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AREA DIFFERENCES IN PREVALENCE OF NEURAL TUBE MALFORMATIONS IN SOUTH WALES

A STUDY OF POSSIBLE DEMOGRAPHIC DETERMINANTS

I. D. G. RICHARDS,* C. J. ROBERTS, AND S. LLOYD

In England and Wales as a whole the frequency of neural tube malformations is highest in the north and north-west, and lowest in the east, south-east, and south (Rogers, 1969). Differences have also been reported in the regional frequency of anencephalus, spina bifida, and hydrocephalus in Scotland (Edwards, 1958), and Hewitt (1963) found that the mortality attributed to spina bifida was two to three times greater on the Atlantic than on the Pacific coasts in both Canada and the U.S.A. (in the latter among the white population only).

While the significance of differences from country to country may be difficult to interpret, the presence of regional differences within a country and, more particularly, area differences within a region are strong indicators of environmental influence. Marked local variation in the prevalence of neural tube malformations in South Wales was first reported by Laurence, Carter, and David (1968) in a study (covering a six-year period 1956–62) confined to the agricultural Vale of Glamorgan and the mining valleys of Glamorgan and Monmouthshire, an area with a total population of approximately 850,000 and a birth population during the survey period of 102,786. Laurence *et al.* (1968) examined possible geographical and climatic factors but none was thought to be related to the local variation in malformation prevalence.

More recently, Lowe, Roberts, and Lloyd (1971) and Richards (1971) confirmed the presence of significant area differences in a large study covering the whole of South Wales. Lowe *et al.* found that the mean annual prevalence of these defects in 48 local authority areas was negatively correlated with estimates of the mean total hardness of the related water supplies but concluded that this relationship may well be secondary. In the present paper, we examine other possible determinants of the striking area differences in malformation rates within South Wales.

*Present address : Social Paediatric and Obstetric Research Unit, 23 Montrose Street, Glasgow G1 1RN

METHODS

For births in the three years 1964–66, we have collected information about all infants born to women resident in South Wales and about all the congenital defects identified in that birth population. Data on the congenital defects were derived from four sources—birth notifications, malformation notification forms, hospital diagnostic indices, and stillbirth and infant death registrations (Richards and Lowe, 1971).

The survey area was composed of two counties, Glamorgan and Monmouthshire, and the four county boroughs within their boundaries, Cardiff, Swansea, Merthyr, and Newport, and comprised a total of 48 local authority areas. However, since the numbers of births in some local authority areas were too small to permit valid comparisons of area incidence these areas were combined into eight grouped areas (Figure), viz., (1) the Eastern Valleys region of Glamorgan comprising largely coal mining areas; (2) the Western Valleys region of Glamorgan, also largely comprising coal mining areas, but including Port Talbot with its large steel-making plant; (3) the 'Rest of Glamorgan', which includes urban areas (Barry, Penarth, Bridgend, and Porthcawl) and large rural areas (Vale of Glamorgan and the Gower Peninsula); (4) the Monmouthshire Valley region (largely urban with coal mining, steel-making, and light industry); (5) the 'Rest of Monmouthshire' comprising small urban areas (Monmouth, Usk, Abergavenny, and St. Mellons) and large rural areas; (6) Cardiff; (7) Swansea, and (8) Newport.

RESULTS

In the three years of the investigation 92,980 infants (live and stillbirths) were born to women resident in these areas; 90,921 infants were the outcome of singleton pregnancies, of whom 743 were ascertained as having neural tube defects.

The prevalence of malformations by individual local authority areas varied by a factor of five (Lowe *et al.*, 1971), but the interpretation of this observation is difficult. Because the birth populations at the two ends of the range were small (i.e. less than one thousand births for the three years of the study), the differences recorded could be due to a small-number effect. Furthermore, the number of malformed births within many local authority areas was often so small that the year-to-year consistency of rates within any one area could not be examined.

