly from arteriosclerotic disease. According to Forsdahl “the findings suggested that great poverty in childhood and adolescence followed by prosperity is a risk factor for arteriosclerotic disease”.

Since this paper is often cited^{3–5 7 9} as being the first to provide evidence for the hypothesis regarding poverty in early life and later cardiovascular disease, it merits particular attention. First, it is important to note that Forsdahl changed the hypothesis during the paper. He set out initially to examine the correlation between poverty during adolescence and the risk of dying from arteriosclerotic disease. Then, in his discussion, he added the role of “later affluence” to the ingredients of this relationship. Second, while for both males and females there was a strong correlation between infant mortality during 1896–1926 and total mortality in the 1960s, the relation varied between men and women for specific causes. Third, while acknowledging that current cigarette smoking by men may be more widespread in those counties where the social conditions were previously unfavourable, he did not provide any data on this or on other potential confounding factors.

Instead, he suggested that poverty in childhood may have created an increased susceptibility to lung cancer in later life for men but *not* for women. He also assumed, but provided no evidence, that county differences in present day living standards had indeed disappeared.

Seeking to explain the relationship between childhood poverty, later affluence, and adult cardiovascular disease, Forsdahl conducted a further ecological study in 19 municipalities in northern Norway. Here he found a positive correlation between infant mortality earlier this century and mean *cholesterol* levels among adults in the mid-1970s.¹⁴ There was no association with adult blood pressure levels. He suggested that this “increased the suspicion that cholesterol is the intermediate risk factor in the chain between childhood poverty and arteriosclerotic disease” and proposed that those who grew up in poverty may later have a reduced tolerance to certain types of fats.

COUNTIES IN ENGLAND AND WALES

Williams and his colleagues set out “to determine whether the relationship between recent ischaemic heart disease death rates and past infant mortality observed in Norway also obtained in England and Wales”.³ For 53 counties in England and Wales, ischaemic heart disease mortality between 1969 and 1973 was compared with infant mortality in the same area earlier this century. For each 10 year cohort, significant correlations were found in all but the youngest group of females (table I). This was consistent with the Norwegian data published by Forsdahl.² However, infant mortality rates during the period 1969–73 also varied markedly between the English and Welsh counties. The authors found that “although in each county there has been a marked reduction in infant mortality from 1885 to the present day, the relative rankings of the counties have stayed largely the same”. Consequently, geographic variations in infant mortality between 1969 and 1973 were significantly correlated with ischaemic heart disease death rates in the same period (males, $r=0.52$; females, $r=0.51$ at age 55–64 years). The authors thought it unreasonable to conclude that, in England and Wales, poor living conditions in childhood *alone* gave rise to an increased risk of dying from ischaemic heart disease. Counties that were poor in the past appeared to have remained relatively poor to the present day. They concluded that their study had “failed to support the hypothesis that, in England and Wales, the transition from poverty in early life to prosperity in middle age is a causal determinant of death from ischaemic heart disease”.

As with all ecological studies there are problems with this analysis. Boundary changes in the south east of England may have introduced bias. Because of the limited data only 43 counties could be analysed for the oldest cohorts. However, the strength of the paper lies in the authors having ranked county infant mortality for different time periods between 1885 and 1973. In this way they specifically addressed the question as to whether areas that were poor in the past remained so today. The authors also suggested that the lack of any significant variation between *Norwegian* counties in their present day infant mortality rates² might

well have been explained by the small number of infant deaths occurring in any one county. Between 1971–75 there were fewer than 850 infant deaths in the whole of Norway, compared with about 12 000 in England and Wales.

REGISTRATION STATES IN THE USA
Using data from 17 US “registration states”, Buck and Simpson found a positive correlation between infant mortality in 1917 and adult mortality in 1961 and 1971.⁴ There was, however, no association between infant mortality in 1927 and subsequent adult mortality, a discrepancy on which the authors failed to comment. Buck and Simpson added a new piece to the aetiological jigsaw puzzle concerning childhood experience and adult cardiovascular disease—infantile diarrhoea and enteritis. For the period 1917–21, infant deaths from diarrhoea and enteritis were strongly correlated with adult mortality from all causes and arteriosclerotic heart disease in both 1961 and 1971 (table I). Infant deaths from diarrhoea and enteritis were also correlated with respiratory cancer in men but *not* women.

