Problems of Ascertainment of Congenital Anomalies

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Abstract. Problems of ascertainment bedevil the investigation of the etiology of congenital anomalies in singletons and in multiple births by epidemiological methods. It is shown that the definition of the population of affected births is ambiguous and that the problem of tracing etiology is complicated by the systematic way in which anomalies may be missed at birth. The available methods of dealing with problems of ascertainment are reviewed. Methods of adjusting for possible bias of ascertainment of affected births, by fitting statistical models to data from several sources, have been employed in some previous studies. In these methods, it is assumed that there are no errors of diagnosis or of recording. However, it is shown that there may be discrepancies in recorded diagnoses between sources, rendering this assumption untenable. In these methods, it is also assumed that the model which is the best fit to the data on the ascertained cases in also the best model for the cases which were not ascertained. This assumption is tested indirectly in a retrospective analysis of data from Aberdeen and Belfast collected concurrently through routine recording systems. It is demonstrated that there was a social process in ascertainment which renders the methods of adjusting for bias of ascertainment at best very complicated and at worst inapplicable.

Key words: Ascertainment, Congenital anomalies, Twins, Prevalence, Diagnosis, Social biases in recording, Epidemiological methods

INTRODUCTION

The investigation of the etiology of congenital anomalies (whether in singletons or in multiple births) depends upon the accurate definition of the general population. The identification of the affected population depends upon unbiased ascertainment. Note that whilst this paper is not confined to the ascertainment of congenital anomalies in twins — but considers the problems of ascertainment in general — the problems of ascertainment of congenital anomalies in singletons are also applicable to twins.

Certain methods have been adopted for dealing with problems of ascertainment of anomalies. The purpose of this paper is to show that the process of ascertainment is more complex than these methods typically assume, and therefore that greater refinement of method has to be sought. There are three critical factors. First, it is shown that the definition of the population of affected births is ambiguous and that the problem of tracing etiology is complicated by the systematic way in which anomalies may be missed at birth. Second, there may be discrepancies in recorded diagnosis between sources, discrepancies which lead to ambiguous categorisation. Third, in two populations studied, namely Aberdeen and Belfast, a social process is shown to be involved in ascertainment. All three factors are important in considering the extent to which proposed methods of adjusting for bias of ascertainment may appropriately be applied.

DEFINITION OF POPULATIONS

The definition of congenital anomalies has to be arbitrary, eg, the range of anomalies specified in the International Classification of Disease [22]. As yet, there is no universally agreed definition [20]. There are two reasons for this ambiguity. First, even some of the generally accepted congenital anomalies are not readily detectable at birth, eg, some heart defects. Second, some anomalous conceptuses are lost prior to birth so that affected births with anomalies are a biased sample of conceptuses with anomalies of early development. This is being increasingly studied [1,4,5,8,15,17,18].

It is, thus, necessary to range before and after birth to ascertain anomalies which would be and were present at birth. It is, therefore, difficult to argue for the exclusion of many other patterns of abnormal development of possibly similar etiology to the generally accepted congenital anomalies.

Problems of ascertainment may be considered at the level of conceptions and at the level of births. At the level of conceptions, there are the particular problems associated with abortions, whether spontaneous or induced. From the point of view of estimating the prevalence of congenital anomalies, there are two problems. First, unlike births, it is difficult to define the general population of conceptuses. Second, even if fetal material is recovered, it is often difficult to detect anomalies in spontaneous abortions because of maceration, and in terminations because of fragmentation. Many conceptuses with anomalies remain unidentified because of fundamental problems such as these.

The remainder of this paper concentrates upon births with anomalies, but it must be remembered that this is only a small sample of conceptuses with anomalies – the tip of the iceberg.

