CHAPTER 12

HYPOTHESIZED FOETAL AND EARLY LIFE INFLUENCES ON ADULT HEART DISEASE MORTALITY: AN ECOLOGICAL ANALYSIS OF DATA FOR THE REPUBLIC OF IRELAND

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Introduction

Spatial disparities in the prevalence of heart disease are frequently explained in terms of adult lifestyle factors (e.g. diet, smoking, alcohol consumption, stress, exercise, etc.). However, in recent years a number of researchers have suggested an alternative mode of explanation: namely, that the risk of heart disease in adult life may be influenced either by factors related to living conditions shortly after birth or by foetal development before birth. These propositions may be referred to collectively (if loosely) as the "perinatal" hypothesis. Much of the early research on the perinatal hypothesis was prompted by observed ecological correlations between adult heart disease mortality and infant mortality within the same age cohort several decades previously. However, correlations of this type have so far been reported for a limited number of countries, raising the question as to what extent they are replicable in other geographical contexts. This paper reports the results of an ecological analysis of adult heart disease and infant mortality in the Republic of Ireland.

The first part of the paper traces the origins and evolution of the perinatal hypothesis and identifies some of the major issues which have arisen in the literature. The middle sections of the paper report the results of an empirical study using data on infant mortality and deaths from ischaemic and other forms of heart disease in the Republic of Ireland. The final part of the paper discusses the extent to which these findings provide support, or otherwise, for the perinatal hypothesis.

The perinatal hypothesis

The origins of the perinatal hypothesis may be traced to a series of ecological studies by Forsdahl in the 1970s (e.g. Forsdahl, 1977, 1978). Forsdahl observed that mortality from arteriosclerotic heart disease in Norway varied considerably from county to county, but that these variations did not correspond to contemporary variations in living conditions. Using infant mortality as an indicator of living conditions, Forsdahl (1977) found that: (1) there were considerable variations in infant mortality rates in Norway at the beginning of the century, but that these variations had more or less disappeared by the 1960s; (2) there was a strong correlation between the patterns of mortality from

arteriosclerotic heart disease amongst people aged 40-69 in 1964-1967 and 1969-1972 and infant mortality from 1896 to 1925; i.e. people were dying in greater numbers as adults in the same areas as people from the same age cohort had died 50 years previously as infants.

Forsdahl interpreted the equalization of the infant mortality rates as evidence of a reduction in the spatial inequalities in living conditions. This in turn implied that the areas which initially had the highest levels of infant mortality must have experienced more rapid improvements in living conditions. This led him to hypothesize that people who experienced poverty in childhood and adolescence were more susceptible to heart disease in later life than people raised in the areas which were originally the most prosperous. He further suggested that "the prerequisite is a later exposure to affluence and its consequence in the form of our present way of life. Where this latter condition is not fulfilled as in the underdeveloped countries the mortality rates from arteriosclerotic heart disease remain low" (Forsdahl, 1977, p. 95).

In a subsequent study, Forsdahl (1978) reported a strong correlation between infant mortality in the early parts of the century and mean serum cholesterol levels, but not with blood pressure, amongst adults in the mid-1970s in municipalities in Finnmark. This led him to suggest that people brought up in poverty may have a reduced tolerance to certain types of fat.

Forsdahl's study may be criticized on at least two counts (Elford *et al.*, 1992):

1. Although Forsdahl showed links between adult mortality and infant mortality 50 years previously, he did not provide any direct evidence that prosperity in later life is a factor. Later prosperity is assumed (on the basis of declining infant mortality rates) rather than measured directly. Also, the areas identified as having experienced the greatest increases in prosperity are (by definition) those which were poorest to begin with adult mortality could just as easily be a function of childhood poverty as of later prosperity.

2. Forsdahl did not take sufficient account of possible confounding factors. He acknowledged, for example, that cigarette smoking may have been more widespread in the high mortality areas, but he then ignored smoking (and other later lifestyle factors) when proposing his theory to explain adult mortality. If smoking happened to be more widespread in the areas which previously had the highest infant mortality rates, significant ecological correlations between adult heart disease and infant mortality could arise without there necessarily being any direct causal link between heart disease and conditions around the time of birth.

Taking these points together, one can identify at least three sets of possible explanations (plus hybrids) for Forsdahl's empirical observations:

1. Adult heart disease may be a function of initial poverty followed by later prosperity (as hypothesized by Forsdahl); or

2. Adult heart disease may be a function of lifestyle factors (such as smoking) in adult life, which simply happen to be found in the areas which previously had high rates of infant mortality; this is consistent with the "orthodox" view; or

3. Adult heart disease is a function of factors around the time of birth, irrespective of whether or not this is followed by later prosperity the "perinatal" hypothesis.

Ecological correlations between adult heart disease and infant mortality in earlier decades have been reported in other studies. Williams *et al.* (1979), for example, in one of the earlier UK studies, found that ischaemic heart disease mortality in English and Welsh counties in 1968-1973 was ecologically correlated with infant mortality in the period 1885-1948. However, they also found that the pattern of infant mortality had changed very little over time. In other words, there was no evidence to suggest that adult mortality in England and Wales was necessarily associated with rapid prosperity (as hypothesized by Forsdahl).

Buck and Simpson (1982) found that infant mortality in 1917 in 17 US registration states was correlated with adult arteriosclerotic heart disease mortality (and also respiratory cancer mortality amongst men) in 1961 and 1971. However, they did not find a correlation between infant mortality in 1927 and adult mortality in either 1961 or 1971. Buck and Simpson suggested that adult heart disease may in some way be triggered by the immunological responses to diarrhoea and enteritis, which were common sources of infant deaths in 1917, but less common in 1927. This might explain the absence of an ecological correlation with infant mortality in 1927.

Much of the more recent work on the perinatal hypothesis is associated with Professor David Barker and his associates in the MRC Environmental Epidemiology Unit in Southampton. Barker and his associates have produced a series of thought-provoking studies, at both ecological and individual levels of analysis, many of which are reprinted in Barker (1992).