TABLE I

NEURAL TUBE MALFORMATION RATES IN SOUTH WALES (1964–66) BY YEAR AND REGION OF BIRTH

Region	No. of Singleton Births	Rates per 1,000 Births			Mean Rate 1964–66
		1964	1965	1966	
Glamorgan E. Valleys	17,738	7·96	10·96	11.25	10·03
Glamorgan W. Valleys	11,278	8·95	8·65	10·69	9·40
Monmouthshire Valleys	13,309	7·92	9·11	9·60	8·87
Swansea	8,419	8·04	6·65	9·62	8·08
Cardiff	14,451	6·93	8·55	7·16	7·54
Rest Glamorgan	13,823	6·21	6·76	7·67	6·87
Rest Monmouthshire	5,361	6·25	4·18	9·47	6·53
Newport	6,540	5·65	6·64	3·25	5·20

Rank correlation coefficients:
1964–65 r = 0·55
1965–66 r = 0·60
1964–66 r = 0·86

The Figure and Table I show that the grouped area prevalence of total neural tube malformations varied by a factor of two, being highest in the East and West Valleys of Glamorgan and the Monmouthshire Valleys; and lowest in Newport and the Rest of Monmouthshire. The rank order of grouped area prevalence is similar for each year of the study and an estimate of the year-to-year consistency of trend can be obtained from the rank correlation coefficients at the foot of Table I.

TABLE II

MAJOR CATEGORIES OF NEURAL TUBE MALFORMATION (RATES PER 1,000 BIRTHS) BY REGION OF BIRTH

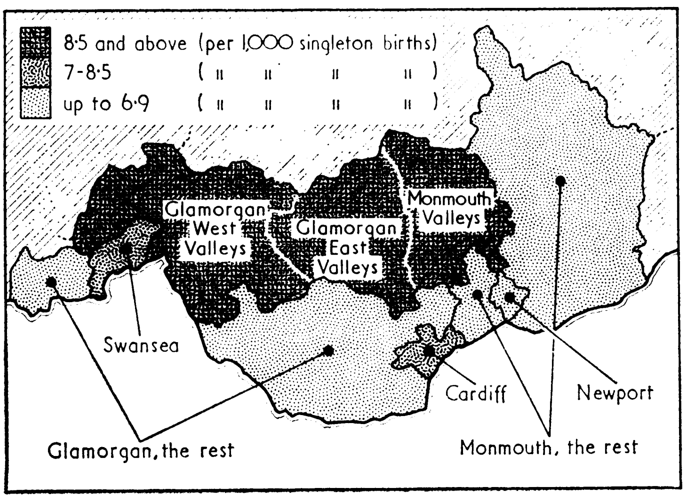
Region of Birth	Anencephalus	Spina Bifida (without Anencephalus)	Hydrocephalus (without Spina Bifida)
Glamorgan E. Valleys	3·72	4·96	1·13
Glamorgan W. Valleys	3·28	5·05	0·71
Monmouthshire Valleys	3·83	3·61	1·35
Swansea	3·33	4·16	0·36
Cardiff	2·91	3·18	1·11
Rest Glamorgan	2·82	2·97	0·72
Rest Monmouthshire	2·42	3·54	0·37
Newport	0·76	3·36	0·76

Table II shows grouped area prevalence by the three major categories of neural tube malformation. Anencephalus had the highest prevalence in the Monmouthshire Valleys, Glamorgan East Valleys, and Glamorgan West Valleys; and the lowest prevalence in Newport. Spina bifida was highest in Glamorgan West and East Valleys and Swansea. The recorded prevalence of hydrocephalus was highest in the Monmouthshire Valleys, Glamorgan East Valleys, and Cardiff.

The observation that the highest rates for all categories were in the mining valleys supports the earlier findings of Laurence *et al.* (1968) but, in our data, we found no evidence of a west/east gradient of rising prevalence for any category of neural tube malformation.

