The Relationship of the Presence of Disease to Birth Order and Maternal Age

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DURING ANALYSIS of epidemiological data, a question frequently posed is whether the presence or absence of a disease is correlated with birth order. According to the nature of the data, this question translates itself into one of two more specific ones. Firstly, within fraternities containing affected individuals, are sibs in some birth ranks affected more frequently than those in other ranks? Or secondly, within the population to which the affected individuals belong, does the incidence of the disease vary with birth rank? This paper is concerned with methods of analysis which seek to answer these two questions and with methods which determine whether a correlation between the presence of a disease and birth order reflects a correlation with maternal age.

ANALYSIS OF BIRTH RANK DISTRIBUTION WITHIN FRATERNITIES

When the data are appropriate to the first question, permitting analysis of the birth rank distribution of affected individuals within their fraternities, the method devised by Greenwood and Yule (1914) is commonly used. This method depends on comparison of the observed number of affected individuals in each birth rank with an expected number; but it can be shown that this expected number, the calculation of which is shown in Table 1, is often incorrect (Barker and Record, 1966). Haldane and Smith (1948), Slater (1962), and Bennett (1963) described methods which summarise birth rank distributions by a single number, whose value may be compared with an expected one. These methods require completed fraternities and may be misleading, for example where a disease is more frequent both among first-born children and among children in high birth ranks.

The related frequencies method, described in a previous publication (Barker and Record, 1966), provides an accurate description of the correlation between the presence of a disease and the birth order of affected individuals within their fraternities. The method depends on comparison of numbers of affected in successive birth ranks. If the presence of a disease is unrelated to birth order, it may be predicted that, in the notation of Table 1, $a_1=a_2$, $b_1=b_2=b_3$, and $c_1=c_2=c_3=c_4$. The ratio of the number of affected in birth rank 2 to the number affected in birth rank 1 is given by $(a_2+b_2+c_2)/(a_1+b_1+c_1)$. Similarly, the ratio between birth ranks 3 and 2 is $(b_3+c_3)/$

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TABLE 1. THE GREENWOOD-YULE METHOD USED TO EXAMINE THE RELATIONSHIP BETWEEN THE INCIDENCE OF A DISEASE AND THE BIRTH ORDER OF AFFECTED INDIVIDUALS WITHIN THEIR FRATERNITIES

Size of fraternities *	Numbers of affected in each birth rank				Total number of fraternities
	1	2	3	4	
2	a_1	a_2			A
3	b_1	b_2	b_3		B
4	c_1	c_2	c_3	c_4	C
TOTAL					
Observed (a)	$(a_1+b_1+c_1)$	$(a_2+b_2+c_2)$	(b_3+c_3)	(c_4)	$A+B+C$
Expected (b)	$(A/2+B/3+C/4)$	$(A/2+B/3+C/4)$	$(B/3+C/4)$	$(C/4)$	$A+B+C$

* It is supposed that no fraternity comprises more than four sibs, that all fraternities are complete, and that no fraternity contains more than one affected individual.

TABLE 2. MODEL TO SHOW THE OCCURRENCE OF A DISEASE WHICH AFFECTS EQUAL NUMBERS OF FIRST- AND SECOND-BORN SIBS

X_1 fraternity.....1	2			
Y_1 fraternity.....1	**2**			
	1	2		
	1	**2**		
		1	2	
		1	**2**	
			1	2.....Y_2 fraternity
			1	**2**.....X_2 fraternity

It is supposed that women reproduce at a uniform rate. The pattern of reproduction is represented on a horizontal time scale, with each fraternity occupying one line and each numeral representing the birth rank of the child. Affected individuals are shown in bold type.

(b_2+c_2) and that between birth ranks 4 and 3 is c_4/c_3. In this way, the frequency of the disease in each birth rank can be related to that in the preceding rank, so that a ratio greater than 1.0 indicates a higher frequency of the disease among sibs in that birth rank than in the preceding one.

When the related frequencies or other methods are applied, it may be necessary to take account of four factors which can distort the correlation between the presence of a disease and birth order.

1. *Incomplete fraternities.* All methods of birth order analysis which depend on comparisons within fraternities can give rise to serious inaccuracies when the fraternities are incomplete. But the related frequencies method differs from other methods in that these inaccuracies can be simply avoided.

