Birth prevalence of malformations in members of different ethnic groups and in the offspring of matings between them, in Birmingham, England

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Abstract

***Study objectives* – The aims were: (1) to compare the birth prevalence of malformations in different ethnic groups and (2) to explore the reasons for the ethnic variations found by examining birth prevalence in the offspring of matings between ethnic groups.**

***Design* – Analysis of data from a register of malformations and register of births.**

***Setting* – Birmingham, England.**

***Subjects* – A total of 432 778 infants (including stillbirths) born in 1960–84.**

***Main results* – Significant differences ($p<0.01$) between ethnic groups were exhibited by the birth prevalence of neural tube defects (NTD), cleft palate, cleft lip, oesophageal atresia/fistula, hypospadias, hip dislocation, clubfoot, polydactyly, and syndactyly. In the offspring of matings between parents of European and Caribbean origin, the birth prevalence of NTD, cleft lip, hypospadias, hip dislocation, polydactyly, and syndactyly seemed more likely to be influenced by the ethnicity of both parents than by that of the mother alone. The reverse was true for the birth prevalence of NTD in subjects with one parent of Irish origin and one of British.**

***Conclusions* – Genetic differences may be responsible for Europeans being at lower risk of polydactyly and at higher risk of NTD, cleft lip, hypospadias, hip dislocation, and syndactyly than Caribbeans. Variations in the intrauterine environment are more likely to account for NTD being more common in Irish than in British subjects.**

(*J Epidemiol Community Health* 1995;**49**:171–179)

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Accepted for publication
November 1994

Many types of congenital malformations vary considerably in frequency between different places and races. As with the common cancers and other conditions which behave like this, studies of whether such variations persist when different races live in the same place[1,2] have yielded useful clues to the relative importance of genotype and environment in aetiology. However, even when the prevalence at birth of a malformation is much higher in subjects of one ethnic group than in those of another in the same place, it does not necessarily follow that this contrast reflects genetic differences between the two groups of infants. An alternative possibility is that the risk of malformation is affected by some aspect of the intrauterine environment which varies with ethnically related differences in genotype or lifestyle between mothers.

One way of exploring which of these alternatives is correct for each type of malformation is to examine its prevalence at birth in the offspring of matings between members of different ethnic groups. These offspring would be expected to resemble the ethnic group of their mothers rather than that of their fathers in respect of the birth prevalence of any malformation that was commoner in one ethnic group than another because of maternal factors. If on the other hand a malformation varied in frequency between ethnic groups because the infants themselves differed genetically, its birth prevalence in those of mixed ethnic group would be more likely to lie between the proportions affected in their parents' ethnic groups.

We have already reported that the prevalence of malformations at birth varies between subjects of European, South Asian, and Caribbean descent and between Europeans with British and Irish forebears in Birmingham, England.[3,4] Here, we add to these findings, focussing particularly on subjects of mixed ethnic group. So far as we know, there is no other centre for which the estimated birth prevalence of most malformations in the offspring of crosses between ethnic groups has been published.

Methods

This analysis is based on material from two sources – a health authority database covering all subjects (including stillbirths) born in 1950–84 to mothers resident in Birmingham, England, and a register in what was then the Department of Social Medicine at the University of Birmingham which recorded malformations diagnosed in the members of this cohort. These registers have been described elsewhere.[4]

The data analysed here do not include subjects from one area of present-day Birmingham (Sutton Coldfield), since this area was separately administered and not covered by our data sources before 1970. Subjects born in 1950–59 are also excluded from the analysis, since the health authority did not record ethnicity before 1960.

DATA ON ETHNICITY

Our source of these data was the health authority database. The authority's health visitors normally collected the information, but midwives and maternity hospital staff did so for stillbirths and infants who died without a health visitor seeing them. For subjects born in 1960–62, the database recorded whether the parents were both European, both South Asian (that is, from what are now India, Pakistan, and Bangladesh), both Caribbean, one European and one South Asian, or one European and one Caribbean. Subjects who could not be assigned to any of these categories were divided into two groups – others whose parents' ethnic groups were both known, and those with parents for one or both of whom this information was missing. From 1963, mothers' and fathers' ethnic groups were reported as separate items. A classification which distinguished between British, Irish, other Europeans, and other "whites" was also introduced in 1963, but in 1979 this classification was replaced by one which brought together these four groups under the heading "Caucasian".

In the present study, it was assumed for the subjects born in 1960–62 of European × South Asian and European × Caribbean matings that the European parent was the mother, since during the next three years this was true of most such subjects (95% and 97% respectively of the offspring of European × South Asian and European × Caribbean matings).[3] It was also assumed for the purpose of the present analysis that the parents of subjects born in 1979–84 who had been classified as Caucasian were all of European origin. Evidence that this was virtually true is provided by the distribution of subjects born in the 15 preceding years. Among these subjects, it was recorded that 99·8% of those whose maternal ethnic group would have been classified as Caucasian in 1979–84 had European mothers, and that 99·7% of those whose paternal ethnic group would have been so classified had European fathers.