More generally, then, there are the two related problems of contact and detection. Contact is a blanket term covering the processes by which a conceptus or birth, which may or may not be affected, is referred to a source. In the two populations considered in this paper, and in many other studies of this type, these sources are agencies of service provision such as hospitals and genetic counselling clinics. It is obvious that if a birth with anomalies does not come into contact with one or more sources, there is no opportunity for recording a diagnosis. For example, Sweet [19] explained a rate of Down's syndrome as low as 1 an 56,000 in the Peiping area of China as being due to a reticence in consulting western physicians, especially among the poor. A reluctance to consult physicians is not unknown in western societies – MacKenzie and Wilson [12] comment: 'Every mother thinks her baby is perfect ...'. However, once contact is made, the detection or recording of an anomaly does not automatically follow. For example, in a study

in which physical examinations were performed at birth, 6 months, and 12 months, McIntosh et al [11] found that of all 465 affected births eventually identified in their series, only 201 (43.2%) 'presented signs, symptoms and RG (roentgenographic) abnormalities which were observable at birth'.

THE QUALITY OF THE DIAGNOSTIC DATA

There is a range of possibilities for dealing with the problems of ascertainment and, in particular, underascertainment. One method is population screening, but follow-up studies have shown that cases are missed by this approach [6,11].

The second method is the use of multiple sources of information. This method is widely used, but as Morton et al [13] comment: 'Whatever methods of examination and diagnostic criteria are used, in a large sample there will be some failures of detection or recording'. Clearly, this will also be true, however many sources are used.

To attempt to resolve this, statistical methods of adjusting for bias of ascertainment have been applied to data from multiple sources. There are two main approaches. In the first, models are fitted to the observed numbers of cases ascertained by each source [13]. In the second, which is a variation of capture-recapture methods, models are fitted to the observed numbers ascertained by particular combinations of sources [3,21]. In both these methods, the number of cases which have not been ascertained is estimated by assuming that the model which is the best fit to the observed numbers is also the best fit for the unobserved numbers. The validity of this assumption is the subject of the next section. Here, we consider the problem of the reliability of the diagnosis. To quote Morton et al [13] again, the '... methods make no allowance for misdiagnoses ...'. Misdiagnoses may be taken to include changes in manifestation and possible errors of recording.

In a study of data on cardiovascular anomalies in Northern Ireland over the years 1974-1978, the diagnoses of individuals were compared between a variety of sources. Comparison is made in Table 1 between the clinically validated diagnoses made after a follow-up for a minimum of three years for the Cardiovascular Special Study and two other sources: The Registrar General's Congenital Malformation Notification – an official voluntary notification system [14]; and the Maternity System – a hospital-based obstetric and neonatal pediatric recording system. Both these latter sources record in the perinatal period. It was found that in both comparisons, the later diagnosis differed from the earlier in a substantial number of cases – 41% in the case of the Registrar General and 55% in the case of the Maternity System.

Little else appears to have been published on the comparison of diagnoses between sources. However, the results of one study by Hook et al [7] in Upstate New York, are similar to those for Northern Ireland. In addition, discrepancies in diagnoses between birth and one year of age have been demonstrated for other anomalies, eg, in the USA by Hardy et al [6].

The study in Northern Ireland could be extended to other anomalies and to a wider range of sources. However, it should be noted that there are considerable analytic difficulties in terms of the range of combinations of code which may be recorded. For example, in the congenital anomalies 'chapter' of the 9th revision of the International Classification of Diseases [22] there are 168 four-digit codes. Thus, the number of different possible combinations of code from two sources when one code is recorded in each is in excess of 14,000. More complex combinations are possible. While only a small

fraction of the potential number of combinations is likely to be observed, it may be appreciated that the variety of codes, and of their possible permutations, renders comparison of recorded diagnoses between sources potentially difficult.

Despite these difficulties in principle, the discrepancies already noted suggest that the assumption that there are no, or virtually no errors of recording, is untenable. It has to be accepted that changes in manifestation and of its recording do and will occur. Any method which is proposed to adjust for bias of ascertainment has to take account of the possibility of substantial discrepancy in diagnosis between sources.

A SOCIAL PROCESS OF ASCERTAINMENT?

The fundamental assumption is that the model which is the best fit to the observed numbers of cases is also the best fit to the unobserved numbers.