DISCUSSION

Before formulating aetiological hypotheses to explain the association between area of birth and the prevalence of neural tube malformations, it is necessary to examine the possible influence of certain demographic factors.



FIGURE—Sketch map of regional subdivisions of study area. Shading indicates prevalence of total neural tube malformations.

By the end of the last century South Wales was heavily industrialized; the valleys in particular became completely built up and densely populated. However, the industrial depression which began after the first world war, together with the collapse of the coal trade and other heavy industries in the late 1920s and early 1930s, led to mass unemployment which was followed by both rural depopulation and migration away from the urban centres of Glamorgan and Monmouthshire. In spite of some revival of heavy industry and coal mining since the second world war, the past decade has seen the closure of yet more pits in South Wales, and the population drift from the coalfields has continued unabated. Since the nineteenth century Cardiff has grown from a small market town to a large city with its own range of industries, and this has been accompanied by the rapid expansion of the other South Wales seaports—Newport, Penarth, Barry, and Swansea. Population movements such as these are bound to have influenced the demography of the study area.

The distribution of certain demographic features within the sample is shown in Table III. While there was little difference observed in the distribution of parities and maternal ages, there were marked differences in social class composition, in the proportion of births of 'both Welsh' parentage (explained below), and in the estimates of population loss between 1931 and 1961 by migration. The associations between these demographic characteristics and grouped area prevalence of neural tube malformation will now be examined.

TABLE III

PERCENTAGE OF CERTAIN DEMOGRAPHIC FEATURES BY REGION

Region	Parity 0	Maternal Age under 20 Years	Social Classes I & II	Both Parents Welsh	Population Loss (1931-61) as % of 1931 Population
Glamorgan E. Valleys	34·2	13·6	8·4	19·9	26·4
Glamorgan W. Valleys	32·6	11·8	8·8	22·6	28·9
Monmouthshire Valleys	33·5	12·8	8·4	11·7	5·6
Swansea	33·3	10·4	13·8	15·3	8·7
Cardiff	29·9	12·2	13·0	4·9	3·5
Rest Glamorgan	33·8	10·1	20·8	11·4	*10·6
Rest Monmouthshire	30·0	10·9	19·6	9·2	37·4
Newport	33·1	12·9	11·1	4·7	*1·4

*Indicates a gain in population

PARITY, MATERNAL AGE, AND SOCIAL CLASS

The analyses presented in Tables I and II are insufficient to allow an examination of the specific effects of area of birth on neural tube malformation, since the grouped area prevalence rates can be expected to reflect not only the effects of place of birth but also the proportion of women having their first child, and their distribution by social class and maternal age. The existence of more than one factor influencing neural tube malformation prevalence does not in itself create a problem; the difficulty arises because these factors do not occur independently of one another. Age and parity are highly correlated; older mothers are generally of higher parity than younger ones, and the age groups and parities differ in social class composition. In order to adjust for the interdependences of area of birth, parity, social class, and maternal age we have used a multivariate statistical method described by Feldstein (1966) in his study of factors affecting perinatal mortality. The crude values for grouped area prevalence in Table I have been replaced in Table IV by rates adjusted for the effects of the other factors. The adjusted values are estimates of the grouped area prevalence rates that would have been expected if the factors that have been adjusted for had no effect. Table IV presents the percentage deviation in prevalence by group area adjusted for parity, social class, and maternal age. Column (iii) shows the unadjusted crude deviations, and columns (iv), (v), and (vi) show the effect of adjustments for age, parity, and

TABLE IV

NEURAL TUBE MALFORMATION RATES BY REGION OF BIRTH ADJUSTED FOR MATERNAL AGE, BIOLOGICAL PARITY, AND SOCIAL CLASS AND EXPRESSED AS DEVIATIONS FROM MEAN RATES