Table 2 illustrates the occurrence of a disease which affects equal numbers of first- and second-born sibs, and for which the related frequency in birth rank 2 is therefore unity. Affected children without sibs and children of birth rank 3 or more are omitted since they are not relevant to the calculation

TABLE 3. RELATED FREQUENCIES OF ANENCEPHALY AMONG CHILDREN BORN IN BIRMINGHAM DURING 1940–1947

	Birth rank					Total
	1	2	3	4	5 and over	
Excluding sibs not born during 1940–1947	—	0.5	0.8	0.8	0.7	0.7
	—	(22/42)	(13/16)	(8/10)	(13/18)	(56/86)
Including all sibs born at time of survey (1949)	—	0.9	1.3	1.5	1.3	1.1
	—	(40/44)	(24/19)	(19/13)	(24/19)	(107/95)

The numbers in parentheses are the frequencies of affected sibs in each birth rank over the comparable frequencies in the preceding rank (see text).

of this related frequency. Fraternities are identified by the presence of an affected sib born within the period limited by the two vertical lines, and the model represents data such as those obtained when studies of a congenital abnormality are based on births during a number of consecutive years. Fraternities of types X_1 and X_2 are not identified because the affected children are born outside the period of ascertainment, but this does not alter the related frequency. However, if there is a short interval between birth of the propositi and the time of the study, some fraternities of type Y_2 will not be identified because the second sib will not have been born. This will result in an excess of Y_1 fraternities over Y_2 fraternities and in consequence a related frequency which exceeds unity. But if Y_1 and Y_2 fraternities are excluded from the analysis, the related frequency will be unity; and when, therefore, a study is carried out shortly after the birth of the propositi, it is necessary to disregard sibs born outside the period of ascertainment.

Table 3 shows the related frequencies of anencephaly among patients who were born in Birmingham during 1940–1947 and for whom family histories were recorded in 1949 (Record and McKeown, 1949). (The related frequency for birth ranks 5 and over was obtained by summation of the numerators and denominators of the separate ratios of frequencies in each of the birth ranks, and the total related frequency was obtained by a similar summation over all birth ranks.) When sibs born outside this period are not excluded, the related frequency in each birth rank rises and the raised frequency of the disorder among first-born children is obscured.

Exclusion of sibs born outside the period of ascertainment may considerably reduce the number of fraternities which can be analyzed. But if, for example, a study is carried out five years after birth of the propositi, all known Y_2 fraternities (Table 2) can be included together with those Y_1 fraternities in which the first child was born during the five years preceding the ascertainment period. This will not alter the related frequencies unless there is a difference in interval between births in Y_1 and Y_2 fraternities. When propositi have become affected over a prolonged period of time, inaccuracies resulting

from incomplete fraternities will be trivial because the proportion of Y_1 and Y_2 fraternities is small.

When a disease tends to affect more than one member of a fraternity, Y_2 fraternities cannot be included in the analysis until the later-born child has reached the age when ascertainment of the disease occurs. Disregard of this may lead to an apparent raised frequency among children of low birth rank, and this consideration is relevant to the examination of psychiatric illness (Gregory, 1958) and to published findings such as that of an excess of first-born children among cases of hyperthyroidism who show familial "predisposition" to the disease (Pilot and Kormos, 1964).

2. *Changes in numbers of propositi.* If the propositi in an inquiry have become affected and identified during a short period of time, it is necessary to insure that the numbers of propositi ascertained in each year are approximately equal. The numbers can vary as a result of changes in either the incidence of the disease or the size of the population from which propositi are drawn. Table 4, based on the same model as Table 2, shows that a rise in the incidence of a disease produces a fraternity of type Z. This will not alter the related frequencies if fraternities are complete and if those of type Y are therefore included. But if Y fraternities are excluded, the frequency of the disease in birth rank 2 will exceed that in birth rank 1.