DATA ON MALFORMATIONS

These data came from the University based register. During most of the study period, this register depended on three main sources: (1) reports of malformations on the forms used by health service staff to notify all births (the principal source used by the congenital malformation monitoring programme of England and Wales[5]); (2) health visitors' notifications of malformations known to them; and (3) records of admissions to local hospitals.[4] Cases were also ascertained from stillbirth and death certificates and necropsy reports. Birth notification forms were not used to ascertain cases until 1964, when the national monitoring programme began to operate.[5] Partly for this reason, and partly because the subjects born in 1960–63 were not followed up for as long as those born subsequently, the data on some types of malformations in subjects born in these years were not considered reliable enough to analyse.[3] The analysis of births in 1964–84, by contrast, covered virtually all conditions in the malformations chapter of the *International Classification of Disease* (1975 revision) except for infantile hypertrophic pyloric stenosis, skin tags, and birthmarks.

STATISTICAL ANALYSIS

The prevalence at birth of all malformed subjects and of each type of defect per 1000 total births was calculated for each of the ethnic categories to which subjects had been assigned. Among the categories in which the parents were of like ethnic group (termed "unmixed categories" in what follows), South Asians and Caribbeans were both compared with Europeans, and British with Irish, in respect of the birth prevalence of each type of defect. Comparisons were also carried out involving six "mixed" categories – the offspring of European × South Asian, European × Caribbean, and British × Irish matings, each represented by two categories (one where the mother came from the first mentioned ethnic group and the other where the father did). Each of these six mixed categories was compared in turn with the unmixed categories which were of the same ethnic groups as the mothers and fathers of the mixed category. The χ^2 test with Yates's correction was used to detect significant differences in comparisons where the expected number of affected subjects in each category exceeded five. Otherwise, the one sided probability of the result was calculated by Fisher's exact test, and doubled to give a two sided probability when appropriate.

Finally, in instances where a defect exhibited a difference in birth prevalence between two unmixed ethnic categories which was significant at the 1% level, its birth prevalence in all subjects with one parent from each unmixed category was compared with two "expected" figures:

(1) The midpoint between birth prevalence in the two unmixed categories (an estimate of what the birth prevalence in subjects of mixed origin might be if determined by their own genotypes);
(2) The birth prevalence that would have occurred in the subjects of mixed origin if each had the same risk as the unmixed category from which its mother came (as might be the case if risk depended on the intrauterine environment).

The formulae for these expected figures are $(P_a + P_b)/2$ and $(P_a n_{ab} + P_b n_{ba})/(n_{ab} + n_{ba})$ respectively, where P_a and P_b are the proportions of subjects in the unmixed ethnic categories a and b who were affected by the defect under consideration, and n_{ab} and n_{ba} are the total numbers of subjects in the mixed categories ab (offspring of group a mothers and group b fathers) and ba (offspring of reverse parentage). The two tail statistical probability for each difference between observed and expected figures was determined from χ^2 with Yates's correction when the expected number of affected subjects was five or more, and otherwise from the Poisson distribution.

Results

The study covered 432 778 subjects (including stillbirths) born in the period for which data on the more readily ascertainable types of malformations were analysed (1960–84). Among these subjects, 344 000 were born during the years when the data also covered other malformations (1964–84). These 344 000 subjects included 9829 (2·9%) in whom malformations were reported.

Table 1 shows how all these subjects were distributed between the main ethnic groups that were distinguished throughout the study. Both parents were reported to be South Asian in more than 12% and Caribbean in more than 7% of all subjects. European × South Asian and European × Caribbean matings accounted respectively for 0·7% and 1·7%. In most of these mixed matings the European partner was the female. The birth prevalence of malformed subjects varied significantly between the offspring of bilateral European matings and several other categories: it was relatively high in South Asians and in the group whose parents' origins were not both recorded, and low in the miscellaneous category and in that with European mothers and South Asian fathers.

During the years when the database distinguished between British, Irish, and other European parents (1963–78), 205 560 subjects were born to parents who were both of British or Irish origin. Table 2 shows that among these subjects 82% were of British origin and 11% of Irish origin on both sides, and that the British parent was the mother in two thirds of the 7% of mixed origins. Separate figures are again shown for subjects born during the years when the data on malformations were not confined to the more readily ascertainable types. The proportion of subjects in this subset in whom malformations were reported (2·7%) varied very little between those of British, Irish, and mixed origin.