The authors proposed a variety of immunological mechanisms for the relation between infant death from diarrhoea and enteritis and adult cardiovascular disease. While they recognised the speculative nature of their explanations they believed their research “should encourage further investigation, particularly of the long term consequences of infant diarrhoea, a disease that is still very prevalent in many parts of the world”. Were the authors suggesting that those countries with a high prevalence of infant diarrhoea should experience a correspondingly high rate of cardiovascular disease?

LOCAL AUTHORITIES IN ENGLAND AND WALES
Postnatal environment

Using data from 212 local authority areas in England and Wales, Barker and Osmond found a strong correlation between infant mortality in 1921–25 and adult mortality from leading causes of death between 1968 and 1978.⁵ Positive correlations were found for ischaemic heart disease, bronchitis, stomach cancer, and rheumatic heart disease (both sexes), for stroke and lung cancer (males), and cervical cancer (females) (tables I and II). The authors selectively concluded that “the close geographical similarity between previous infant mortality and current ischaemic heart disease mortality is most readily reconciled with their opposing time trends by the hypothesis that adverse influences in childhood, associated with poor living standards increase susceptibility to other influences, associated with affluence, encountered in later life”. According to the authors, the association with neonatal mortality suggested that nutrition during prenatal

and early postnatal life predisposed to adult ischaemic heart disease, as well as influences acting throughout infancy.

This study was based upon a large number of deaths but the specificity of the relationship with ischaemic heart disease is brought into question by the close geographical relation between past infant and current adult mortality from a wide range of causes of death (table II). In fact, although the data are not provided, it is obvious that a close correlation exists between past infant mortality and recent *all cause* adult mortality. Is it not likely that areas of high mortality, both infant and adult, in the past have simply remained high in the league table today, as shown by Williams *et al*?³ Barker and Osmond were seemingly unaware of Williams’ earlier analysis, since they made no mention of it in their own discussion. Williams had already demonstrated that, in England and Wales, the ecological relation between past infant mortality and subsequent adult mortality was confounded by persisting geographical inequalities in social and economic conditions.

In Barker and Osmond’s study, the correlation between adult ischaemic heart disease and infantile diarrhoea ($r=0.48$) was relatively weak compared with the correlation with other causes of infant death, contradicting the importance of infantile diarrhoea previously reported by Buck and Simpson.⁴

Prenatal environment

The impact of the prenatal environment on the subsequent risk of stroke was the focus of interest in this paper.⁶ The authors “made a detailed geographical comparison of maternal mortality in the early years of this century. . . (with). . . death rates from stroke in the generation born during the same period”. Using data for 154 local authorities in England and Wales, a strong correlation was found between maternal mortality in 1911–1914 and adult mortality from both stroke and ischaemic heart disease between 1968 and 1978 (table I). The correlation between maternal mortality and stroke depended upon causes of maternal death other than puerperal fever.

The authors suggested that high maternal mortality in 1911–14 reflected the poor physique and health of mothers at that time, which would have adversely affected their reproductive efficiency. A poor intrauterine environment was likely to result in low birthweight babies. According to the authors, low birthweight has been associated with raised blood pressure in infants. As a result of “tracking”, in which the rank order of blood pressure persists over time, children in the top blood pressure rank would tend to remain there as adults. As adult hypertension is a risk factor for stroke, “impaired reproductive efficiency is expressed as an increased risk of stroke in the surviving offspring”.

They concluded that current death rates from stroke in different areas of England and Wales could be “closely predicted” from maternal mortality, from causes other than puerperal fever, 75 years ago. Yet their own data indicated that for a maternal mortality of 2/1000 in 1911–14, the standardised mortality ratios for stroke in

Table II Correlation of standardised mortality ratios 1968–78 and infant mortality rates 1921–25, England and Wales⁴

Cause of death 1968–78 (35–74 years)	Correlation coefficient	
	Males	Females
Ischaemic heart disease	0.69	0.73
Bronchitis	0.81	0.77
Stomach cancer	0.74	0.73
Rheumatic heart disease	0.60	0.70
Stroke	0.60	0.40
Lung cancer	0.52	0.09
Cervical cancer	–	0.60

1968–78 ranged from approximately 65 to 120, almost a twofold difference. While the correlation was strong ($r=0.6$), the degree of scatter did not justify the authors' claim concerning the predictive power of past maternal mortality.