Region	No. of Singleton Births	Adjustment for				
		None	Maternal Age	Biological Parity	Social Class	All 3 factors
(i)	(ii)	(iii)	(iv)	(v)	(vi)	(vii)
Glamorgan E. Valleys	17,738	1·86 (0·66)	1·79 (0·61)	1·86 (0·61)	1·72 (0·61)	1·64 (0·61)
Glamorgan W. Valleys	11,278	1·23 (0·84)	1·38 (0·80)	1·46 (0·80)	1·10 (0·80)	1·25 (0·80)
Monmouthshire Valleys	13,309	0·70 (0·75)	0·62 (0·72)	0·72 (0·72)	0·55 (0·72)	0·49 (0·72)
Swansea	8,419	−0·09 (0·93)	−0·10 (0·94)	−0·07 (0·93)	−0·03 (0·94)	−0·07 (0·94)
Cardiff	14,451	−0·63 (0·66)	−0·68 (0·70)	−1·13 (0·69)	−0·58 (0·70)	−0·66 (0·70)
Rest Glamorgan	13,823	−1·30 (0·66)	−1·29 (0·71)	−1·23 (0·71)	−1·02 (0·71)	−1·03 (0·71)
Rest Monmouthshire	5,361	−1·64 (1·08)	−1·37 (1·18)	−1·15 (1·20)	−1·44 (1·18)	−1·04 (1·19)
Newport	6,540	−2·97 (0·88)	−3·01 (1·07)	−2·91 (1·07)	−3·04 (1·07)	−3·03 (1·07)

social class respectively. Simultaneous adjustment for age, parity, and social class in column (vii) reveals the specific grouped area effect. Estimated standard errors appear in parentheses. The adjustments described are found to make no serious difference to the magnitude, order, or range of grouped area prevalence, and these findings suggest than an area effect, independent of age, parity, and social class, does exist.

Ethnic Origin

The population of South Wales is heterogeneous, comprising the Welsh and immigrants who have arrived mostly within the past hundred years. The two populations live in the same physical environment and a good deal of intermarriage has occurred. Ashley and Davies (1966) felt that if these two populations could be identified by some easy marker the relative proportions of Welsh and non-Welsh could be determined and assessed in relation to their illnesses and genetically determined traits. They reported a strong association between Welsh surnames and the possession of a Welsh cultural heritage; those with Welsh names also had a higher frequency of the blood group B, a lower proportion of Rhesus negative antigen, and a lower proportion with light-coloured hair. No differences were noted in height, weight, eye colour, secretor status, and the ability to taste phenylthiocarbamide. Analyses of social class structure, income, and smoking habits showed no significant difference between those with Welsh and non-Welsh surnames. We therefore decided to adopt the suggestion of Ashley and Davies to use surnames as genetic markers for our study participants.

Welsh surnames are characteristically derived from Christian names, either by the simple use of the genitive case, e.g., Davies, Evans, Phillips, Roberts, Thomas, Williams, or by elision of the prefix Ap or Ab ('the son of'), e.g., Pritchard, Pugh, Bevan and Bowen. For our own survey a list of 59 names was compiled (Richards, 1971) based on that of Ashley and Davies; the mother's current surname and her maiden surname were classified as 'Welsh' or 'not Welsh' and analyses were made of malformation incidence according to whether Welsh surnames were possessed by one or neither parent or by both parents.

The Welshness of the parental surnames was recorded for 88,818 singleton births (97·7%). Of these, 3,395 were illegitimate and had only one surname coded. Of the 85,423 legitimate births, both parents had Welsh surnames in 12,022 instances, one parent in 35,087, and neither parent in 38,334.

Striking area differences in the frequency of Welshness in surnames were noted (Table III); the proportion of births to parents, both of whom were Welsh, ranged from 4·2% in Newport to 22·6% in Glamorgan West Valleys. Table V shows the incidence of each malformation category by Welshness of parental surnames. For anencephalus, the incidence in 'both Welsh' births was higher than in 'one Welsh' or 'neither Welsh'. A less clear trend was seen in spina bifida, although 'both Welsh' parents had the highest rate. There was no consistent trend in hydrocephalus. For all major central nervous system malformations combined there was a decreasing trend from 'both Welsh' to 'neither Welsh'. In none of the defects individually, nor in all combined, was the prevalence in the 'both Welsh' group significantly different from the 'neither Welsh' group, and it may be concluded that geographical variations in prevalence are unlikely to be influenced appreciably by ethnic group differences in so far as these are related to the Welshness of surnames.