Among all the categories listed in tables 1 and 2, the highest birth prevalence of malformations (4·8%) occurred in subjects whose parents' origins were not both recorded. This finding reflects the fact that a higher proportion of malformed subjects than of others died without being seen by health visitors and were therefore documented by maternity hospital staff and domiciliary midwives, who were less thorough in recording ethnic origin: the proportion of all subjects for whom this information was deficient was 13% for those who were stillborn or died neonatally and only 2% for others (table 3). The corresponding figures for malformed subjects are 10% and 2%. Only one parent's

Table 1 Ethnic distribution of births to women resident in Birmingham: 1960–84

Parental origin	*1960–84, all births (no)*	*1964–84*		
		All births (no)	*Malformed births*	
			No	*Prevalence/1000*
European	318 000	243 120	6690	27·5
South Asian	53 832	52 414	1689	32·2****
European mother, South Asian father	2927	2348	39	16·6** ††††
South Asian mother, European father	212	205	7	34·1††††
Caribbean	32 551	24 242	681	28·1
European mother, Caribbean father	6530	5539	142	25·6
Caribbean mother, European father	727	720	24	33·3
Miscellaneous (both parents recorded)	8195	7559	179	23·7*
Origin of one or both parents not recorded	9804	7853	378	48·1****
Total	432 778	344 000	9829	28·6

Significance of difference from birth prevalence in subjects whose parents were both classified as European: * 0·05>p>0·01; ** 0·01>p>0·001; **** 0·0001>p
Significance of difference from birth prevalence in subjects whose parents were both of the minority ethnic group indicated (applies only to groups of subjects born to one parent from minority group and one who was European): †††† 0·0001>p.

Table 2 Ethnic distribution of births to parents both of whom were of British or Irish origin: 1963–78

Parental origin	*1963–78, all births (no)*	*1964–78*		
		All births (no)	*Malformed births*	
			No	*Prevalence/1000*
British	169 274	154 701	4176	27·0
Irish	22 241	19 969	551	27·6
British mother, Irish father	9324	8480	237	27·9
Irish mother, British father	4721	4315	115	26·7
Total	205 560	187 465	5079	27·1

Table 3 Recording of ethnic origins: 1964–84

	All births		*Malformed births*	
	Stillbirths and neonatal deaths	*Others*	*Stillbirths and neonatal deaths*	*Others*
Total no born	8534	335 466	2004	7825
No of incompletely recorded origin:				
Total	1108	6745	207	171
Mother's origin recorded	500	2561	108	73
Mother's origin not recorded*	608	4184	99	98
Percentage of incompletely recorded origin	13·0	2·0	10·3	2·2

* The 4792 births for which there was no record of mother's origin included only 20 (none of them malformed) for which father's origin was recorded.

Table 4 Stillbirths and neonatal deaths by social class: 1963–78

Parents' origins	Social class				
	I–III (no)	IV and V		Unrecorded	
		No	(% among cases of known class)	No	(% among all cases)
Both recorded:					
Total	4236	2137	(33·5)	550	(7·9)
Both British	2798	842	(23·1)	281	(7·2)
Both Irish	339	234	(40·8)	29	(4·8)
Both South Asian	369	558	(60·2)	61	(6·2)
Both Caribbean	247	274	(52·6)	92	(15·0)
Other	483	229	(32·2)	87	(10·9)
Not both recorded:					
Total	451	216	(32·4)	375	(36·0)
Only recorded for mother	157	104	(39·8)	191	(42·3)
Not recorded for mother	294	112	(27·6)	184	(31·2)

ethnic group (almost always the father's) was missing for about two fifths of all subjects with deficient ethnic data, including more than half of the subset of this group who had malformations and did not survive to four weeks.

It is important to explore whether the subjects with deficient ethnic data among those who failed to survive included a disproportionate number from the smaller ethnic groups, since any such bias could distort the results of using the present data to study the birth prevalence of lethal malformations by ethnicity. One approach to this question is to consider the social class distribution of the non-survivors. This is examined in table 4 for the years when British and Irish parents were distinguished. Among all non-survivors of known social background, the percentage allocated to the least privileged classes (IV and V) was lower when both parents were British (23%) than when one or both were from the smaller ethnic groups (for which the figures shown range from 32% to 60%). If the smaller groups had been over-represented among the non-survivors whose ethnic data were deficient, a higher proportion of these than of other non-survivors would probably have been in social classes IV and V, whereas the proportions observed (again based on non-survivors of known social background) are 32·4% and 33·5% respectively. The former figure may not be a very reliable guide to the social class distribution of the whole group with deficient ethnic data, since social background was unknown for 36% of this group. However, the resemblance in distribution by social background between those with complete and deficient ethnic data whose social class was recorded does not suggest that the subjects whose ethnic data were deficient were sufficiently atypical ethnically to lead to serious bias.