For example, Barker and Osmond (1986) reported ecological correlations between infant mortality 1921-1925 and a number of major causes of death 1968-1978 for 212 local authority areas in England and Wales. Heart disease recorded a high correlation, but the correlations for

bronchitis and stomach cancer were even higher. These correlations are consistent with the perinatal hypothesis, but they do not necessarily contradict lifestyle hypotheses related to the regionally persistent nature of social deprivation in England and Wales; i.e. the areas which were the most socially deprived, and which had the highest rates of infant mortality in the past, still tend to be the most socially deprived at present and might therefore be expected to be characterized by the lifestyle factors (such as smoking or diet) believed to contribute to heart disease. However, Barker (1994a) argued against this possibility and noted that deaths from lung cancer, which he suggested may be taken as an indicator of tobacco consumption, and dietary fat consumption each have a different geographical distribution from past infant mortality.

Barker and Osmond (1987), in a more detailed study, compared three neighbouring towns in Lancashire (Burnley, Nelson and Colne). The three towns are very similar today in terms of social composition, and most other aspects, i.e. they are all cotton weaving towns. However, Burnley has one of the highest death rates in England, whereas Nelson is close to the national average. Colne is intermediate. These death rates directly parallel the infant mortality rates in the early decades of the century. These differences were attributed, at the time, to differences in development. Burnley and Colne were older towns, and the women working in the mills were usually second or third-generation mill workers. Nelson was newer, and many of the women working there were recent immigrants from nearby rural districts where the women were described as "sturdier and healthier" than those in Burnley. However, whatever the reasons were for the differences in infant mortality at the turn of the century, these differences would seem to be reflected by present-day heart disease mortality rates lending support to the perinatal hypothesis.

Ecological correlations between adult heart disease rates and infant mortality several decades previously could be misleading because of population movements. However, Osmond *et al.* (1990) analysed data coded from almost 2 million death certificates which recorded the place of birth in England and Wales between 1969 and 1972. It was found that about half of the deceased had migrated to a different part of the country during their lives, but it was also found that the increased risk of coronary heart disease and stroke of people born in the northern counties and industrial areas persisted even if they moved to low-risk parts of the country. Conversely, people born in and around London retained a lower risk from these diseases, even if they moved to areas of higher risk.

The most persuasive evidence provided by Barker and his colleagues in support of the perinatal hypothesis is provided by a series of longitudinal studies using archival birth records in places such as Hertfordshire (Barker *et al.*, 1989; Osmond *et al.*, 1993), Preston (Phillips *et al.*, 1994) and Sheffield (Barker *et al.*, 1995). These studies match information on

features such as birth weight, ponderal index, and weight at 12 months of babies born in the early decades of the century with their later medical histories, resulting in a series of statistically significant associations, reinforced by plausible biomedical explanations (e.g. Barker, 1994a,b, 1995). The net effect of this work has been to push the hypothesized critical period further and further back from childhood, to infancy, to the early foetal period, and possibly even to the period before conception (during which, it is hypothesized, maternal nutrition levels may influence subsequent early foetal development).

The thinking of the Environmental Epidemiology Unit in Southampton has clearly moved far beyond Forsdahl's early observations and hypotheses. However, this thinking is largely (although not entirely) informed by empirical studies based in the UK. It is possible that the relationships which have been identified may be peculiar to the UK at a particular stage in its epidemiological history. There is therefore a need to establish to what extent the empirical regularities observed in the UK can be replicated in other geographical contexts. The remainder of this paper reports the preliminary findings of an empirical evaluation of the perinatal hypothesis in a different geographical context namely, the Republic of Ireland.

The data

The author is unaware of any archival birth records which could form the basis of a longitudinal study in Ireland, so the present study is confined to an analysis of ecological data. The data used in this study were extracted from the *Report on Vital Statistics*, and its forerunners, published annually by the Central Statistics Office in Dublin. (The *Report on Vital Statistics* was published under several different titles in the period 1916-1990. It was published in the earliest part of the study period as *The Annual Report of the Registrar General*). Publication of these reports normally occurs within a few years, but publication has recently fallen behind schedule with the result that no data were available at the time of writing for any year after 1990.

The *Report on Vital Statistics* provides data on births and deaths disaggregated by Counties and County Boroughs (Fig. 1). The present territory of the Republic of Ireland is divided for administrative and statistical purposes into 27 Counties and five County Boroughs. [Strictly speaking there are only 26 Counties, but one (Tipperary) is divided into two Ridings, each of which has similar powers to a County, for local government purposes.] The larger urban areas (i.e. Dublin, Cork, Limerick, Waterford and Galway) are incorporated as County Boroughs and have broadly similar administrative powers to Counties. The administrative areas of the Counties and County Boroughs are non-overlapping, so the County Boroughs may in effect be thought of as "urban counties". Most counties have a population between 50 000 and

125 000, although Dublin C.B. and Dublin County with populations of 478 389 and 546 915, respectively, are notable exceptions.

Figure 1. Counties and County Boroughs, 1990.

The *Report on Vital Statistics* provides information on the number of deaths from Principal Groups of Causes, disaggregated by county of normal residence, sex and 10 year age groups. This study analyses deaths from "Ischaemic and Other Forms of Heart Disease" (ICD 393-398, 410-417 and 420-429) amongst people aged 55-64. Although the number of deaths are higher in the older age groups, it was felt desirable to confine the study to deaths which could be regarded as "premature". Deaths in the 65-74 age group, or above, were therefore omitted from the study. Deaths below the age of 55 were also omitted to limit the size of the target cohort.

There were a total of 902 male and 300 female deaths from Ischaemic and Other Forms of Heart Disease amongst people aged 55-64 in 1990. Although this is a substantial number in total, it was felt that the numbers in some counties might be too small to provide a reliable indication of

underlying risk because of stochastic variations. It was therefore decided to aggregate deaths amongst 55-64-year-olds over a 10 year period from 1981 to 1990. This gave a total of 10,596 male and 3,824 female deaths, ranging from 95 male and 37 female deaths in Leitrim to 1,829 male and 806 female deaths in Dublin C.B.