This point is illustrated in Table 5, which shows the related frequencies of pyloric stenosis among cases identified from all children born in Birmingham in the period 1940-1949 (MacMahon *et al.*, 1951). During this time, the ascertained incidence of the disease rose from 2.5 to 4.2 per 1,000 live births; and for this reason when sibs born outside the period of the survey are excluded, the related frequencies fail to show the well-established association with primogeniture. But restriction of the analysis to propositi born during 1940–1945 permits inclusion of sibs born during 1936–1949 (see preceding section) and therefore of most Y fraternities. As a result, the raised frequency of the disease in birth rank 1 is clearly demonstrated.

If the size of the population from which propositi are drawn is increased by immigration, the situation will be identical to that illustrated in Table 4. The 1* 2 fraternities which counterbalance the Z fraternities produced by the immigrant population will not be identified because the affected children are born before the immigrants are exposed to ascertainment. Alternatively, if the size of the population is increased by additional numbers of women commencing reproduction, the result will be that shown in Table 6. If Y fraternities are included in the analysis, there will be a raised frequency of the disease in birth rank 1. But if Y fraternities are excluded, there will be equal numbers of affected in each birth rank. These considerations are relevant to the findings of Cobb and French (1966), who demonstrated an excess of first-born among a group of young men currently at medical school and questioned whether this could result from the increased proportion of first births in the United States during the early 1940's.

In most inquiries, propositi have become affected over a prolonged period of time, and changes in the numbers of propositi according to year of birth

TABLE 4. MODEL TO SHOW THE RESULTS OF INCREASED ASCERTAINED INCIDENCE OF A DISEASE

	Incidence doubles			
1	2			
Y_1 fraternity.....1	**2**	↓		
	1	2		
	1	**2**		
Z fraternity.....1		**2**		
		1	2	
		1	**2**	
		1	2	
		1	**2**	
			1	2.....Y_2 fraternity
			1	**2**
			1	2.....Y_2 fraternity
			1	**2**

The conventions used are the same as for Table 2.

TABLE 5. THE RELATED FREQUENCIES OF PYLORIC STENOSIS AMONG CHILDREN BORN IN BIRMINGHAM DURING A PERIOD OF INCREASING INCIDENCE

	Birth rank					Total
	1	2	3	4	5 and over	
Propositi born 1940–1949	—	1.0	1.8	0.6	1.0	1.1
Sibs born outside this period excluded	—	(93/95)	(46/25)	(13/22)	(16/16)	(168/158)
Propositi born 1940–1945	—	0.6	1.0	0.6	1.1	0.7
Sibs born 1936–1949 included	—	(39/70)	(21/20)	(10/17)	(9/8)	(79/115)

The numbers in parentheses are the frequencies of affected sibs in each birth rank over the comparable frequencies in the preceding rank.

produce alterations in the related frequencies which are trivial and can be disregarded.

3. *Alterations in reproduction following birth of an affected child.* It is well recognized that alterations in the parents' reproduction following the birth of an affected child may lead to an apparent correlation between the presence of a disease and birth order. If, for example, birth of an affected child deters parents from further reproduction, the related frequencies will exceed unity in each birth rank. But in this situation, an unbiased value for the related frequency in a given birth rank may be obtained by exclusion of fraternities in which that birth rank is terminal.

Boyer *et al.* (1961), using a modification of the Greenwood-Yule method,

TABLE 6. MODEL TO SHOW THE RESULTS OF AN INCREASE IN THE SIZE OF THE POPULATION FROM WHICH PROPOSITI ARE DRAWN

	Number of women commencing reproduction doubles			
1	2			
Y_1 fraternity..... 1	**2**	↓		
	1	2		
	1	**2**		
		1	2	
		1	**2**	
		1	2	
		1	**2**	
			1	2..... Y_2 fraternity
			1	**2**
			1	2..... Y_2 fraternity
			1	**2**

The conventions used are the same as for Table 2.

found a slight excess of first-born individuals affected by chromatin-negative Turner's syndrome, but they attributed this to a chance variation. Analysis of their published data shows that the related frequency in birth rank 2 is 0.8 (21/26); but if fraternities of size 2 are excluded, the related frequency becomes 0.5 (10/20), suggesting a correlation between the presence of Turner's syndrome and primogeniture. This finding is confirmed if cases of XO Turner's syndrome described by Lindsten (1963) and Insley (1966) are added to these data, for the related frequencies in birth rank 2 then become 0.9 (42/46) when all fraternities are included and 0.5 (16/31) when fraternities of size 2 are excluded. The exclusion of fraternities of size 2 eliminates not only fraternities in which the birth of an affected second child terminated the parents' reproduction but also fraternities in which an affected second child was identified during infancy and details of the fraternity were recorded before the third child was born. Since, however, Turner's syndrome is often not diagnosed until late childhood or early adult life, further data are required in order to establish this apparent correlation between the disease and primogeniture.