When the non-survivors for whom ethnicity was not recorded for the mother are separated from those for whom only the father's ethnicity was missing, a much lower proportion of the former (28%) than of the latter (40%) are found to be in classes IV and V (table 4). This suggests that the proportion of subjects from the ethnic minorities was also relatively low in the group whose mothers' origins were not given and high in the group for whom information was only lacking about the father. However, table 5 shows that although subjects with Irish mothers are over-represented in the latter group, this group includes a smaller proportion of subjects with mothers from the ethnic minorities as a whole (29%) than that found in the offspring of matings whose paternal as well as maternal origins were recorded (37%). This is largely because the subjects whose mothers' ethnicity but not fathers' was known include hardly any whose mothers' origins were South Asian.

Table 5 Stillbirths and neonatal deaths for which origin of mother was known: 1963–78

Mother's origin	Father's origin known		Father's origin not known	
	No	(%)	No	(%)
Great Britain	4380	(63·3)	322	(71·2)
Ireland	759	(11·0)	77	(17·0)
South Asia	993	(14·3)	2	(0·4)
Caribbean	626	(9·0)	45	(10·0)
Other	165	(2·4)	6	(1·3)
Total	6923	(100)	452	(100)

In view of the above evidence that the ethnic minorities were in general not over-represented among the stillbirths and neonatal deaths for which ethnic group was not fully recorded, it seems reasonable to use the figures for children of known origin to examine the birth prevalence of malformations by ethnicity. The denominators used in calculating birth prevalence have already been presented (tables 1 and 2). The numerators are shown in table 6 and 7 respectively for the types of malformations which were studied in subjects born in 1960–84 and in 1964–84.

Table 8 shows the birth prevalence of each type of defect in subjects whose two parents' ethnic origins were broadly similar – both European, both South Asian, or both Caribbean – and in those within the European group whose parents were both British or both Irish. All the more heterogeneous categories – anomalies of heart and great vessels, intestinal obstruction, "other" eye, ear, genitourinary, and limb anomalies, and miscellaneous anomalies of other systems – are significantly more common in South Asians than in Europeans.

Even apart from the heterogeneous categories, most types of malformations exhibit variations in birth prevalence between unmixed ethnic groups that are significant at the 5% level. Five of these variations (spina bifida between Europeans and South Asians; accessory auricle between British and Irish subjects; and congenital cataract, rectal/anal atresia, and non-hiatal diaphragmatic hernia between Euro-

Table 6 Ethnic distribution of subjects with malformations for which data were available for 1960–84

Year of birth	*1960–84*								*1963–78*			
Mother's origin	*Any*	*Eu*	*SA*	*Eu*	*SA*	*Ca*	*Eu*	*Ca*	*Br*	*Ir*	*Br*	*Ir*
Father's origin	*Any*	*Eu*	*SA*	*SA*	*Eu*	*Ca*	*Ca*	*Eu*	*Br*	*Ir*	*Ir*	*Br*
Neural tube defects:												
Total affected	1495	1125	168	8	1	31	16	1	606	123	34	17
Anencephaly	645	455	79	3	0	17	8	0	246	51	15	8
Spina bifida (without anencephaly)	723	571	71	5	1	13	6	1	317	59	15	9
Encephalocele, iniencephaly	142	113	18	0	0	1	2	0	49	13	4	0
Cleft palate (lip intact)	268	211	40	1	0	7	4	0	106	15	2	4
Cleft lip (palate intact)	153	112	23	1	0	9	1	0	53	8	4	3
Cleft lip and palate	298	235	42	1	0	8	0	0	115	17	5	2
Oesophageal atresia/fistula	155	119	24	0	0	2	0	0	65	6	4	1
Rectal/anal atresia	239	175	38	0	0	7	2	1	89	11	8	3
Bilateral renal agenesis	90	54	10	0	0	4	0	0	35	2	1	1
Limb reduction deformities	217	160	27	0	0	17	0	0	92	7	4	4
Diaphragmatic hernia (not hiatal)	159	115	23	0	0	3	2	0	51	9	5	2
Exomphalos	155	107	18	0	0	11	1	0	56	5	1	2
Down's syndrome	618	466	78	4	0	36	6	1	236	43	15	10

Eu = European; SA = South Asian; Ca = Caribbean; Br = British; Ir = Irish.

Table 7 Ethnic distribution of subjects with malformations for which data were available only for 1964–84