The total numbers of deaths were expressed as rates using the population aged 55-64, as recorded in the 1986 Census of Population. Age-specific rates were estimated using both empirical Bayes and conventional maximum likelihood techniques. However, the differences between the two sets of estimates were found to be minimal, so the present paper reports only the findings based on the maximum likelihood estimates.

People in the 55-64 age cohort in 1990 were born between 1925 and 1935; those aged 55-64 in 1981 were born between 1916 and 1926. The date of birth of those dying between 1981 and 1990 therefore ranged from 1916 to 1935. Data on infant deaths (i.e. deaths under the age of 12 months) were extracted from the Reports for 1916-1935. There was a total of 87,368 infant deaths. The numbers of deaths in each area were aggregated and expressed as a rate using the aggregated number of live births over the same time period. As before, little difference was found between empirical Bayes and maximum likelihood estimates, so only the findings based on the maximum likelihood estimates are reported here.

The boundaries between Counties remained virtually unchanged from 1916 to 1990, but the number of County Boroughs in the study area increased from one in 1916, to four in 1923, to five in 1986. Also, the boundaries between some County Boroughs and the surrounding County areas were redefined (as, for example, in Dublin in 1930) to take account of urban expansion. Given that the mortality rates between the County Boroughs and the adjoining rural areas are often strikingly different, it was decided to retain the County-County Borough distinction, although to do this it was necessary to ignore the effects of minor boundary changes. The study is therefore based on 27 Counties and the four County Boroughs which have been in existence since 1923. Galway County and Galway County Borough are regarded for the purposes of this study as a single area (which, in fact, they were until 1986). The numbers of births and deaths in Cork, Limerick and Waterford County Boroughs before 1923 are not recorded, so the births and deaths in these cities for the period 1916-1922 are allocated between the County and County Borough areas in the same ratio as was recorded for the period 1923-1935. It is believed that the errors arising from this expediency are minimal.

Study design and limitations

The objectives of the present study are necessarily limited in scope. The study is intended as an exploratory investigation of whether the Irish data are broadly consistent with the perinatal hypothesis: it is not intended as

a rigorous test of detailed causal hypotheses. If adult heart disease is a function of conditions in early life or (as argued by Barker) foetal development, then one would expect to find a significant ecological correlation between adult heart disease and infant mortality in the same age cohort several decades previously. The presence of a significant correlation would not "prove" the perinatal hypothesis to be correct, but it could be regarded as providing supporting evidence. Conversely, the absence of a significant correlation would not necessarily prove the perinatal hypothesis is false, but it would point to "inconsistencies" which need to be explained if the perinatal hypothesis is not to be rejected.

Some of these inconsistencies may be generated by the methods used. There are a number of well-documented methodological problems associated with ecological correlations, such as the modifiable areal units problem (Openshaw, 1983) and the problem of ecological inference (Robinson, 1950). There are also a number of less-documented problems, such as "data closure" (Chayes, 1971) and "correlated components" (Pearson, 1897). None of these problems invalidate the use of ecological correlations, especially when used as an exploratory tool, but they must be taken into account when interpreting the results.

In this instance, we wish to make inferences about causal processes affecting individuals. In addition to the usual problems of making inferences about individuals from aggregate data, the fact that the two death rates necessarily refer to different individuals requires us to give some thought to how the death rates should be interpreted. The implicit assumption in many of the studies referred to above is that infant mortality may be regarded as a surrogate measure of living conditions (e.g. Forsdahl, 1977, 1978), although Buck and Simpson (1982) suggested that raised infant mortality may be an indicator of diarrhoea or enteritis. Infant mortality was initially regarded in the present study as an indicator of unspecified social conditions: however, this interpretation (as will be explained later) turned out to be more problematic than was originally envisaged.

Heart disease mortality should also be regarded as a surrogate measure: in this instance, as a surrogate for heart disease morbidity (which is what we would ideally like to explain). It is possible that heart disease survival rates may be higher in some areas, giving a misleading impression of relative heart disease morbidity. However, although this must be regarded as a possibility, the author is unaware of any evidence to suggest that Irish mortality rates do not provide a reasonable indicator of morbidity.

The adult and infant mortality rates should ideally refer to the same cohort. Everyone dying aged 55-64 between 1981 and 1990 would have been born between 1916 and 1935, but people born in some years will have had a greater "opportunity" of dying at the "right" age between

1981 and 1990 than those born in other years. For example, those born in 1916 would be the correct age for at least part of 1981, but would have been too old by 1982. Those born in 1926, in contrast, could have died at the right age in any year between 1981 and 1990. Given that the patterns of infant mortality remained relatively stable in the period from 1916 to 1935 (see below), this is not believed to be a major problem.

A more serious problem is that an unknown percentage of the people dying in each area would have been born in a different area. If the risk of heart disease is influenced by factors at the beginning of life (as hypothesized), then the adult mortality rates in some areas may be inflated by the in-migration of high-risk people or the out-migration of low-risk people, whereas the mortality rates in other areas will be deflated by flows in the opposite direction. The extent to which adult mortality rates are inflated or deflated will depend upon the extent of these flows. This issue will be addressed again in the final section.

Finally, as in all correlation studies, one must be alert to the possibility that the observed correlation between two variables could be influenced by a third, unidentified, variable. If this third variable is positively correlated with the two variables being observed, the net effect may be to induce a significant positive correlation between the observed variables even if they are causally unrelated. If the third variable is positively correlated with one of the observed variables but negatively correlated with the other, the net effect will be to deflate the observed correlation between the variables. The most likely situation, in the present context, is that the pattern of adult heart disease mortality could be influenced by lifestyle factors or conditions in adult life which have a similar spatial distribution to the social conditions which pertained in childhood. This would cause the observed ecological correlation between heart disease mortality and infant mortality several decades previously to be inflated. Although a far from perfect solution, this study attempts to control for social conditions in adult life using infant mortality in the 1980s as an indicator of unspecified living conditions, following Buck and Simpson (1982).