While the authors' interest was stroke mortality in the "generation" born between 1911–14, people who died between 1968 and 1978 aged 55–74 years were born over a 30 year period between 1894 and 1923. This was not, in fact, a cohort study, but an ecological analysis of data collected over two time periods (1911–14 and 1968–78).

The striking feature of this paper is that the emphasis on childhood adversity shifted from *post-natal*^{2–5} to *pre-natal* life. According to this aetiological model, not only are circumstances during the first few years of life crucial for adult cardiovascular disease, but conditions in utero may also play a critical role. According to the authors "there is increasing evidence that hypertension originates in childhood". This hypothesis is examined in greater detail in the second part of the review.¹⁵

This paper raises an important question concerning the long term effects of an adverse prenatal environment. However, the possibility that persisting geographical differentials in nutrition and socioeconomic conditions accounted for geographical variations in both maternal mortality earlier this century and current stroke mortality was not discussed.

Prenatal and postnatal environment

Barker and colleagues extended their earlier analyses of the England and Wales data for 212 local authorities to discriminate "more closely between the geographical relations of cardiovascular disease with past neonatal and post-neonatal mortality".⁷ The findings were contrasted with those for geographical variations in chronic bronchitis. The 212 local authority areas were ranked according to their neonatal and postneonatal mortality in 1911–25. Adult stroke mortality between 1968–1978 was related to earlier neonatal mortality, adult bronchitis mortality with postneonatal mortality, while death from ischaemic heart disease was related to both. This suggested to the authors that stroke was related to the intrauterine environment, bronchitis to the postnatal environment, and ischaemic heart disease to both.

This is an elegant analysis which synthesises the ideas and data presented in the authors' earlier papers. Inevitably, it also incorporated some of the limitations of these earlier papers.

COUNTIES IN ENGLAND AND WALES

Barker and Osmond examined the geographical relation between height and adult mortality in England and Wales, to further explore "the relationships between adult diseases and childhood influences".⁸ Data on height were available for three birth cohorts (1946, 1958, and 1970) and their parents (born around 1920, 1930, and 1945 respectively). The 60 counties of England and Wales were ranked into five groups according to the mean height of the children (at ages 10 or 11 years) and the self reported height of their parents. On average, people living in

northern or western counties were shorter than those living in the south and east. Using national mortality data for men and women aged 35–74 years who died between 1968 and 1978, the authors found that standardised mortality ratios for bronchitis, rheumatic heart disease, ischaemic heart disease, and stroke fell progressively from the shortest to the tallest group of counties (table I). Prostatic, breast, and ovarian cancer showed an opposite trend. There was apparently no clear trend for lung cancer.

The authors concluded that the "inverse geographical relation of height with chronic bronchitis and cardiovascular disease is consistent with other evidence of risk factors for these diseases acting in childhood". Furthermore "the lack of a consistent trend in lung cancer mortality with height suggests that the link is not through an association between cigarette smoking and height".

North-south differences in mortality are well established,¹⁶ as indeed are geographical differences in height.¹⁷ Nobody disputes the importance of prenatal, postnatal, and infant influences on height.¹⁸ By correlating geographical variations in height and mortality the authors claim to have found further evidence to support the hypothesis concerning childhood experience and adult mortality. However, this study singularly failed to consider, or even mention, the role of potential confounding factors. Persisting geographical inequalities in socioeconomic conditions could well have explained the equally persistent geographical differences in both height and mortality. Concerning lung cancer, London was placed in the intermediate height group, yet some London boroughs have exceptionally high lung cancer mortality.¹⁶ Had London been removed from the analysis a north-south gradient in male lung cancer would almost certainly have emerged.