The assumption cannot be tested directly. However, the assumption requires that the process of ascertainment by one source or a combination of sources is a random process, that is, the probability of ascertainment does not differ according to extraneous factors (such as sociodemographic characteristics of population groups or individuals whether alone or in interaction with characteristics of the recording agencies). Yet, a priori, this seems unlikely when the kind of errors that might occur are considered. Thus, for sources of the screening type, either variations in manifestations or errors in diagnosis or recording or any combination of these are possible. These problems of detection are likely to bias the observed affected population [10]. For sources of the 'opportunistic' type, in addition to these problems there is also the assumption that contact is random from among the affected population which seems implausible.

If the process of ascertainment is not random, then the magnitude and direction of bias need to be identified. Whilst the existence and nature of any bias cannot be tested for directly, it is possible to construct an indirect test.

The rationale for the analysis proceeds as follows. If the subpopulations of cases identified from each source separately were random samples of the total affected populations of both observed and unobserved cases, then the difference between the membership of the samples from the various sources should also be random. Equally, the subpopulations identified by each of the various sources should only differ randomly from the total observed affected population. Observation of significant associations between ascertainment by particular sources and sociodemographic variables would indicate that the differences between the subpopulations and the total observed population were nonrandom and that social processes were implicated.

The dependence of the probability of ascertainment in Aberdeen and Belfast for the period 1974-1979 on extraneous variables was analysed by regression methods. The aim of the analysis was to determine whether or not the overall inclusion of a variable or set of variables significantly affects that probability rather than the more usual estimation of particular coefficients for the purposes of prediction. The GLIM package [2] has been used as this provides a convenient way of testing for these inclusions.

Two groups of anomalies were considered in Aberdeen, anomalies of the nervous system other than dysraphic and anomalies of the cardiovascular system, and five groups in Belfast — the same two, plus dysraphic anomalies of the CNS, anomalies of the digestive system, and Down's syndrome. The analysis treated the ascertainment of a group of anomalies by a particular

TABLE 1. Comparison of Diagnoses between Sources: Northern Ireland 1974-1978

a

Diagnosis in Registrar General's Notification compared with that in Cardiovascular Special Study	N.	%
Agrees totally	35	33
Differs	44	41
Not specific: general diagnosis only	22	21
Insufficient information for comparison	6	6
Total	107	100

b

Diagnosis in Maternity System compared with that in Cardiovascular Special Study	N	%
Agrees totally	21	28
Differs	41	55
Not specific: general diagnosis only	11	15
Insufficient information for comparison	2	3
Total	75	100

TABLE 2. Role of Extraneous Variables for Aberdeen 1974-1979

EXTRANEOUS VARIABLES	OUTCOME VARIABLES Groups of Anomalies Ascertained by Particular Sources						
	Other Nervous System (N = 96)				Cardiovascular System (N = 170)		
	Neonatal records	Children's hospital	Preschool assessment centre	Other sources	Neonatal records	Children's hospital	Other sources
a Entry into Best Fit Regression Models							
* = enters best fit model							
− = association significant in univariate analysis but not in best fit model							
Maternal age/Year of birth	−		−			−	
Parity/Previous pregnancies	−						*
Class	−	−	*	−			
Baby's birth − Quarter	−		−				
Baby's birth − Year	−	−		*			*
Multiplicity							*
Associated anomaly	*	*		−		*	*
b Interaction Effects of Extraneous Factors upon Interdependencies							
Y = Yes N = No	N	N	✝	N	N	N	Y
✝ = No dependencies between sources							