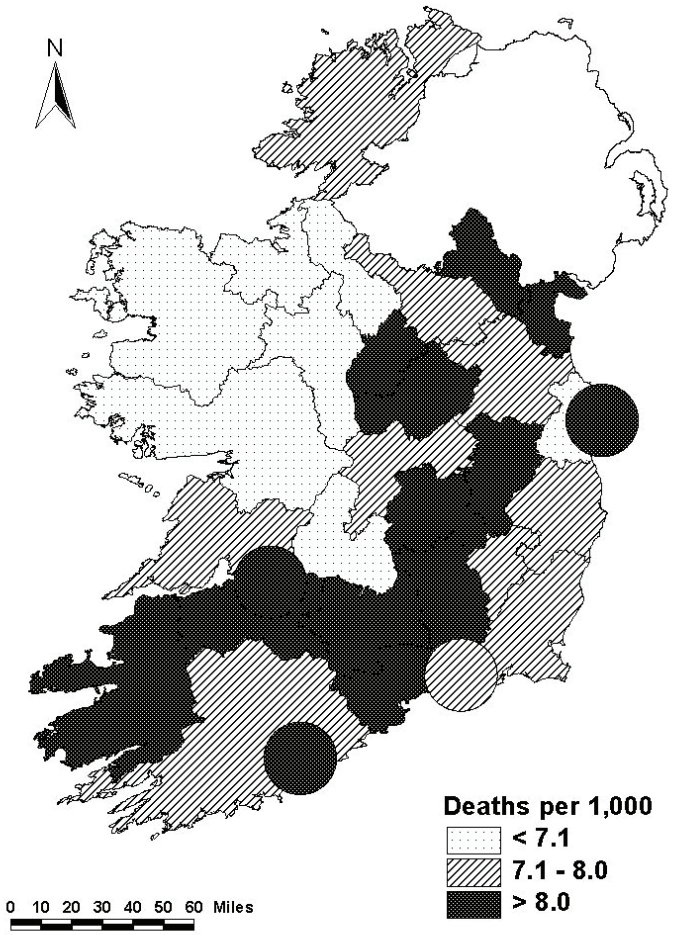
Empirical results

There were 10,596 male and 3,824 female deaths from Ischaemic and Other Forms of Heart Disease between the ages of 55 and 64 in the Republic of Ireland between 1981 and 1990, giving an estimated mean annual age specific death rate of 7.69 deaths per thousand for males and 2.65 deaths per thousand for females. The age-specific death rates per county ranged from a low of 6.27 per thousand to a high of 9.49 per thousand for males, and from a low of 1.98 per thousand to a high of 3.44 per thousand for females. There was a downward trend in deaths from heart disease during the study period: the national age-specific death rate for males fell from 7.98 in 1981 to 6.63 in 1990, whereas that for females fell from 2.90 in 1981 to 2.14 in 1990. (These rates were

calculated using population estimates for 1981 and 1990, based on information from the 1981 and 1991 censuses.)

The distribution of ischaemic heart disease mortality for males in the 1980s is shown in Fig. 2. There is a striking cluster of low mortality counties in the north-west of the country. The areas of highest mortality do not form any obvious pattern. Three of the four County Boroughs, represented by the circles, display above average death rates, but they are by no means the highest in the country.

Figure 2 Age-specific death rates from ischaemic heart disease for males, 1981-1990.

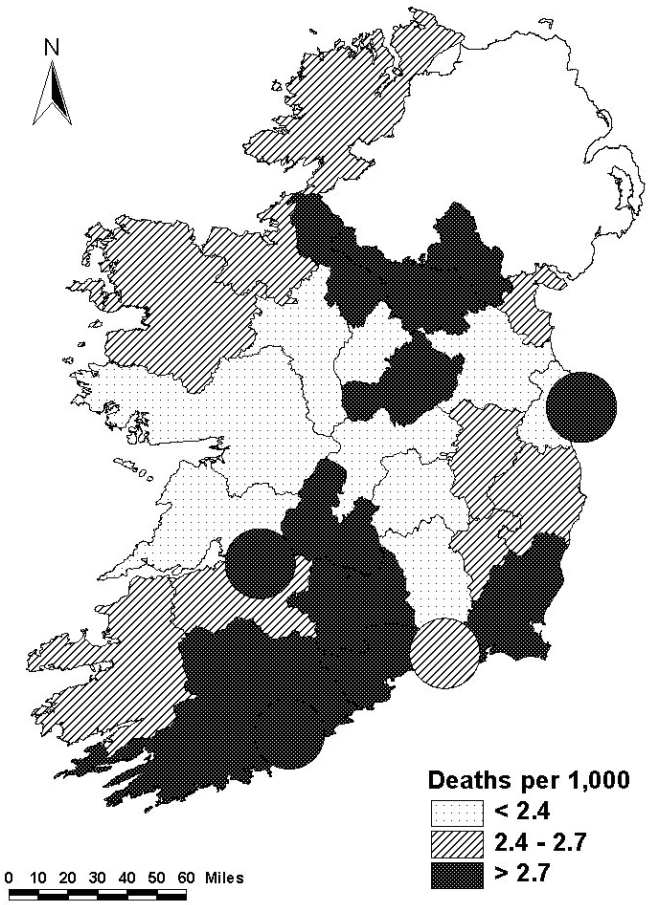


The distribution of ischaemic heart disease for females in the 1980s (Fig. 3) shows some similarities, to the extent that there is a cluster of low mortality counties in the west and clusters of high or moderately high mortality in the south and the north. However, the low mortality cluster for females is located further south and extends more into the midlands. Three of the four County Boroughs again have above-average rates of

mortality. The partial similarity between the two distributions is reflected by a positive, but non-significant, ecological correlation (r=0.25).