The ecological association between height and adult mortality does raise an interesting question. What is the health experience of the relatively short northerners when they move to the south, or of the relatively tall southerners when they move north? Do the powerful early life experiences which shaped their height continue to exert an effect on their health? This is considered in the second part of the review.¹⁵

COUNTIES IN ENGLAND AND WALES REVISITED

Ben-Shlomo and Davey Smith⁹ reanalysed Williams's³ data set for 43 counties in England and Wales. They compared infant mortality between 1895 and 1908 with adult mortality between 1969 and 1973, taking into account contemporary deprivation which is known to be related to current levels of mortality. Their deprivation index for each county was based on car ownership, overcrowding, unemployment, and class distribution.

As in earlier ecological analyses, strong correlations were found between infant mortality at the turn of the century and subsequent cardiovascular mortality (table I). However, adjusting for current deprivation dramatically reduced the association between past infant mortality and recent adult mortality from ischaemic heart disease (correlation coefficients

after adjustment: males 0.15, females 0.19). Clearly, areas which were poor in the past, as indicated by their high infant mortality, remained deprived to the present day. They concluded that previous ecological studies which had failed to consider current deprivation provided little support for the childhood origins of adult cardiovascular disease.

Blood pressure in childhood and adult cardiovascular disease

BRITISH TOWNS

Among middle aged men in the British Regional Heart Study (BRHS) blood pressure levels were higher in the north of England and Scotland than in the south.¹⁹ As a consequence of these findings, a further survey was conducted in nine of the 24 BRHS towns "to establish whether a similar geographical pattern of blood pressure differences was present in children aged 5 to 7 years".¹⁰ This study also examined the association between each town's mean systolic blood pressure for children and the town's standardised mortality ratio for adult cardiovascular disease.

For the nine towns, there was a positive correlation between the children's mean systolic blood pressure in 1987–88 and the town's standardised mortality ratio for cardiovascular disease in 1979–83. However, the relation was heavily dependent on one town (Guildford) with both low adult mortality and low mean blood pressure in children. The authors suggested that blood pressure patterns may be established at an early age. While they produced evidence that childhood, as well as adult, blood pressure may be related to adult cardiovascular mortality, they did not speculate as to which was the more important.

LOCAL AUTHORITIES IN ENGLAND AND WALES

In this paper Barker and colleagues made "geographical comparisons within England and Wales to examine the relation between intrauterine influences and cardiovascular disease". Using data from the 1970 birth cohort, they investigated the ecological relations between adult cardiovascular mortality and blood pressure, pulse rate, and height at the age of 10 years, birthweight, and both maternal blood pressure and height.¹¹

The 1970 cohort comprised approximately 98% of all births in Great Britain during one week in April 1970. Information recorded at the time of birth included birth weight, gestation, and mothers' blood pressure. At the age of 10 years, height, weight, blood pressure (usually to the nearest 10 mm), pulse rate, and mother's height were measured in surviving children. This analysis was based on 9921 children born in England and Wales.

Using national mortality data for men and women aged 35–74 years who died from cardiovascular disease between 1968 and 1978, 154 local authority areas in England and Wales were ranked, according to their standardised mortality ratios, into five groups of roughly equal population size. High mortality areas tended to be in the north and west, while low mortality areas were mostly in the south and east. Maternal diastolic (but not systolic) blood pressure

increased from the lowest to the highest mortality areas. This finding was consistent with the geographical gradient in blood pressure reported among middle aged men in the British Regional Heart Study.¹⁹ Among the children themselves, however, there was *no* geographical relation between adult cardiovascular mortality and systolic blood pressure at the age of 10 years. This observation is at variance with the findings of Whincup *et al* in the nine British towns.¹⁰ This might be due to the fact that blood pressure measurements in the 1970 birth cohort were poorly standardised and rounded to the nearest 10 mm.

There was no geographical relation between adult mortality (1968–78) and birthweight (1970). However, had the data been available, a more appropriate comparison would have been between birthweight *earlier* this century and current adult mortality. The heights of both the mothers and their children were inversely related to mortality. And pulse rates at age 10 years increased from the low to high mortality areas. In the 1970 cohort, pulse rate at age 10 was inversely related to birthweight but this was not significant at the 5% level.

