Contrasting effects of maternal fertility and birth rank on the occurrence of neural tube defects

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SUMMARY The relationships between the occurrence of anencephalus and spina bifida, sibship size and birth rank were examined, using linked records for births in British Columbia. Comparison of 414 sibships in which at least one infant had a neural tube defect with 1362 randomly chosen unaffected sibships showed that the affected sibships were larger. There were both more births than expected after the affected birth, and shorter intervals between births before the affected birth. Within sibships, the risk of anencephalus or spina bifida decreased strongly with increasing birth rank. No associations were seen with maternal age at first birth.

The relationships between the prevalence at birth of neural tube defects (anencephalus and spina bifida) and maternal birth order and age have not been adequately explained, despite their evident aetiological significance. Most studies which compare prevalence rates in populations at one point in time report U-type associations, with high rates at both low and high birth orders or maternal ages (Elwood *et al.*, 1978; James, 1969). However, population data studied by birth cohort, without any control for birth rank, show a decreasing risk with increasing maternal age (Janerich, 1972a; 1972b). A Canadian case control study has shown that anencephalus risk decreases with an increase in the number of previous livebirths, but increases with the occurrence of a previous stillbirth or infant death (Elwood *et al.*, 1978). Such differences in the results given by population data and by more detailed studies suggest that the associations seen in population data may be influenced by differences in fertility between mothers of infants with neural tube defects and other mothers (Elwood *et al.*, 1978; James, 1969). The present study used linked sibship records to evaluate the associations of both birth rank and fertility with the occurrence of neural tube defects.

Methods

SOURCE OF DATA

For some time the Division of Vital Statistics of the Ministry of Health of British Columbia has been

involved in a collaborative record linkage project with the Population Research Branch of the Chalk River Nuclear Laboratories and the Department of Medical Genetics of the University of British Columbia (Newcombe, 1967; Trimble, 1976). This involves the integration of existing files of vital and ill health registrations into individual and family histories. One of the ill health sources is a handicapped children's register, based on multiple sources of ascertainment including stillbirth, birth and death registrations, hospital discharge information, and voluntary reporting (Trimble, 1976). There are 390 796 sets of records of marriages in British Columbia between 1946 and 1970 and their linked births. From these, 414 sibships were identified in which (a) at least one birth with anencephalus or spina bifida occurred between 1952 and 1970 (b) the first birth occurred during these years and (c) the linkage weight was sufficiently high to make the probability of incorrect linkage minimal. To provide comparison sibships, a random sample of 4000 unaffected sibships was drawn from the total, and of these 1362 were eligible for study on the criteria given above. It is assumed that these sibships are representative of the total numbers of eligible and unaffected sibships, estimated as $1362 \times 390\,796 / 4000 = 132\,652$.

ANALYSIS

For variables characteristic of sibships, the cross-products ratio from cross-tabulations was used to

estimate relative risk. Confounding by other variables was controlled by stratification and computation of a maximum likelihood estimate of relative risk (Gart, 1970). For variables related to individual births, the prevalence rate at birth of neural tube defects per 1000 births, r , was given by $A/(B/f + A + S)$ where A = number of affected births, S = number of unaffected siblings of affected births, B = number of births in comparison sibships, and f = sampling fraction of comparison sibships or births = 1362/136 252. As A and S are total counts, the variance of this rate is dependent on the variance of B and is given by r^2/B (Elwood *et al.*, 1978). Sibship size refers to the number of births recorded (livebirths and stillbirths from 28 weeks' gestation before 1963 and from 20 weeks' gestation thereafter). Multiple births are regarded as sharing the same birth rank.

Results

Sibship size. There were 414 eligible sibships in which there was at least one infant with a neural tube defect, and 1362 randomly chosen unaffected sibships. The risks of sibships of size 3, 4, and 5 or more having at least one affected member are respectively 3.6, 7.4, and 7.5 times that for sibships of size 1 (Table 1). If

Table 1 Numbers of neural tube defect (NTD) and comparison sibships, and relative risks, by sibship size

Sibship size	NTD sibships No.	Comparison sibships No.	Relative risk ¹	Relative risk after control for age at first birth ²	Expected relative risk ³
1	47	414	1.0	1.0	1.0
2	87	470	1.6	1.6	2.0
3	114	282	3.6	3.6	3.0
4	97	115	7.4	7.2	4.0
5 +	69	81	7.5	7.2	5.7
	414	1362			

¹Risk of sibship including a neural tube defect infant, compared with the risk for sibships of size 1.