Year of birth	*1964–84*								*1964–78*			
Mother's origin	*Any*	*Eu*	*SA*	*Eu*	*SA*	*Ca*	*Eu*	*Ca*	*Br*	*Ir*	*Br*	*Ir*
Father's origin	*Any*	*Eu*	*SA*	*SA*	*Eu*	*Ca*	*Ca*	*Eu*	*Br*	*Ir*	*Ir*	*Br*
Hydrocephaly (without spina bifida)	321	215	55	2	0	16	3	1	145	17	4	2
Congenital cataract	63	40	10	0	1	10	0	0	23	2	3	1
Miscellaneous eye anomalies	92	58	22	0	0	6	2	0	32	8	2	0
Accessory auricle	228	153	40	0	0	14	3	1	111	6	3	7
Miscellaneous ear anomalies	144	93	33	0	0	8	2	0	61	8	3	1
Anomalies of heart and great vessels	1286	883	222	6	2	84	14	1	615	74	34	12
Hiatus hernia	39	26	4	0	0	5	0	0	20	2	2	1
Intestinal obstruction	202	124	43	1	0	12	3	1	84	11	6	2
Hypospadias, epispadias	534	386	99	2	1	15	4	2	218	29	15	7
Miscellaneous genitourinary anomalies	445	284	84	2	0	31	6	1	194	26	11	6
Hip dislocation	791	673	72	2	0	16	5	3	417	43	24	6
Clubfoot	1936	1290	409	6	2	116	34	5	719	84	43	19
Polydactyly	657	232	112	2	0	231	41	5	153	17	9	3
Syndactyly	391	313	40	2	0	12	3	0	190	29	14	5
Miscellaneous limb anomalies	209	114	58	1	0	17	1	1	70	6	6	3
Anomalies not elsewhere classified	904	586	170	3	0	63	12	2	365	48	21	9

peans and Caribbeans) do not reach the 1% level of significance. The total number of comparisons (excluding those relating to heterogeneous categories of defects and those where the statistical probability fell below 1%) which were made between unmixed ethnic groups was 55, so that one would expect the results of two or three of these comparisons to

Table 8 Birth prevalence of malformations in different ethnic groups (per 1000 total births)

	Ethnic group of both parents				
	Eu	*SA*	*Ca*	*Br*	*Ir*
Anencephaly	1·43	1·47	0·52****	1·45	2·29**
Spina bifida (without anencephaly)	1·80	1·32*	0·40****	1·87	2·65*
Encephalocele, iniencephaly	0·36	0·33	0·03**	0·29	0·58*
Any neural tube defect(s)	3·54	3·12	0·95****	3·58	5·53****
Hydrocephaly	0·88	1·05	0·66	0·94	0·85
Congenital cataract	0·16	0·19	0·41*	0·15	0·10
Other eye anomalies	0·24	0·42*	0·25	0·21	0·40
Accessory auricle	0·63	0·76	0·58	0·72	0·30*
Other ear anomalies	0·38	0·63*	0·33	0·39	0·40
Anomalies of heart and great vessels	3·63	4·24*	3·47	3·98	3·71
Cleft palate (lip intact)	0·66	0·74	0·22**	0·63	0·67
Cleft lip (palate intact)	0·35	0·43	0·28	0·31	0·36
Cleft lip and palate	0·74	0·78	0·25**	0·68	0·76
Cleft lip ± cleft palate	1·09	1·21	0·52**	0·99	1·12
Oesophageal atresia/fistula	0·37	0·45	0·06**	0·38	0·27
Hiatus hernia	0·11	0·08	0·21	0·13	0·10
Intestinal obstruction	0·51	0·82**	0·50	0·54	0·55
Rectal/anal atresia	0·55	0·71	0·22*	0·53	0·49
Hypospadias, epispadias†	3·06	3·68	1·23***	2·72	2·79
Bilateral renal agenesis	0·17	0·19	0·12	0·21	0·09
Other genitourinary anomalies	1·17	1·60*	1·28	1·25	1·30
Hip dislocation	2·77	1·37****	0·66****	2·70	2·15
Clubfoot	5·31	7·80****	4·79	4·65	4·21
Polydactyly	0·95	2·14****	9·53****	0·99	0·85
Syndactyly	1·29	0·76**	0·50**	1·23	1·45
Limb reduction deformities	0·50	0·50	0·52	0·54	0·31
Other limb anomalies	0·47	1·11****	0·70	0·45	0·30
Diaphragmatic hernia (not hiatal)	0·36	0·43	0·09*	0·30	0·40
Exomphalos	0·34	0·33	0·34	0·33	0·22
Down's syndrome	1·47	1·45	1·11	1·39	1·93
Miscellaneous anomalies	2·41	3·24***	2·60	2·36	2·40

Significance of difference from birth prevalence in subjects whose parents were both classified as European (British where figures relate to subjects of Irish parentage): * 0·05>0·01; ** 0·01>p>0·001; *** 0·001>p>0·0001; **** 0·0001>p.
† Per 1000 male births
Eu = European; SA = South Asian; Ca = Caribbean; Br = British; Ir = Irish.

lie between the 5% and 1% levels even if there was no non-random variation. The five findings of this kind cannot therefore be regarded as very strong evidence of ethnic differences.