The authors suggested that geographical differences in the intrauterine environment could partially explain subsequent regional differences in blood pressure and cardiovascular mortality. Yet neither birthweight nor blood pressure at the age of 10 years varied across the five areas ranked according to cardiovascular mortality. Furthermore, migrant studies suggest that geographical differences in adult blood pressure are more likely to be explained by factors present in the adult, rather than in the intrauterine environment.²⁰ The inverse ecological relation between mortality and height could simply have reflected persisting geographical inequalities in social and economic circumstances; and, in the 1970 birth cohort, there was no significant relation between pulse rate and intrauterine conditions, indexed by birthweight. Consequently, the data presented in this paper do not actually support the authors' conclusion that regional differences in the intrauterine environment could partially explain subsequent geographical differences in blood pressure and cardiovascular mortality.

Discussion

It has been proposed that experiences very early in life influence the risk of cardiovascular disease in later adult life. In particular, that poverty in childhood followed by affluence in adult life may present an increased cardiovascular risk. We have examined 10 ecological studies which considered this hypothesis. They all explored the relation between *geographical* variations in present day cardiovascular mortality and an index of early life experience. How well have these ecological studies fulfilled the following established criteria for causality—strength, dose-response, independence from confounding factors, specificity, and consistency?

STRENGTH AND DOSE-RESPONSE

These investigations have all found dose related associations of similar strength. In four

populations, there was a strong correlation between infant mortality earlier this century and present day adult cardiovascular mortality.^{2-5 7 9} A correlation was also found between maternal mortality in 1921–25 and adult stroke mortality between 1968 and 1978.⁶ Geographical variations in recent adult mortality were inversely related to height^{8 11}; and in nine British towns, adult cardiovascular mortality was positively associated with blood pressure levels among children.¹⁰

Clearly all these studies point to a strong association between experiences early in life and subsequent adult mortality. The critical issue, therefore, is the *interpretation* of the observed relation. On the one hand, these ecological studies may have revealed a causal relation of considerable strength and magnitude. On the other hand, the ecological relationships may be heavily confounded by persisting geographical differentials in social and economic conditions. Those born into relative disadvantage at the beginning of the century may experience poor health as adults as a result of continuing hardship. Consequently the role of confounding is crucial here.

INDEPENDENCE FROM CONFOUNDING FACTORS

Only two studies^{3 9} seriously considered the possibility that geographical areas with high mortality in the past may have remained areas of high mortality to the present day. When examining geographical differences in infant mortality in England and Wales, Williams and his colleagues observed that the relative rankings had stayed largely the same throughout this century.³ This comes as no surprise. Geographical variations in mortality have been reported in England and Wales for over 100 years. The most recent decennial supplement on mortality and geography confirmed “the continuation of the familiar regional gradient in total mortality. . . from high in the north and west to low in the south and east”.¹⁵ Those parts of the country that were poor in the past appear to have remained relatively poor to the present day.

Ben-Shlomo and Davey Smith⁹ also demonstrated that, in England and Wales, the relation between infant mortality at the turn of the century and subsequent cardiovascular mortality was dramatically reduced once current deprivation was taken into account.

Clearly, in all the studies considered here, the ecological relation between early life experience and adult disease was confounded by persisting social and economic disadvantage. Yet most authors failed to address this issue adequately, if at all.

SPECIFICITY

The formulation of the *hypothesis* itself lacked specificity. In particular, the precise timing of the early life disadvantage differed between the studies. The role of poverty and adversity during adolescence, childhood, infancy, the immediate postnatal period, and in utero has been examined in different papers. Furthermore, the aetiological role of “later prosperity” is unclear; it is central to some of the analyses, but not to others.

The specificity of the *relationship* between early life experience and cardiovascular disease must be

brought into question since, in most studies, the early life index appeared to be correlated with a number of causes of death and with total mortality.^{2 4 5 8 9} Cardiovascular mortality appears to have been selected for special treatment in a somewhat arbitrary manner, without any explanation as to why the other causes of death were so casually disregarded.

Overall, both the formulation of the hypothesis and the relationships described in the ecological studies lacked specificity.