²Maximum likelihood estimate of relative risk after control for maternal age at first birth.

³'Expected' on the null hypothesis that the risk of any individual birth being affected is independent of sibship size and birth order.

the risk of a birth being the first affected in the sibship were independent of sibship size and birth order, the relative risks would be 3, 4, and 5.7 respectively; thus the average risk to individual births in large sibships must be greater than that to births in small sibships.

Neural tube defects may be more common in less favoured socioeconomic groups, and such groups may tend to have larger sibship sizes, related to the fact that marriage and the start of reproduction occur at younger ages. Therefore we calculated the relative risks by sibship size, after controlling for

maternal age at first birth—the relative risks for large sibships were only slightly reduced, as maternal ages at first birth were similar in affected and unaffected sibships. Table 2 shows the distribution of births by

Table 2 Numbers of neural tube defect births and unaffected siblings, and of births in comparison sibships, and prevalence rates of neural tube defects per 1000 births, by sibship size

Sibship size	NTD sibships		Comparison sibships Nos. of births	Mean prevalence rate at birth per 1000 births	Standard error
	Affected births ¹ No.	Unaffected births ² No.			
1	47	0	414	1.16	0.06
2	87	87	940	0.95	0.03
3	114	228	846	1.38	0.05
4	97	291	460	2.15	0.10
5 +	69	328	449	1.56	0.07
Total	414	934	3109	1.36	0.02

¹First affected births only.

²Total number shown; births subsequent to the first affected birth ignored in the calculation of prevalence rates.

sibship size and confirms that the mean prevalence rate at birth is greater for births in larger sibships. The prevalence rate is that of a first affected birth in the sibship; thus births subsequent to affected births are excluded from the denominator.

Birth rank. An increased risk of neural tube defects in larger sibships would be expected if infants of higher birth rank had higher risks. We therefore compared the prevalence rates at birth by birth rank and by sibship size. Table 3 and the Figure show that within sibships, the prevalence rate of neural tube defects decreases sharply with increasing birth order. The decline appears to level off at birth orders beyond four, although the numbers of cases are too small for definite conclusions. The increased risk at large sibship sizes therefore occurs not because of, but in spite of, the birth order association, and is stronger if birth order is controlled. The birth order-specific rates appear to increase from sibship size 1 to 4, but may fall at higher sibship sizes.

Differential fertility. The increased risk with larger sibship size could occur either because mothers who have had an affected infant subsequently have more children than 'comparison' mothers, or because mothers at risk of bearing infants with neural tube defects are more fertile even before the affected birth, in which case they would tend to have more closely spaced pregnancies before the affected birth. To examine the first alternative (reproductive compensation) we compared the number of births after an affected birth at each birth rank, with the number of births after a birth of the same rank in the comparison sibships.

Table 3 Numbers of neural tube defect births, unaffected siblings, and comparison births, and prevalence rates per 1000 births, by sibship size and birth rank

Sibship size	Birth rank	Affected births ¹ No.	Unaffected siblings ² No.	Comparison sibships Nos. of births	Prevalence rate per 1000	Standard error
1	1	47	0	414	1.16	0.06
2	1	51	36	472	1.11	0.05
	2	36	0	468	0.79	0.04
3	1	50	64	284	1.80	0.11
	2	37	27	283	1.34	0.08
	3	27	0	279	0.99	0.06
4	1	39	59	116	3.42	0.32
	2	23	35	116	2.03	0.19
	3	18	17	117	1.57	0.14
	4	17	0	111	1.57	0.15
5	1	14	25	54	2.64	0.36
	2	10	15	55	1.86	0.25
	3	7	8	53	1.35	0.18
	4	4	4	54	0.76	0.10
	5	4	0	54	0.76	0.10
6	1	4	14	17	2.39	0.58
	2	6	8	15	4.07	1.04
	3	2	5	16	1.28	0.32
	4	3	3	16	1.92	0.48
	5	2	1	16	1.28	0.32
	6	1	0	16	0.64	0.16

¹First affected births only.²Including only siblings born prior to the first affected birth.