4. *Deaths before the age at which the presence of disease can be ascertained.* When a birth order is assigned to an individual, it may be necessary to take previous miscarriages and stillbirths into account. This problem associated with the definition of birth order was discussed by MacMahon *et al.* (1960). The definition used can be varied depending on whether the suspected etiological agent acts in early or late prenatal life, or postnatally, and it seems unnecessary to insist (as did Metrakos and Metrakos, 1963) that all previous pregnancies should always be included.

Any death before the age at which ascertainment of a disease becomes

possible may necessitate omission of a fraternity, or part of one, when related frequencies are calculated. Usually the number of omitted fraternities will be small, but if they are large they can be analyzed by calculation of related frequencies based on comparisons between birth ranks which are not consecutive. If death of affected individuals before ascertainment occurs more frequently in some birth ranks, this must affect the results of any investigation into the relationship between the presence of a disease and birth order.

Maternal Age

Whenever analysis reveals a correlation between the presence of a disease and birth order within fraternities, it is necessary to determine whether this reflects a correlation with parental age. (A correlation with parental age must always give rise to a correlation with birth order within fraternities except, of course, in the unlikely event of an association with birth order exactly counterbalancing one with parental age.) Since, within fraternities, birth order and parental age increase together, distinction between a correlation with either one of them must depend on comparison of fraternities in which children of a given birth rank are born at different parental ages. Using experimental animals it might be possible to vary parental age at breeding while keeping fraternities identical in all other respects. But in human populations, variation in parental age for a given birth rank is associated with variations in many other characteristics such as social class and fertility. Therefore, a sample selected from a population by the presence of a certain disease may be nonrandom with respect to parental age. Decisions as to whether, within fraternities containing affected individuals, the presence of a disease is correlated with age changes in the parents cannot therefore be made on the basis of tests of significance. Although correlation with age change in one parent will result in a correlation with age changes in the other, the present discussion will be restricted to maternal age, and methods for distinguishing between correlations with maternal and paternal age will not be considered.

Penrose (1934) described a method for distinguishing between relationships with maternal age and with birth order. In fraternities containing an affected individual, each sib's expectation of the disease is calculated on the assumption that the presence of the disease is correlated with only one of the two variables. The observed distribution of the other variable is then compared with that derived by summation of the expectations. This complex procedure has the same defects as the Greenwood-Yule method for birth order analysis; and similarly, when applied to hypothetical data, it gives inaccurate results.

A correlation between the presence of a disease and maternal age, independent of birth order, can be simply demonstrated by the use of related frequencies. If, for example, the frequency of a disease rises with increasing maternal age, the related frequency in a given birth rank will vary with the interval between the births of children in that and in the preceding rank. Where the interval is only one or two years, children in both ranks are born at similar maternal ages, and the excess of affected later-born children will be slight. But where the interval is long, the later-born children are born at much

higher maternal ages and the excess who are affected will be large. Table 7 shows the related frequencies of mongolism, derived from the data of Penrose (1934). With an interval between births of less than three years, the total related frequency is only 1.2, but with a longer interval there is a higher related frequency in every birth rank and the total is 2.6. These findings suggest that the frequency of mongolism is correlated with increasing maternal age (although similar findings would result from data in which fraternities were incomplete and incidence was rising). For this analysis, no information about maternal age of propositi and their sibs is required if their dates of birth are known.