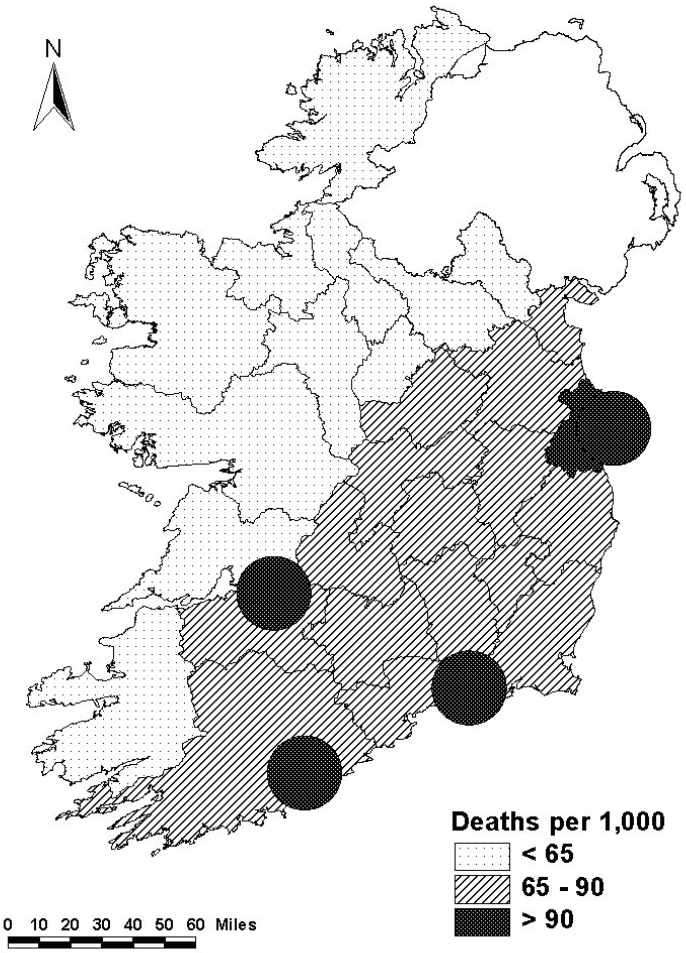
There was a total of 49,401 male and 37,967 female infant deaths between 1916 and 1935, giving mean annual infant mortality rates of 79.70 per thousand live births for males and 64.66 per thousand live births for females. Infant mortality rates fell slightly during the study period, from 86.8 per thousand in 1916 to 78.2 per thousand in 1935 for males and from 75.5 per thousand in 1916 to 58.2 per thousand in 1935 for females. However, the spatial distribution of infant mortality remained stable throughout the study period for both sexes (Table 1). It would therefore appear reasonable to regard rates based on all infant deaths between 1916 and 1935 as a reliable indicator of the spatial distribution of infant mortality at the time of birth for all those dying between 1981 and 1990.

Figure 3. Age-specific death rates from ischaemic heart disease for females, 1981-1990.



The infant mortality rates for males born between 1916 and 1935 display a very striking spatial distribution (Fig. 4). The distribution exhibits a high degree of spatial order, yet it is almost a mirror image of what one might have expected from a knowledge of the literature on social inequalities in Ireland. Conventional wisdom is that living conditions in Ireland have always been poorer in rural areas; and also, within rural areas, they have always been much worse in the north and west of the country than in the south and east. One would therefore expect infant mortality to have been highest in the north-west of the country and lowest in the urban areas, but the map for male infant mortality between 1916 and 1935 indicates that the opposite was actually the case. Further, the distribution exhibits a very strong positive skew, in which the major urban areas record rates approximately twice as high as those prevailing throughout most of the north and west.

Figure 4. Infant mortality rates for males, 1916-1935.



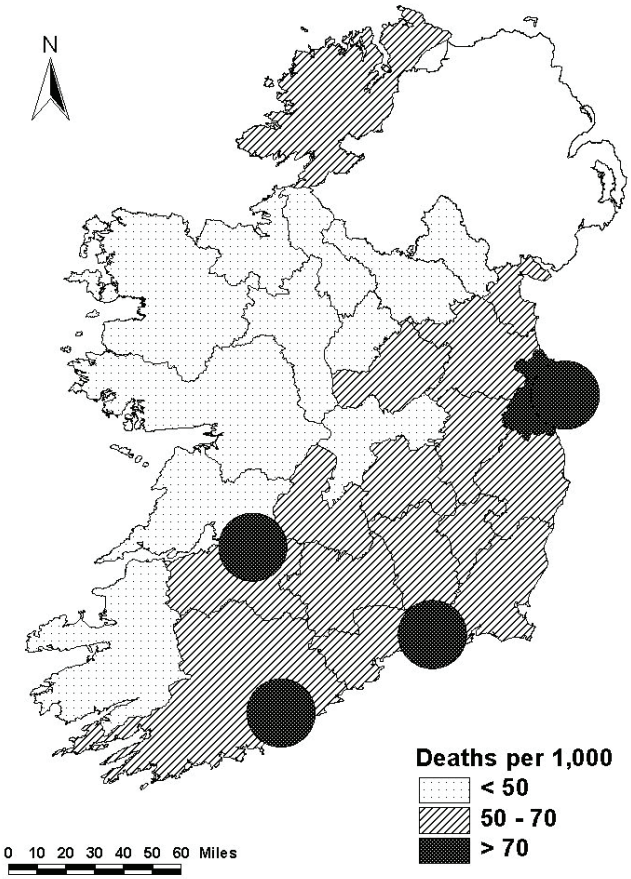
The pattern of infant mortality for females is, as one might expect, very similar (Fig. 5). The ecological correlation between male and female infant mortality between 1916 and 1935 is positive and highly significant (r=0.98).

If the perinatal hypothesis is correct, one would expect a significant positive ecological correlation between the heart disease rates and infant mortality, as reported in the UK, US and Norwegian studies.