Figure Prevalence rates at birth per 1000 for first occurrences of anencephalus or spina bifida in the sibship by sibship size and birth rank.

Because both biological fertility (Wyshak, 1969) and reproductive compensation are likely to be different for mothers of twins and of triplets, the ten affected sibships and seventeen 'comparison' sibships in which a multiple birth occurred were excluded from these analyses. Table 4 shows that in sibships with the first or second birth affected, significantly more births occur subsequently than in comparison sibships. Where the infant with a neural tube defect has a higher birth rank, the number of subsequent births is only slightly, and not significantly, greater than that in unaffected sibships. Mean numbers of subsequent births are shown for descriptive purposes, but as the distributions are markedly non-normal, statistical significance was assessed by a χ^2 test of trend over categories of numbers of subsequent births (Armitage, 1971).

We then compared the time interval between births before the affected birth with the interval between births before the birth of that rank in comparison sibships, for affected birth ranks of 3 or greater. We did not use the interval immediately before the affected birth in these calculations because it is influenced by the gestation period of the affected birth. Inspection of the distribution of birth intervals showed them to be adequately fitted by a log normal distribution. Table 5 shows that the mean birth interval is significantly shorter in affected than in comparison sibships.

Table 4 Comparison of numbers of births subsequent to affected births of given birth rank in neural tube defect (NTD) sibships with births subsequent to births of the same rank in comparison sibships¹

Birth rank	NTD SIBSHIPS		COMPARISON SIBSHIPS		χ^2	χ^2 trend ²
	Sibships No.	Mean no. subsequent births	Sibships No.	Mean no. subsequent births	Total (df)	(1 df) and P value
1	204	1.71	1345	1.26	36.9(5)	22.4 P <0.001
2	110	1.18	931	0.82	15.5(4)	12.0 P <0.001
3	52	0.67	463	0.66	2.4(3)	0.1
4	27	0.70	186	0.64	3.0(2)	0.1

¹All sibships containing a multiple birth are excluded.

² χ^2 test for trend over categories defined by number of births; 1 df.

Table 5 Comparison of birth intervals between births before the first affected birth in neural tube defect (NTD) sibships with those before births of the same rank in comparison sibships¹

Rank of affected birth	NTD SIBSHIPS			COMPARISON SIBSHIPS			Student's <i>t</i> test ³
	Sibships No.	Mean birth interval ² (years)	Variance ²	Sibships No.	Mean birth interval ² (years)	Variance ²	
3	52	2.05	1.16	463	2.89	1.33	4.5
4	27	1.63	1.10	186	2.31	1.18	4.2
5	7	1.43	1.10	78	2.06	1.12	2.8

¹All sibships containing a multiple birth are excluded.

²Geometric mean, and antilog of variance of log interval.

³Student's *t* test for difference between means of log interval, using pooled variance estimate.

All P values <0.001.

Discussion

The data we used were records of marriages, births, and stillbirths occurring after 1946 to residents of British Columbia; the records were linked by computer-assisted matching of numerical data and matching of names using Soundex codes (Newcombe, 1967). This study is limited to sibships in which the affected birth and the first birth occurred between 1952 and 1970. The births studied are not representative of all births in British Columbia; for example, the prevalence rate at birth of anencephalus and spina bifida in our study group was 1.36 per 1000 births compared with 1.55 in the total population in the same period (McBride, 1978). The difference is probably largely due to the study group representing long-term residents of British Columbia, as the parents had to be married in British Columbia for inclusion, while the population rate is influenced by migrants from other parts of Canada and from Europe where the prevalence rates of neural tube defects are higher (Elwood, 1974a). This does not limit the interpretation of the study because the criteria for eligibility are identical for affected and for 'comparison' sibships. The sibships studied are not necessarily complete, but exclude births occurring after 1970. This would bias the results if there were a secular trend in the occurrence of neural tube defects; however, the prevalence at birth has shown no trend in British Columbia (Elwood, 1974a; Trimble and Baird, 1977) and, in the current data, controlling for year of first birth did not affect the results.