The same is true of the findings observed when the birth prevalence statistics for unmixed ethnic groups which did not differ significantly at the 1% level are compared with figures for the mixed ethnic categories to which the unmixed groups were related. The results of these comparisons are not tabulated here. Differences that were significant at the 5% level only occurred:

(1) Between the birth prevalence of accessory auricle in the Irish (0·3/1000) and in the offspring of Irish mothers and British fathers (1·6/1000), for which $p = 0·0035$;
(2) Between the birth prevalence of cataract in both Europeans and South Asians (0·2/1000) and in the offspring of South Asian mothers and European fathers (4·9/1000 based on a single case); $p = 0·034$ and 0·042 for the differences between the mixed group and the Europeans and South Asians respectively.

Instead of there being more significant differences here than would be expected to occur by chance, the expected number is greater: four mixed-unmixed comparisons (one between each of two unmixed groups and each of two mixed categories) were carried out in relation to each of the 55 comparisons between unmixed groups to which the last paragraph refers, and 11 (5%) of these 220 comparisons would be expected to yield significant results by chance.

Far more of the figures in table 8 differ significantly from each other at the 1% level than would be expected to do so by chance. Caribbeans were 10 times as likely as Europeans to be affected by polydactyly, while neural tube defects (NTD), cleft palate, cleft lip, oesophageal atresia/fistula, hypospadias (with which the much rarer condition of epispadias was classified), hip dislocation, and syndactyly were more than twice as prevalent in Europeans as in Caribbeans. South Asians were at intermediate risk of hip dislocation, polydactyly and syndactyly, but had a higher birth prevalence of clubfoot than the other two groups. Among Europeans, the Irish were more prone than the British to NTD.

The birth prevalence statistics which exhibited these differences are compared in table 9 with findings for the mixed ethnic categories to which these unmixed groups were related. Significant differences between individual mixed categories and the relevant unmixed groups are indicated. The overall birth prevalence of each relevant defect in the offspring of matings between unmixed ethnic groups (irrespective of which parent was from which group) is also shown, together with estimates of the probability of this prevalence ratio (or a ratio further from that expected) occurring in two alternative situations – one where the risk to subjects of mixed ethnicity was affected equally by the mother's and father's ethnic groups, and the other where the only parent whose ethnic group affected the risk was the mother.

The figures in table 9 suggest that differences in the intrauterine environment may be responsible for clubfoot being more common in South Asians than in Europeans. Its birth prevalence among subjects of mixed European-South Asian descent is low where the mother was European and high where she was South Asian, and the proportion of subjects affected in the two mixed groups combined differs significantly ($p = 0·04$) from the midpoint between birth prevalence in the two unmixed groups but not from the figure expected if birth prevalence was the same as in the mother's group.

Conversely, the findings for the mixed groups make it seem unlikely that maternal factors alone are responsible for polydactyly being

Table 9 Malformations for which the birth prevalence in two unmixed ethnic groups differed significantly at the 1% level: birth prevalence in unmixed and mixed groups, and ratios of observed birth prevalence in each pair of mixed groups to two "expected" figures – E_1 (the midpoint between birth prevalence in the two related unmixed groups) and E_2 (the birth prevalence that would have occurred in the two mixed groups combined if each had experienced the same birth prevalence as the unmixed group to which its mothers were related)

	Birth prevalence/1000 total births, by ethnic group								
	Parents both Eu	*Parents both SA*	*Mother Eu, father SA*	*Mother SA, father Eu*	*All Eu × SA matings (O)*	O/E_1	*p for* O/E_1 (p_1)	O/E_2	*p for* O/E_2 (p_2)
Hip dislocation	2·77	1·37	0·85	0·00	0·78	0·38	0·23	0·29	0·10
Clubfoot	5·31	7·80	2·56††	9·76	3·13	0·48	0·04	0·57	0·14
Polydactyly	0·95	2·14	0·85	0·00	0·78	0·51	0·45	0·75	0·78
Syndactyly	1·29	0·76	0·85	0·00	0·78	0·76	0·78	0·63	0·60
	Parents both Eu	*Parents both Ca*	*Mother Eu, father Ca*	*Mother Ca, father Eu*	*All Eu × Ca matings (O)*				
Any neural tube defect(s)	3·54	0·95	2·45††	1·38	2·34	1·04	0·97	0·71	0·20
Cleft palate (lip intact)	0·66	0·22	0·61	0·00	0·55	1·25	0·78	0·89	1·00
Cleft lip (±cleft palate)	1·09	0·52	0·15*	0·00	0·14	0·17	0·07	0·13	0·03
Oesophageal atresia/fistula	0·37	0·06	0·00	0·00	0·00	0·00	0·28	0·00	0·19
Hypospadias, epispadias§	3·06	1·23	1·42	5·12	1·87	0·87	0·88	0·66	0·38
Hip dislocation	2·77	0·66	0·90*	4·17*	1·28	0·75	0·50	0·51	0·07
Polydactyly	0·95	9·53	7·40****	6·94†††	7·35	1·40	0·03	3·79	<10 [10]
Syndactyly	1·29	0·50	0·54	0·00	0·48	0·54	0·37	0·40	0·14
	Parents both Br	*Parents both Ir*	*Mother Br, father Ir*	*Mother Ir, father Br*	*All Br × Ir matings (O)*				
Any neural tube defect(s)	3·58	5·53	3·65+	3·60	3·63	0·80	0·12	0·86	0·30