Table 1. Ecological correlations between infant mortality rates for different time periods (males top right, females bottom left)

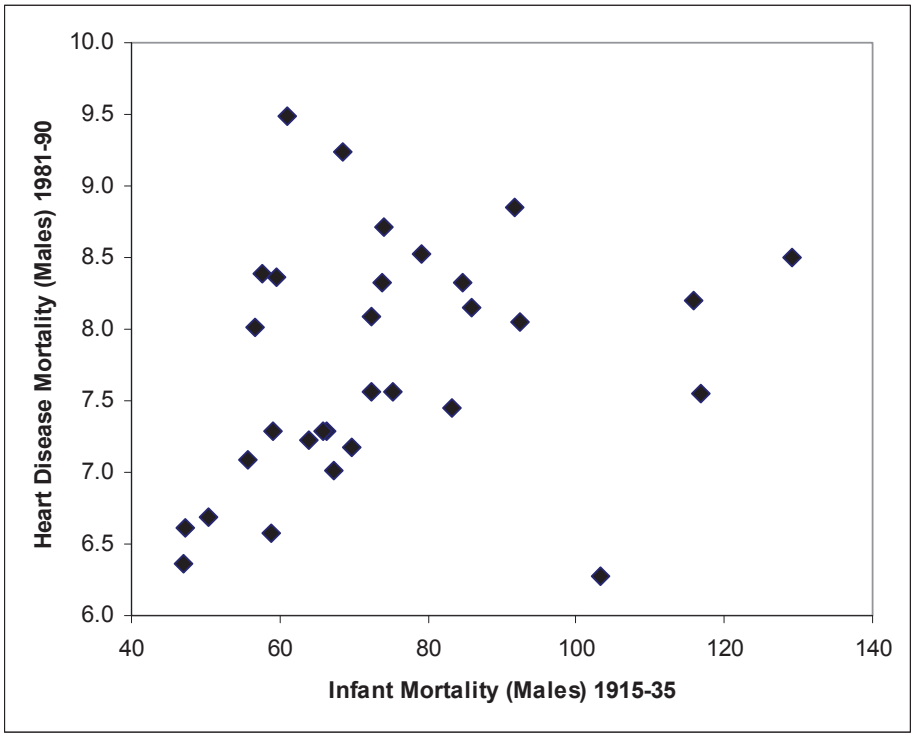
	1916-1920	*1921-1925*	*1926-1930*	*1931-1935*
1916-1920		0.9453	0.9072	0.8272
1921-1925	0.9361		0.9213	0.8533
1926-1930	0.9299	0.9216		0.8992
1931-1935	0.8799	0.8689	0.9447	

Figure 5. Infant mortality rates for females, 1916-1935.



The Pearson product moment correlations between ischaemic heart disease and infant mortality are found to be 0.26 and 0.29 for males and females respectively. These correlations are positive and sufficiently large to suggest that there may be a relationship of some sort, but they are not sufficiently large to be regarded as statistically significant at the 0.05 significance level. (Correlations were also calculated after excluding Dublin C.B. and Dublin County, which have much larger populations than the other areas. The correlation coefficients were larger, but still remained non-significant.) The scattergrams reveal a wide scatter of points, although there are some indications of a weak linear trend (Figs 6 and 7).

Figure 6. Scattergram of ischaemic heart disease rates 1981-1990 against infant mortality 1916-1935 for males.

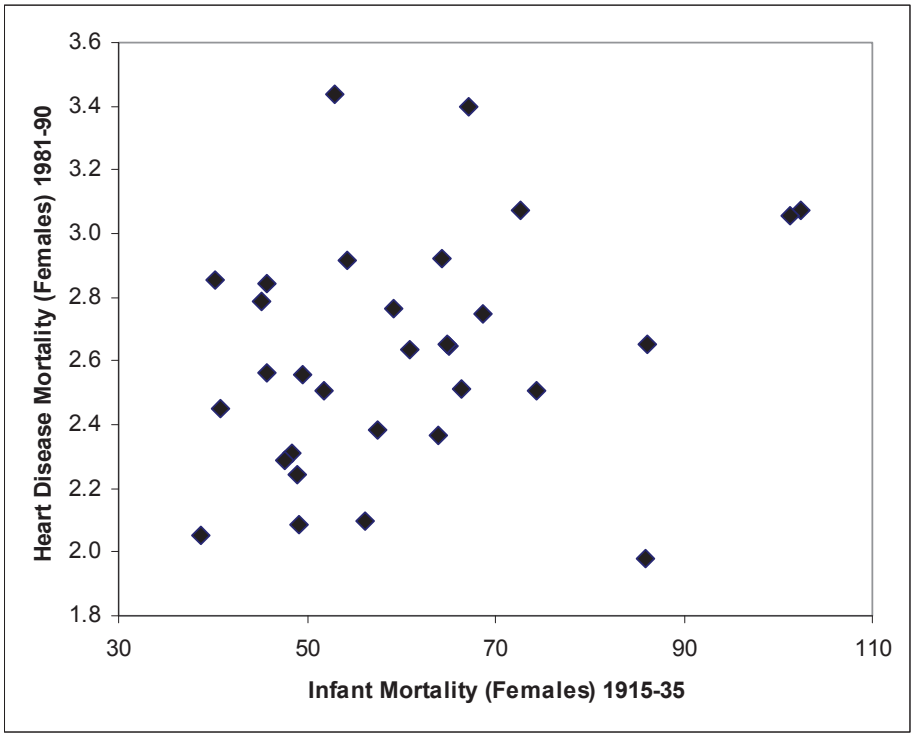


Both scattergrams also indicate a strong positive skew in the infant mortality rates. Normalizing both variables using logarithmic transformations made little difference to the Pearson product moment coefficients. However, Spearman and Kendall rank order correlations were found to be significant at the 0.05 significance level for males (r_s=0.39, tau=0.30), although not for females (r_s=0.30, tau=0.21).

The effects of possible confounding variables were tested using infant mortality rates for the 1980s as an indicator of modern living conditions. The partial correlations between the heart disease rates and infant mortality, controlling for infant mortality in the 1980s, were virtually

identical to the zero-order correlations for both males (r=0.26) and females (r=0.31), suggesting that the observed relationships, although weak, are not spurious.