An alternative method of analysis is the calculation of the total related frequencies of propositi born in different maternal age-groups. Table 8, based on Malzberg's data (1950), shows that the total related frequencies of mongolism rise steeply with increasing maternal age. But this rise may reflect only an increasing tendency for older mothers to discontinue reproduction after the birth of a mongol child, and for this reason the Table also shows the total related frequencies calculated for each birth rank after exclusion of fraternities in which that birth rank is terminal. These related frequencies rise less steeply with increasing maternal age. When the presence of a disease is correlated with maternal age, independent of birth order, the related frequency in a given birth rank is a product of the maternal ages of the propositi and the intervals between their births and those of sibs in the previous rank. Therefore, an increasing disease frequency with maternal age could be counterbalanced by a decreasing interval between births, so that related frequencies would be identical in each maternal age-group. However, this possibility can be explored by use of the method of analysis shown in Table 7. Given extensive data, the most informative analysis is obtained by calculation of related frequencies at varying birth intervals for propositi within each maternal age-group.

If the presence of a disease is correlated both with low birth rank and with high maternal age, this may be revealed when related frequencies are calculated for propositi born shortly after sibs in the preceding rank or when related frequencies are calculated for propositi in the lowest maternal age-groups. In Malzberg's data (1950) for example, the related frequency in birth rank 2 is 0.6 (27/48) at maternal ages below 25 years, suggesting that mongolism is correlated with primogeniture.

If the presence of a disease is correlated with high birth rank and, independently, with increasing maternal age, it may be predicted that, when the influence of maternal age is standardized, the ratio between the frequency of the disease in a given birth rank and that in the preceding rank will be smaller than the ratio between the frequency in the rank and that in the preceding rank less one. For example, if third-born propositi are selected from maternal age-group 25-29 and if, using the notation of Table 1, $(b_3+c_3)/(b_2+c_2)$ is calculated for fraternities in which second and third births were separated by four to six years, the product will be less than that of $(b_3+c_3)/(b_1+c_1)$ calculated for fraternities in which first and third births were likewise separated by four to six years. To make comparisons of this kind, for each

TABLE 7. RELATED FREQUENCIES OF MONGOLISM ACCORDING TO INTERVAL BETWEEN BIRTH IN EACH RANK AND IN PRECEDING RANK

Interval between birth in each rank and in preceding rank	Birth rank										
	1	2	3	4	5	6	7	8	9	10	Total
Less than three years	— —	0.8 (8/10)	1.2 (6/5)	1.3 (4/3)	1.3 (4/3)	2.0 (4/2)	1.3 (4/3)	— (5/0)	1.0 (3/3)	— (0/2)	1.2 (38/31)
Three years or more	— —	3.0 (15/5)	2.0 (14/7)	2.5 (10/4)	2.7 (8/3)	6.5 (13/2)	2.2 (9/4)	1.5 (9/6)	3.0 (6/2)	6.0 (6/1)	2.6 (90/34)
TOTAL	— —	1.5 (23/15)	1.7 (20/12)	2.0 (14/7)	2.0 (12/6)	4.2 (17/4)	1.9 (13/7)	2.3 (14/6)	1.8 (9/5)	2.0 (6/3)	2.0 (128/65)

The numbers in parentheses are the frequencies of affected sibs in each birth rank over the comparable frequencies in the preceding rank.

TABLE 8. TOTAL RELATED FREQUENCIES OF MONGOLISM ACCORDING TO MATERNAL AGES OF PROPOSITI

	Maternal age-group				
	Under 25	25–29	30–34	35–39	40 and over
All fraternities	0.6 (38/68)	1.6 (74/47)	2.2 (111/51)	4.6 (169/37)	11.1 (155/14)
Excluding fraternities in which birth rank is terminal (see text)	0.8 (22/28)	1.0 (19/19)	1.9 (39/21)	2.1 (31/15)	2.6 (13/5)

The numbers in parentheses are the sum of the frequencies of affected sibs in each birth rank over the sum of the comparable frequencies in the preceding ranks.

birth rank and maternal age-group, extensive data are required. In practice, therefore, if the related frequencies of a disease exceed unity and if the methods described reveal that the presence of the disease is correlated with increasing maternal age, it usually will be possible to distinguish an independent correlation with low birth rank but not one with high birth rank.