CONSISTENCY

Inconsistent results were found within and between a number of studies. In the 17 US registration states, no correlation at all was found between infant mortality in 1927 and adult mortality in 1961 or 1971.⁴ This is at variance with the other papers. While a geographical relation was found between children’s blood pressure and adult cardiovascular mortality in nine British towns,¹⁰ no such relation was seen in a nationwide sample of 10 year olds from the 1970 birth cohort.¹¹ In England and Wales infant deaths from diarrhoea were less strongly correlated with adult heart disease than other causes of infant death,⁵ whereas in the USA the reverse was the case.⁴

The studies also failed to agree on an aetiological pathway between experiences early in life and adult cardiovascular disease. Forsdahl suggested that early poverty created an intolerance to certain fats, which raised blood cholesterol.¹⁴ Buck and Simpson suggested that infantile diarrhoeal infections were associated with an increased risk of death from heart disease in later life.⁴ Barker *et al*, on the other hand, proposed that an adverse intrauterine environment and poor infant nutrition were the critical factors.^{5-7 11} Whincup *et al* suggested that blood pressure patterns in adults might have their origins in early childhood.¹⁰ Each study has generated its own, sometimes unique, mechanism. Overall, there is a striking inconsistency in the aetiological mechanism offered for a relation between early life experience and adult cardiovascular mortality.

Conclusion

Ecological studies are invaluable for generating rather than testing hypotheses.¹² The ecological studies reviewed here²⁻¹¹ have served an important function by bringing to our attention the possibility that experiences early in life may have a long term influence on adult cardiovascular mortality.

The ecological studies have all described strong, dose related relationships between present day adult cardiovascular mortality and an index of early life experience. However, they failed to satisfy several other established criteria for causality.¹ Inconsistencies were found between and within the studies; both the formulation of the hypothesis and the relationships described lacked specificity; and, most important of all, the role of confounding was treated inadequately in most papers. Consequently, the relations found in these studies between present day adult cardiovascular disease and early life experience should be

interpreted with extreme caution. Hypotheses generated by ecological studies need to be rigorously tested in epidemiological studies based on individuals rather than groups. These are considered in the second part of this review.¹⁵

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Review article

The maternal and fetal origins of cardiovascular disease

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The limited ability of known risk factors to predict the occurrence of cardiovascular disease in individuals is often forgotten.¹ Rose has pointed out that for a man falling into the lowest risk groups for plasma lipid concentrations, blood pressure, cigarette smoking, and presence of pre-existing symptoms of coronary heart disease, the commonest cause of death is coronary heart disease.² Nor is the paradoxical social and geographical distribution of ischaemic heart disease understood. Why is it that a disease that is associated globally with affluence is now commonest in the poorest parts of Britain and among people with the lowest incomes?

Geographical studies

A possible explanation for the geographical differences in mortality from cardiovascular disease in England and Wales is that its causes begin to operate not in adult life but during fetal development and infancy. Records of infant mortality dating from the beginning of the century allow current death rates in the 212 local authority areas of England and Wales to be compared with infant mortality rates in the same places 60 or more years ago. The correlation between past infant mortality and current mortality from cardiovascular disease ($r = 0.73$) is strikingly close.³ Infant mortality is, of course, no more than a general indicator of adverse environmental conditions. But such a strong

relation is, at the very least, suggestive that some aspect of poor living conditions in early childhood determines risk of cardiovascular disease in adult life.

The records of infant mortality in England and Wales are sufficiently detailed to allow neonatal mortality (ie, deaths before one month of age) to be distinguished from postneonatal mortality (ie, deaths between the ages of one month and one year). A further analysis using these separate categories showed that adult cardiovascular mortality is more closely linked to neonatal mortality 60 years earlier than to postneonatal mortality.⁴

Neonatal mortality in the past was high in places where many babies were born with low birth weight.⁵ Neonatal mortality is also known to have been associated with high maternal mortality. High rates for both neonatal and maternal mortality were found in places where the physique and health of women were poor.⁶ Cardiovascular disease is therefore associated more strongly with poor maternal physique and health and poor fetal growth than with conditions, such as overcrowding, that predispose to high postneonatal death rates.

Animal studies

Ideas about the importance of early life in determining risk of disease in adulthood are reinforced by studies in animals. Transient events

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