Fig. 7. Scattergram of ischaemic heart disease rates 19811990 against infant mortality 1916-1935 for females.



Discussion

Three aspects of the empirical findings require further comment: (1) the striking differences in heart disease mortality between males and females; (2) the apparent anomalies in the pattern of infant mortality in Ireland between 1916 and 1935; (3) the weak ecological correlations between infant mortality 1916-1935 and adult heart disease in the 1980s.

Mortality rates from Ischaemic and Other Forms of Heart Disease are almost three times higher amongst males aged 55-64 than amongst females of the same age. This might appear to cast some doubts upon the perinatal hypothesis: it is easy to explain how such disparities might be generated by differences in adult lifestyles (e.g. smoking, alcohol consumption, occupation), but it is less obvious how they could be generated by factors before or soon after birth. However, the observed disparities are not as damaging to the perinatal hypothesis as they might first appear. Males and females are genetically different. There is evidence to suggest, for example, that females are "genetically stronger": male infant mortality rates are noticeably higher than female infant mortality rates, yet the "lifestyles" of male and female infants are unlikely to be

dissimilar. Males and females also develop in different ways. Boys are more likely to be born "short", because they are more vulnerable to undernutrition in late gestation because of their more rapid "growth trajectory", whereas girls are more likely to be born "thin". Barker (1994a) suggests that "thin" babies were undernourished in mid-gestation, and are subsequently likely to suffer elevated blood pressure and a disturbed glucose-insulin metabolism, whereas "short" babies were undernourished in late gestation, and are subsequently likely to suffer from raised blood pressure, and disturbed cholesterol metabolism and blood clotting. Both groups are vulnerable to coronary heart disease in later life, but for different reasons. Barker suggests that this "provides a framework within which the lower rates of cardiovascular disease in women than in men can be explored" (Barker, 1994a,bp. 49).

The second striking finding of this study is the spatial distribution of infant mortality in Ireland between 1916 and 1935 contradicts all the traditional assumptions about the geography of social disadvantage in Ireland. There are only three possible explanations for this apparent anomaly: (1) the true pattern of social deprivation in Ireland may be different from that traditionally believed; (2) the infant mortality rates for the period 1916-1935 are in some way spurious; or (3) infant mortality rates are not in fact related to social conditions, as generally believed; or that the relationship, for some unknown reason, is different in Ireland.

The first possibility is that, contrary to popular belief, social conditions may have been much worse in the urban areas than in rural areas. There is little doubt that the living conditions of the Dublin working classes in the early decades of the twentieth century were extremely poor (Daly, 1984). Indeed, Aalen (1992) claimed that housing conditions in Dublin in the period under review were possibly the worst in Europe. The finding that infant mortality rates were high in Dublin and the other major cities (which experienced similar conditions) is therefore not in itself a major source of surprise. However, there is strong documentary evidence to suggest that living conditions were equally poor, if not worse, in the rural west and north-west of the country, as reflected by very high rates of poverty driven out-migration dating back to the middle parts of the nineteenth century. Although it is possible that the extent of rural poverty may have been overstated by contemporary observers, and the extent of urban poverty correspondingly understated, it is difficult to believe that so many government reports and contemporary social observers could have misinterpreted the situation to the extent that would be necessary to account for infant mortality rates which in the study period were twice as high in urban areas as in the most deprived rural areas.

Further, whatever doubts may or may not surround the extent of relative deprivation between urban and rural areas, no-one would seriously argue that the counties in the south and east of the country were more deprived

than those in the west and north-west. Counties in the south and east persistently score higher on a broad spectrum of social indicators (e.g. land quality, farm size), yet they recorded higher infant mortality rates than those in the north and west. It is possible that there may have been a hidden underclass of farm labourers working on the large prosperous farms in the south and east, in contrast to the more self-reliant cottiers who struggled to eke out a living in the west and north-west, but it is again difficult to believe that contemporary social observers could have misjudged the situation to the extent that would be required to explain the spatial distribution of infant mortality rates.

The second possibility is that the observed infant mortality rates are not a true indicator of the infant mortality. For example, some infant deaths may have been incorrectly attributed to the urban areas in which most of the hospitals are located, rather than to the area in which the mother was normally resident. This would tend to artificially inflate the observed mortality rates in the urban areas. However, if this was the case, one would also expect the number of live births (which serves as the denominator when calculating the infant mortality rates) to be distorted to a similar degree; i.e. the two distortions should therefore, to a large extent, cancel one another out. Another possibility is that the number of deaths in rural areas may have been under-reported because of non-registration or non-certification. There is evidence to suggest that problems of this type were significant, and more common in the west and north-west, even in quite recent times (e.g. Dean, 1969; Dean and McLoughlin, 1980; Dean and Mulvihill, 1972), although probably not to the extent that would be required to explain the observed differences in infant mortality rates. Besides, one would again expect any undercounting of the number of deaths to be more or less counterbalanced by a corresponding under-reporting in the number of births.

If one accepts that the observed infant mortality rates provide a reasonable indication of the spatial variations in the actual incidence of infant deaths, and if one also accepts that the widely held perceptions about the geography of social disadvantage in Ireland are not totally unfounded, then one is left only with the third possibility, namely that the variations in infant mortality rates in Ireland between 1916 and 1935 did not reflect spatial variations in living conditions.

This interpretation, if generalizable to other contexts, raises questions about the interpretation that should be placed on studies using infant mortality as an indicator of non-specific living conditions, including Forsdahl's seminal studies in Norway. Forsdahl argued that the rates of adult heart disease in Norway were highest in the areas that had experienced the fastest rates of economic growth, but he did not directly measure living conditions; rather, he assumed an equalization in living conditions based upon an observed equalization in infant mortality rates. However, the apparent lack of an association between infant mortality

and living conditions in Ireland suggests that infant mortality need not necessarily be a reliable indicator of living conditions.