We have shown that mothers of infants with neural tube defects have larger families, and that for a given birth rank the risk of a birth being affected increases with sibship size. The high fertility of such mothers could be involuntary (for example, due to higher biologic fertility related to hormonal mechanisms) or voluntary (for example, due to reproductive compensation after an affected birth, or to other biosocial factors). More births occur after the affected birth than after a birth of the same rank in 'comparison' sibships, but births before an affected birth occur more rapidly than the corresponding births in comparison sibships. Thus, the higher fertility precedes the birth of an affected child, and reproductive compensation alone does not explain the large sibship sizes. The association could be produced by social class differences, because lower socioeconomic status is associated with a higher risk of neural tube defects and also with more frequent pregnancies in some populations. We studied maternal age at first birth initially because of its potential as an indicator of intrinsic hormonal mechanisms, as demonstrated by its importance in regard to breast cancer, but it also seems likely to be a reasonable indicator of socioeconomic status. The similar distribution of age at first birth between mothers of infants with neural tube defects and 'comparison' mothers suggests that large differences in risk by socioeconomic group do not occur in British Columbia, and that consequently the associations with fertility cannot be due to socioeconomic factors. The low and stable prevalence at birth of neural tube defects in British Columbia is

consistent with the absence of environmental influences which may produce the social class association seen in areas of higher prevalence (Elwood, 1974a). However, there is a need for more information on socioeconomic factors.

We had no information about abortions. Spontaneous abortions are more common in neural tube defect sibships than in unaffected sibships (Record and McKeown, 1950; Richards *et al.*, 1972) and within anencephalus sibships show a negative association with birth order (James, 1978). The occurrence of unrecorded spontaneous abortions would be expected to increase birth intervals for mothers of neural tube defect sibships compared with 'comparison' mothers, so the shorter intervals shown in the current study may underestimate the true difference. We did not consider maternal age at the time of an affected birth in this study because a previous study in Canada (Elwood *et al.*, 1978) shows that maternal age has no association with anencephalus risk if birth rank is controlled.

We conclude that mothers of infants with neural tube defects are more fertile than randomly chosen 'comparison' mothers. In a study of 580 mothers of infants with anencephalus or spina bifida and 710 control mothers in Birmingham in the 1940s, Record and McKeown (1950) showed a shorter mean fallow period (date of marriage or preceding birth to date of conception) for mothers of affected infants, both for the periods preceding the affected birth and for those preceding sibling births. Other studies have shown no differences (Fedrick and Adelstein, 1973; Smithells *et al.*, 1964; Smithells and Chinn, 1965) or a suggestion of a longer fallow period before the affected birth (James, 1973). Less direct measures have been used to suggest either lower or higher fertility of mothers of infants with neural tube defects (Spiers, 1973; Elwood, 1974b).

The prevalence at birth of neural tube defects shows a strong and consistent fall with increasing birth rank when sibship size is controlled. Canadian population data show the U-type associations of prevalence with birth order and with maternal age that have been seen elsewhere (Elwood *et al.*, 1978). This U-type association appears to be due to the negative effect of birth order within sibships accompanied by the higher fertility of mothers prone to have affected births, as has been shown using sibship data (James, 1969). Analysis by birth cohort, or by multivariate control for secular trends and history of previous stillbirths or childhood deaths, also reveals a unidirectional inverse relationship between the prevalence of anencephalus and the mother's number of previous live births (Elwood *et al.*, 1978).

This strong negative association with birth order

appears to be a major feature of the occurrence patterns of these defects. It seems more likely to be due to a decrease in incidence than to an increase in early fetal loss with increasing birth rank, as spontaneous abortions show no association with birth rank in normal sibships (James, 1978). It is not clear whether this feature of neural tube defects can be reconciled with aetiological hypotheses dependent on previous abortions (Clarke *et al.*, 1975; Rogers, 1976) and more information on the occurrence of early fetal losses is essential for adequate judgment.

The record linkage project is a collaborative programme involving the British Columbia Division of Vital Statistics, the Department of Medical Genetics of the University of British Columbia, and the Population Research Branch of the Chalk River Nuclear Laboratories. It is supported in part by Health and Welfare Canada. Permission to use the vital and health records was conditional upon the strict observance of the oath of secrecy respecting the non-statistical information contained in the records.

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