TABLE 3. Role of Extraneous Variables for Belfast 1974-1979

OUTCOME VARIABLES
Groups of Anomalies Ascertained by Particular Sources

EXTRANEOUS VARIABLES	Dysraphic CNS (N=319)			Other nervous system (N=143)				Digestive system (N=150)			Cardiovascular system (N=418)				Down's syndrome (N=71)						
	Child health system	RG's notification	Maternity system	Child health system	RG's notification	Maternity system	Other sources	Child health system	RG's notification	Maternity system	Child health system	RG's notification	Maternity system	Other sources	Child health system	RG's notification	Maternity system	Medical genetics	Hospital records	Death certificate	Special care
a																					
Entry into Best Fit Regression Models																					
* = enters best fit model																					
— = association significant in univariate analysis but not in best fit model																					
Maternal age/Year of birth																		—			
Parity/Previous pregnancies		*																			
Class																					
Baby's birth – Quarter																					
Baby's birth – Year				*	*	*			*	*	*	*	*	*			*	—	*	*	*
Associated anomaly	*		*	*	*	*		—	*	*	*	*	*	*	*		*	—			
b																					
Interaction Effects of Extraneous Factors upon Interdependencies																					
Y = Yes N = No																					
≠ = No dependencies between sources	N	Y	Y	N	N	Y	N	N	N	Y	Y	Y	Y	Y	N	≠	≠	N	Y	N	N

source among all sources as an outcome variable. The analysis was restricted to sources which had recorded at least 20% of the cases either independently or in combination with other sources. This restriction was adopted in the absence of any more rigorous conventions which could be adopted in this context.

The extraneous factors included in the analysis were: woman's age or the year of her birth, number of previous pregnancies or parity, social class as classified by the Registrar General [16], quarter and year of baby's birth, multiplicity of birth, and presence of an anomaly of another type. In addition to these extraneous variables, as it appears unlikely that ascertainment by one source is independent of ascertainment by another [3,20], the possibility of this kind of dependency was also considered in the analysis.

The results of the regression analyses are presented in Tables 2 and 3. Tables 2a and 3a show that a variety of different extraneous variables do affect the source-specific probability of ascertainment in terms of reducing the 'unexplained' variance. Except for ascertainment in Aberdeen of anomalies of the nervous system other than dysraphic by the preschool assessment centre, and in Belfast of Down's syndrome by the Maternity System, the relative probability of ascertainment by one source was found to be dependet upon ascertainment by another. Interaction effects of extraneous factors upon these dependencies were found in a substantial number of cases for Belfast (Table 3b), but not for Aberdeen (Table 2b).

The nature of the influences of the extraneous variables renders the assumption that the model which is the best fit to the observed number of cases is also the best fit to the unobserved numbers unacceptable. For, two general observations can be made about the results (for a detailed presentation of which see [9]):

1) In the majority of analyses the presence or absence of an anomaly of another group entered the estimated models. But, if the process of ascertainment varies within the observed group according to presence or absence of additional anomalies, then it does not seem reasonable to assume that the process for observed and unobserved cases will be the same.

2) For many groups, the year of birth is also a significant variable, that is, the likelihood of ascertainment from specific sources varies from year to year. As there is no evidence that differences in the completeness of reporting between the sources varied from year to year, this implies that the absolute probability of ascertainment over all sources varies from year to year. As it is difficult to believe that the absolute likelihood of being affected varies from year to year in such a fashion, this variation suggests that social processes are implicated in ascertainment. That social processes are involved in the relative probability of ascertainment by any one source, makes it untenable to extrapolate from the observed numbers to the unobserved numbers.

CONCLUSIONS

This paper has raised three problems associated with ascertainment. First, the appropriate definition of the population; in particular, there is the problem posed by the unknown number of affected conceptuses which are aborted. Second, substantial discrepancies may occur in diagnoses between sources which are difficult to quantify precisely and which therefore make for ambiguous categorisations. Third, the source-specific probabilities of ascertainment are affected by a range of extraneous variables so that the total affected population cannot be estimated. Clearly, these problems are exacerbated in the

studies of anomalies amongst multiple births because of the small numbers involved.

In these circumstances, the investigation of the etiology of congenital anomalies, whether among multiples or singletons, is complicated. But, as none of the three problems raised above can be solved technically, the question which must then be asked is: how useful and justifiable is it to seek to refine our methods of ascertainment of congenital anomalies in births? More generally, can the etiology of congenital anomalies be inferred from epidemiological analysis?

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