This study also points to a second set of reasons for questioning Forsdahl's interpretation. Forsdahl reported much lower ecological correlations in Norway between arteriosclerotic heart disease and contemporary infant mortality rates than between heart disease and infant mortality rates several decades earlier. Similar results were found in Ireland: the correlations between ischaemic heart disease and infant mortality in Ireland between 1981 and 1990 are considerably lower than those with infant mortality between 1916 and 1935. Forsdahl inferred that the weaker association between heart disease and contemporary infant mortality indicated that we should look towards living conditions in early life, rather than at present, for an explanation of the causes of heart disease. However, closer examination of the Irish data suggests that the reduced ecological correlations may be a statistical artefact rather than necessarily reflecting changes in living conditions. The number of infant deaths in Ireland is now less than 10% of what it was in the earlier part of the century; consequently, estimates of infant mortality rates are now much more susceptible to stochastic variations because of the smaller absolute numbers of deaths; i.e. it is now more difficult to isolate the "signal" indicating variations in the underlying risk of infant mortality from the stochastic noise. Correlations based on these "noisy" estimates of infant mortality will inevitably produce smaller coefficients, irrespective of whether or not there has been change in the pattern of underlying risk.

Norwegian counties, in terms of mean population, are only slightly larger than Irish counties: they would therefore be expected to be subject to similar stochastic effects; in which case the smaller ecological correlation coefficients reported by Forsdahl would not necessarily indicate an equalization in infant mortality or (by inference) living standards. In contrast, UK counties, and more especially English counties, have a much larger mean population; consequently, UK infant mortality rates would provide more reliable estimates of the underlying risk. This may partly explain why the observed patterns of infant mortality in England and Wales have tended to be more stable over time than those in either Norway or Ireland.

The third aspect of the present study requiring further comment is the weak ecological correlations found between heart disease mortality and. infant mortality. The correlations are positive and sufficiently large to suggest that there may be a relationship; but they are not large enough (with the exception of the non-parametric correlations for males) to be regarded as statistically significant. It might be argued that the areas used in this study form a statistical population (i.e. a complete set of areas) rather than a sample, and that the concept of "statistical significance" is not really applicable, in which case there is nothing special about the

value which must be obtained for a correlation to be regarded as "significant". However, irrespective of whether one accepts this argument or not, the fact remains that the correlations are too small to provide convincing evidence in support of the perinatal hypothesis.

This does not necessarily mean we need to reject the perinatal hypothesis. There are several reasons why the correlations could be low, even if the perinatal hypothesis is correct. For example, many people no longer live in the county of their birth; consequently, the prevalence of heart disease amongst the current inhabitants of a given county may provide only an approximate guide to the prevalence of heart disease amongst the people who were born and raised in that county. The 1991 Census reported that 20.4% of those enumerated did not normally reside in the county in which they were born (Central Statistics Office, 1996). The percentage is slightly higher amongst those aged 55-64, but more than three-quarters of those who died between 1981 and 1990 probably lived in the county of their birth. This is a much larger percentage than reported by Osmond *et al.* (1990) for England and Wales, but it must be remembered that Ireland has traditionally been characterized by much higher levels of outmigration.

Net migration flows within the Republic are generally from rural areas, especially those in the north and west, towards Dublin and adjoining counties (Walsh, 1991). Dublin would be expected, on the basis of its past infant mortality rates, to have very high rates for heart disease. However, many of Dublin's poorest (who might be assumed under the perinatal hypothesis to have a higher risk) have been obliged to emigrate, whereas those who have remained have been supplemented by generally well-educated (and presumably low-risk) immigrants from other parts of the country. Both movements would have the effect of lowering the heart disease mortality rates relative to what would be expected under the perinatal hypothesis. Conversely, heart disease rates in low infant mortality counties in the north and west may have been inflated by the loss of some of their better educated (and presumably low-risk) inhabitants to Dublin. The net effect of these movements is that the ecological correlations between heart disease and past infant mortality probably understate the strength of the relationships between infant mortality rates by county and subsequent heart disease rates amongst the males and females actually born in those counties, including those who subsequently migrated to other counties.

On the other hand, it must also be accepted that the observed ecological correlations could have been inflated by the effects of confounding variables. Attempts to control for possible confounding factors using contemporary infant mortality as an indicator of unspecified living conditions made little difference to the observed correlations, but (as noted above) it is questionable whether contemporary infant mortality rates can actually be regarded as a reliable indicator of living conditions

(let alone other factors believed to be related to living conditions). However, given that neither adult heart disease mortality rates for the period 1981-1990 nor infant mortality rates for the period 1916-1935 appear to be positively correlated with living conditions (as generally perceived), either past or present, there is little reason to believe that the observed ecological correlations are in fact inflated.

Summary

The evidence provided in support of hypothesized foetal or early life influences on adult heart disease by the ecological correlations between heart disease mortality 1981-1990 and infant mortality 1916-1935 in Ireland is ambiguous. The ecological correlations suggest that there may be an association, but they are not sufficiently strong to be regarded as statistically significant. Conversely, given the likely effects of migration, they are not sufficiently weak to suggest the hypotheses should be rejected, especially given the very convincing evidence accumulated by Barker and his associates from longitudinal studies of individuals (e.g. Barker, 1992, 1994a).

The ambiguous nature of the Irish results contrasts with the strong ecological correlations reported elsewhere, especially in England and Wales. One possible explanation for these differences is that heart disease may be a function of both perinatal factors and present-day adult lifestyle factors. In the UK, the geographies of these two sets of factors are similar and therefore their effects are mutually reinforcing, resulting in strong ecological correlations between heart disease and both past infant mortality and present-day living conditions. In Ireland, these two sets of factors would appear to have different geographies, therefore their effects are contradictory, resulting in much weaker ecological correlations between heart disease and either past infant mortality or present-day living conditions.

The totally unexpected pattern of infant mortality identified in this study for the period 1916-1935 requires further investigation. If, as suggested above, infant mortality in Ireland was not associated with adverse living conditions, then it would be useful to establish why the spatial disparities reported above were so pronounced. This in turn might provide further insights into whether heart disease in adult life is associated with specific factors linked with infant mortality or to other more general social conditions which affect people around the time of birth.

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