Significance of differences from birth prevalence in mothers' ethnic group: * 0·05>p>0·01; **** 0·0001>p.
Significance of difference from birth prevalence in fathers' ethnic group: † 0·05>p>0·01; †† 0·01>p>0·001; ††† 0.001>p>0·0001.
§ Prevalence per 1000 male births.
Eu = European; SA = South Asian; Ca = Caribbean; Br = British; Ir = Irish.

more common and cleft lip and hip dislocation less common in Caribbeans than in Europeans. The birth prevalence of polydactyly in each mixed group is lower than in Caribbeans and significantly higher than in Europeans. Hip dislocation is significantly commoner in the offspring of Caribbean mothers and European fathers than in Caribbeans, and significantly less common in subjects with European mothers and Caribbean fathers than in Europeans. The latter is also true of cleft lip. The probability that the numbers observed in the two mixed groups combined would have occurred if the risks for these groups had been the same as for their mothers (p_1 in table 9) is only 0·03 for cleft lip, 0·07 for hip dislocation, and $<10^{-10}$ for polydactyly. The probability of the observed numbers occurring if the risks lay midway between those for the two unmixed groups (p_2) is higher than p_1 for each of these defects, although low enough in polydactyly (0·03) and cleft lip (0·07) to suggest that the true risks to subjects of mixed ethnic group are higher for polydactyly and lower for cleft lip than the midpoints between the risks to the two unmixed groups.

The figures yield less evidence as to the origins of the other nine differences between unmixed groups. In the relevant mixed groups, none of the defects that exhibited these differences is significantly more or less common either than the midpoint between the risks in the fathers' and mothers' ethnic groups or than the figure expected if only maternal group influenced risk. However, in four of these nine instances p_1 is more than twice p_2 – that is, the birth prevalence observed in the mixed groups would be more than twice as likely to occur if the true risk was midway between the maternal and paternal figures as it would if the risk to the mother's group applied. The defects that exhibit this pattern are hip dislocation in subjects with one European and one South Asian parent, and NTD, hypospadias and syndactyly in the offspring of European-Caribbean matings. The reverse is true of the birth prevalence of NTD after British-Irish matings. Despite this difference, the category with European mothers and Caribbean fathers and that with British mothers and Irish fathers (the two largest mixed categories) are alike in that each differs significantly from the ethnic group of its fathers in respect of the birth prevalence of NTD.

Another feature of table 9 is that nine of the 13 observed figures for mixed groups with which the last five columns are concerned are lower than either of the expected values with which they are compared – that is, O/E_1 and O/E_2 are both below unity. These nine figures include all the four for the offspring of European-South Asian matings, which recalls the relative rarity of malformations of any kind in these subjects (table 1).

Discussion

RELIABILITY OF DATA

The records of ethnicity on which this study depends can be criticised on several grounds – firstly, that too imprecise an ethnic classification was used, secondly, that the staff who recorded the data must sometimes have made mistakes (especially about father's ethnicity), and, thirdly, that in nearly 4% of malformed subjects the ethnic group of one or both parents was not stated. The first criticism applies particularly to the use of a single category for all South Asians, since in Birmingham this group includes Hindus, Moslems, and Sikhs, whose life styles differ substantially even though almost all originated in Pakistan and the adjacent Indian Punjab.[2]

Despite these limitations, it seems reasonable to regard as genuine the highly significant variations observed when the ethnic categories which could be distinguished were compared. Mistakes which result in subjects being assigned to the wrong ethnic groups are more likely to reduce variations in birth prevalence between groups than to contribute to them. The relatively high frequency of missing ethnic data in malformed subjects reflected an even higher frequency in cases of stillbirth and neonatal death (table 3), and reasons have already been given for thinking that the stillborn and dead subjects with missing ethnic data were not atypical enough for their exclusion from the population that was analysed by ethnicity to have seriously biased the results. The most atypical feature to which the available evidence (tables 4 and 5) points is that the subjects whose fathers' ethnicity was not stated may have included relatively few South Asians; but even if the subjects with missing ethnic data had all been European, the total birth prevalence of cases of malformation among Europeans (7068/250 973, or 28·2/1000, according to the figures in table 1) would have been only 2·5% higher than the figure for those recorded as European (27·5/1000), and much lower than the South Asian figure (32·2/1000).