ANALYSIS OF BIRTH RANK DISTRIBUTION WITHIN THE POPULATION

Calculation of the relative or absolute incidence of a disease in each birth rank (the "control group method") may be demonstrated by reference to pyloric stenosis, the incidence of which was found to vary among children of different birth ranks in the following way (McKeown *et al.*, 1951):

Birth rank	1	2	3	4 and over
Incidence per 1,000 livebirths	4.3	2.8	2.5	1.4
Number of cases	244	139	57	38

Table 9, based on hypothetical data, illustrates three ways in which this declining incidence with increasing birth rank could occur. For convenience the recorded incidences have been rounded to the nearest whole number and children of birth rank greater than 4 are disregarded. The hypothetical population comprises 60,000 fraternities of size 1 to 4, and the number of fraternities of each size, and consequently the number of individuals (146,000), is the same in each model. In Model A, there is a constant incidence among children of the same birth rank irrespective of the size of the fraternity to which they belong. In Model C, the incidence is higher among children in smaller fraternities but does not vary among individuals of different birth ranks within

fraternities of the same size. Model B shows a situation intermediate between the other two. Only in Model A does the control group method accurately describe the correlation between the presence of a disease and the birth order of affected individuals within their fraternities.

The possibility that the control group method may show changes in incidence with birth rank solely as a result of changes with fraternity size (Model C) is well recognized, and it is usual to compare fertility in the control and affected groups. There are various indices of fertility, such as duration of marriage prior to the birth of a child and intervals between births, but only fraternity size is directly relevant to the present issue. It is sometimes suggested that, if fertility in the control and affected groups is the same, then the percentage distribution of individuals in the two groups according to their fraternity size will also be the same. However if, within fraternities of the same size, there is any variation in disease incidence with birth rank, this must be reflected in the distribution of the affected group according to fraternity size. In Model A, the proportion of individuals from small fraternities who are affected by pyloric stenosis exceeds that of individuals from large fraternities because small fraternities contain only individuals from low birth ranks, among whom incidence is highest. In Models B and C, there is a greater excess of affected individuals from small fraternities because the disease has a higher incidence among individuals from small fraternities irrespective of their birth rank. Therefore, comparison of the fraternity size distribution of the affected group with that of a control group from the population will not permit distinction between the situations represented by Models A, B, and C.

MacMahon *et al.* (1960) suggested that "the patient series may be compared with the related population within given family sizes, to determine whether any association with birth order exists when family size is held constant." This comparison will provide all the information shown in Table 9 and will therefore permit accurate assessment of the variation of incidence with both birth rank and fraternity size. But a group of affected individuals usually can be identified with a related population only when the disease is ascertained at or shortly after birth; and in these circumstances, fraternities are incomplete and the information obtained about variation of incidence with fraternity size is very limited.

Maternal Age

Variations in the incidence of a disease with birth order within fraternities may result from variation in incidence with maternal age. This may be illustrated by reference to Type 1 placenta praevia, whose incidence was found to vary with maternal age in the following way (Record, 1956):

Maternal age	Under 25	25-29	30 and over
Incidence per 1,000 total births	1.1	1.6	1.9
Number of cases	58	86	145

Table 10 illustrates three ways in which this increasing incidence with

TABLE 9. HYPOTHETICAL DATA SHOWING VARIATIONS IN INCIDENCE OF PYLORIC STENOSIS WITH BIRTH ORDER AND FRATERNITY SIZE

Size of fraternities	Incidence per 1,000 livebirths according to birth rank				Number of fraternities	
	1	2	3	4	Affected group	Population
Model A						
1	4.0 (56)				56	14,000
2	4.0 (64)	3.0 (48)			112	16,000
3	4.0 (80)	3.0 (60)	2.0 (40)		180	20,000
4	4.0 (40)	3.0 (30)	2.0 (20)	1.0 (10)	100	10,000
TOTAL	4.0 (240)	3.0 (138)	2.0 (60)	1.0 (10)	448	60,000
Model B						
1	5.3 (74)				74	14,000
2	4.8 (76)	3.9 (63)			139	16,000
3	3.6 (72)	3.0 (60)	2.4 (48)		180	20,000
4	1.8 (18)	1.5 (15)	1.2 (12)	1.0 (10)	55	10,000
TOTAL	4.0 (240)	3.0 (138)	2.0 (60)	1.0 (10)	448	60,000
Model C						
1	7.3 (102)				102	14,000
2	4.9 (78)	4.9 (78)			156	16,000
3	2.5 (50)	2.5 (50)	2.5 (50)		150	20,000
4	1.0 (10)	1.0 (10)	1.0 (10)	1.0 (10)	40	10,000
TOTAL	4.0 (240)	3.0 (138)	2.0 (60)	1.0 (10)	448	60,000
Number in each birth rank in population	60,000	46,000	30,000	10,000		

It is supposed that no fraternity comprises more than four sibs or contains more than one affected individual. Numbers of cases are given in parentheses.