Migration

One important feature of the South Wales population is that a large amount of migration, both into and out of the area, has taken place over at least two centuries. While large-scale migration from an area is often associated with poor socio-economic condi-

TABLE V

PREVALENCE OF NEURAL TUBE MALFORMATIONS ACCORDING TO ETHNIC GROUP OF PARENTS

Major Categories of Neural Tube Malformation	Prevalence per 1,000 Singleton Births according to Parental Surnames					Statistical Significance of Difference between (ii) and (iv)
	Both Welsh	One Welsh	Neither Welsh	Not known or Illegitimate	Total	
(i)	(ii)	(iii)	(iv)	(v)	(vi)	χ^2 P(df=1)
Anencephalus	3·42 (41)*	3·14 (110)	2·63 (100)	(30)	3·10 (281)	1·715 ns
Spina bifida (without anencephalus)	4·83 (57)	3·76 (132)	3·94 (151)	(16)	3·93 (356)	1·555 ns
Hydrocephalus (alone)	0·83 (10)	0·68 (25)	0·94 (36)	(11)	0·90 (82)	0·026 ns
Total	9·08 (108)	7·58 (267)	7·51 (287)	(57)	7·93 (719)	2·678 ns

*Actual numbers in parentheses

tions and industrial depression, there is some evidence to suggest that migration is selective, e.g., it tends to involve those of greater than average physique. Cochrane and Higgins (1961), in a study on pulmonary ventilatory function of coal miners, quote evidence to suggest that emigrants from the Rhondda valleys (since 1920) were taller and heavier than those who remained behind. Macdonald (1963) has suggested that selective migration may have an adverse effect on stillbirth and neonatal rates, presumably by dilution of the quality of the residual genetic pool.

The population changes in the study area for the years 1931 to 1961 were calculated using census data and the Annual Reports of the Registrar General. The effects of migration were greatest in the 'Rest of Monmouthshire' and in the east and west mining valleys of Glamorgan (Table III). The rank order correlation coefficient between area malformation prevalence and population loss from migration was not statistically significant. Although it is reasonable to assume that migration of the magnitude experienced by the Valleys of Glamorgan and the 'Rest of Monmouthshire' had an effect on the genetic composition of those areas, these results do not support the hypothesis that high malformation prevalence in the grouped areas derives from a dilution of the quality of the genetic pool due to migration.

These findings, considered alongside the absence of an association between grouped area prevalence and ethnic origin, social class, parity, or maternal age, suggests that the factors principally responsible for the area differences in neural tube malformation prevalence in South Wales, though still unknown, may well be external environmental characteristics associated with the nature of the area itself, such as the softness of local water supplies (Lowe *et al.*, 1971), rather than personal environmental factors associated with the population of that area, such as diet, occupation, recreational activities, and religion.

Summary

Marked area differences were found in the prevalence of neural tube defects among 90,921 singleton births in South Wales between 1964 and 1966. These areas differ in their social class, parity, maternal age, and ethnic composition. Also a large amount of migration both into and out of the region has taken place over the last two centuries. We could find no evidence that any of these demographic features were associated with differences in area prevalence.

It is suggested that these findings add some support to the view that the factors principally responsible for the area differences in neural tube malformation prevalence in South Wales, though still unknown, may well be external environmental characteristics associated with the nature of the area itself, such as the softness of local water supplies (Lowe *et al.*, 1971), rather than personal environmental factors associated with the population of that area, such as diet, occupation, recreational activities, and religion.

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