TABLE 10. HYPOTHETICAL DATA SHOWING VARIATIONS IN THE INCIDENCE OF TYPE 1 PLACENTA PRAEVIA PER 1,000 TOTAL BIRTHS WITH BIRTH RANK AND MATERNAL AGE

Population

Maternal age	Birth rank			All birth ranks
	1	2 and 3	4 and over	
Under 25	30,000†	18,000*	2,000*	50,000
25–29	15,000‡	27,000†	8,000*	50,000
30 and over	15,000‡	30,000‡	25,000*	70,000
All maternal ages	60,000	75,000	35,000	170,000

* Fertility group 1. See text.
† Fertility group 2. See text.
‡ Fertility group 3. See text.

Model D

Maternal age	Birth rank			All birth ranks
	1	2 and 3	4 and over	
Under 25	1.0 (30)	1.0 (18)	1.0 (2)	1.0 (50)
25–29	1.5 (22)	1.5 (41)	1.5 (12)	1.5 (75)
30 and over	2.0 (30)	2.0 (60)	2.0 (50)	2.0 (140)
All maternal ages	1.4 (82)	1.6 (119)	1.8 (64)	(265)

Model E

Maternal age	Birth rank			All birth ranks
	1	2 and 3	4 and over	
Under 25	0.5 (14)	1.6 (29)	3.3 (7)	1.0 (50)
25–29	0.5 (7)	1.6 (42)	3.3 (26)	1.5 (75)
30 and over	0.5 (8)	1.6 (49)	3.3 (83)	2.0 (140)
All maternal ages	0.5 (29)	1.6 (120)	3.3 (116)	(265)

(*Continued on following page*)

TABLE 10 (Continued)

Model F

Maternal age	Birth rank			All birth ranks
	1	2 and 3	4 and over	
Under 25	1.1 (32)	0.9 (16)	0.9 (2)	1.0 (50)
25–29	2.6 (39)	1.1 (29)	0.9 (7)	1.5 (75)
30 and over	2.6 (39)	2.6 (78)	0.9 (23)	2.0 (140)
All maternal ages	1.8 (110)	1.6 (123)	0.9 (32)	(265)

Numbers of cases are given in parentheses.

maternal age could occur in a hypothetical population of 170,000 individuals, whose distribution by birth rank, maternal age, and fertility group is shown. The crude division into fertility groups depends on the assumption that Group 1 contains the greatest proportion of children of very fertile women, who have large families and begin reproduction at an early age, while Group 3 contains the greatest proportion of children of relatively infertile women, who have small families and begin reproduction later in life. Group 2 is intermediate. In Model D, there is a constant incidence among children in the same maternal age-group, irrespective of birth rank and fertility group. In Model E, incidence is constant within each birth rank. In Model F, incidence is constant within each fertility group. In all three models, the over-all incidence according to maternal age is the same.

Data on the relative incidences of Types 3 and 4 placenta praevia (Table 11) exemplify Model D. An inference which may be made from these findings is that the occurrence of placenta praevia is dependent on changes associated with maternal aging but is independent of changes associated with increasing parity. And variations in the incidence of pyloric stenosis (Table 12), which correspond with Model E, suggest that the presence of the disease is dependent on birth order but is independent of maternal age. It seems unlikely that a constant incidence among children of the same birth rank, irrespective of maternal age, would occur when variations in incidence with birth rank were the result of variations with fraternity size, as in Model C (Table 9). The control group method used in these circumstances therefore permits conclusions about the correlation between the presence of a disease and birth order within fraternities, in the absence of data on fraternity size.

When the incidence of a disease varies with parental fertility (Model F) the over-all changes with birth rank and maternal age tend to be contrary. In Model F, incidence rises with maternal age but falls with increasing birth rank. Death rates from childhood leukemia show similar changes (MacMahon

TABLE 11. THE RELATIVE INCIDENCE OF PLACENTA PRAEVIA, TYPES 3 AND 4, ACCORDING TO MATERNAL AGE AND PARITY (RECORD, 1956)

Maternal age group	Parity			All parities
	1	2 and 3	4 and over	
Under 25	0.2 (7)	0.4 (8)	— (1)	0.3 (16)
25–29	0.7 (15)	0.8 (27)	1.0 (7)	0.8 (49)
30–34	1.3 (10)	1.3 (35)	1.0 (12)	1.2 (58)
35 and over	2.3 (10)	1.9 (26)	2.3 (38)	2.2 (74)
All maternal ages	0.6 (42)	1.0 (97)	1.6 (58)	1.0 (197)

Numbers of cases are given in parentheses.

TABLE 12. THE INCIDENCE OF PYLORIC STENOSIS PER 1,000 LIVEBIRTHS ACCORDING TO MATERNAL AGE AND BIRTH RANK (MCKEOWN ET AL., 1951)

Maternal age group	Birth rank			All birth ranks
	1	2 and 3	4 and over	
Under 25	4.0 (115)	2.6 (38)	— (2)	3.5 (155)
25–29	4.8 (87)	2.4 (59)	1.3 (7)	3.2 (153)
30–34	4.1 (27)	2.7 (60)	1.6 (13)	2.7 (100)
35 and over	4.8 (15)	3.3 (39)	1.2 (16)	2.4 (70)
All maternal ages	4.3 (244)	2.7 (196)	1.4 (38)	(478)

Numbers of cases are given in parentheses.

and Newill, 1962). On the other hand, postneonatal death rates (Table 13) rise with birth rank and tend to fall with increasing maternal age. Although these findings demonstrate associations with fertility, they do not permit elucidation of independent correlations with either birth rank or maternal age. Thus they demonstrate the serious limitations of a method of investigation whose use is becoming more frequent as the application of computers to analysis of population data becomes more widespread (Newcombe, 1964).

TABLE 13. POSTNEONATAL DEATHS PER 1,000 LIVEBIRTHS (BIRMINGHAM, 1950–1954

Maternal age	Birth rank				All birth ranks
	1	2	3	4 and over	
Under 25	6.3 (112)	10.3 (71)	17.5 (35)	25.1 (17)	8.6 (235)
25–29	5.2 (51)	5.6 (55)	12.5 (63)	14.5 (56)	7.9 (225)
30–34	3.9 (15)	5.8 (35)	4.6 (20)	12.0 (68)	6.9 (138)
35 and over	7.4 (12)	6.9 (18)	6.4 (17)	11.3 (72)	9.0 (119)
All maternal ages	5.7 (190)	7.1 (179)	9.6 (135)	12.8 (213)	(717)

Numbers of deaths are given in parentheses.

APPLICATION OF METHODS OF ANALYSIS

It has been shown that, in order to demonstrate a correlation between the presence of a disease and birth rank or maternal age, information about fraternities is usually required. However, if data are available about the birth rank and maternal age distribution of the related population, conclusions are possible when the variations in incidence of the disease correspond with those shown in Models D or E (Table 10). In all other circumstances, it seems necessary to know the size of the fraternities of affected individuals and, if the control group method is used, that of the related population also.

If the inquiry concerns a disease manifest in adult life, identification of a related population is usually impossible. However, the related frequencies method can be applied; and since incomplete fraternities and changes in incidence or population size produce only trivial errors when propositi become affected over a prolonged period, it will not usually be necessary to allow for them. But when the disease is manifest in childhood, these factors must be taken into account, and small numbers of propositi may make interpretation difficult. In this situation, it may be helpful to apply both the related frequencies and the control group methods.

Since a correlation between the presence of a disease and maternal age will produce a correlation with birth order within fraternities, it is unnecessary to investigate parental age if birth order analysis is negative.

SUMMARY

This paper discusses methods of analysis which determine whether the presence of a disease is correlated with either birth order or maternal age. A new method for analysis within fraternities is described, and the interpretation

of variations of disease incidence with birth rank, maternal age, and fertility is explored.

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