BIRTH PREVALENCE OF ALL MALFORMED SUBJECTS

As in an earlier Birmingham study,[6] the South Asians were the only ethnic group studied in which malformed subjects as a whole were significantly more prevalent than in Europeans. Other British studies indicate that mortality from malformations is relatively high in the offspring of women from South Asia (especially those of Pakistani origin) and that some at least of the excess cases are due to homozygosity for autosomal recessive genes.[7-11] One would expect recessively inherited disorders to be especially common in subjects of Pakistani descent, since Pakistani marriages are often consanguineous[12,13]; and it may be because the more heterogeneous categories of malformations in the present series included recessive conditions that they were most prevalent among the South Asians (table 8).

In contrast to the subjects whose parents were both South Asians, the offspring of European mothers and South Asian fathers included a relatively small proportion with malformations (table 1). Perhaps this finding too reflects the frequency of recessive genetic dis-

orders, since the greater the genetic differences between parents the lower the expected level of homozygosity in their offspring.

BIRTH PREVALENCE OF SPECIFIC TYPES OF MALFORMATIONS

Among the nine relatively homogeneous categories of malformations that exhibited variations in birth prevalence that were significant at the 1% level, there are two – cleft palate with intact lip and oesophageal atresia/fistula – for which our findings provide no real basis for speculating about the relative importance of genotype and intrauterine environment as influences on birth prevalence. These two defects were more common in Europeans than in Caribbeans, and similar trends between white and black infants have been observed in Atlanta, Georgia.[14] For both these defects in the present study, neither Europeans nor Caribbeans differed significantly in birth prevalence from the offspring of matings between them, and p_1 (the probability that the observed birth prevalence in these offspring would have occurred if their true risk was midway betwen the risks to the mothers' and fathers' ethnic groups) did not differ much from p_2 (the probability of this observed birth prevalence occurring if the true risk was the same as in the mothers' group).

Among the six defects in which p_1 for the offspring of European-Caribbean matings was more than twice p_2, NTD are considered later. For the other five – cleft lip, hip dislocation, polydactyly, hypospadias, and syndactyly – birth prevalence in subjects of mixed ethnic group seems more likely to be related to the ethnicity of both parents than to that of the mother alone. This would suggest that the ethnic differences in the risks of these defects mirror variations in the genotype of the conceptus rather than in its intrauterine environment. The case for this hypothesis is strongest in cleft lip, hip dislocation, and polydactyly. Each of these differed significantly in birth prevalence between at least one mixed category and the ethnic group of this category's mothers, and in hip disclocation p_1 was more than twice p_2 for the offspring of European-South Asian as well as of European-Caribbean matings.

The differences between the risks of these five defects to the Europeans and Caribbeans in the present series (polydactyly being much commoner in Caribbeans and the other four more common in Europeans) are similar to trends between white and black subjects reported for all five defects in the United States.[14 15] The patterns we found in South Asians – risks of hip dislocation, polydactyly and syndactyly which were intermediate between the European and Caribbean risks – do not seem to have been described in other populations. The evidence from elsewhere that the genotype has more influence than the environment on risk is stronger for cleft lip, polydactyly, and syndactyly than for hypospadias and hip dislocation. It seems from epidemiological observations in many parts of the world that the birth prevalence of cleft lip is relatively low in Negroid, intermediate in Caucasoid, and high in Mongoloid populations wherever they live, suggesting that it is influenced much more by the genetic differences between ethnic groups than by the environment.[1] Less is known about how the birth prevalence of the other four defects varies across the world; but there is genetic evidence for autosomal dominant inheritance of the common types of both polydactyly (postaxial polydactyly) and syndactyly (cutaneous syndactyly of fingers 3 and 4 and toes 2 and 3),[16] and for multifactorial causation involving both genotype and environment in hypospadias[17] and hip dislocation.[18] Links between the last two conditions and the environment are also suggested by reports that hypospadias became more common in several European countries during the 1970s, and by many associations between the frequency of hip dislocation and factors that affect the position in which the joint is held before or after birth.[19]

It remains to consider our findings for clubfoot and NTD in relation to previous work. Like the European-South Asian differences observed in hip dislocation, polydactyly, and syndactyly, our finding that clubfoot was commoner in South Asians than in Europeans does not seem to be matched by any reports from other centres. Although our figures for the offspring of European-South Asian matings initially suggested that the high risk of clubfoot in South Asians was of environmental origin, this risk could alternatively be increased by the high frequency of consanguinity in this group. The reason why the latter hypothesis fits the low birth prevalence of clubfoot in the subjects of mixed ethnicity is that their parents would inevitably not be consanguineous. The genetic background to each of the main types of clubfoot is believed to be multifactorial,[20] which is consistent with them being more common in the offspring of consanguineous matings.[21] However, the fact that clubfoot and several other defects were less common in the offspring of matings between two ethnic groups than in either parent's group (table 9) also raises two further possibilities: trends of this kind would be likely to occur if in these groups similar-appearing malformations had come under the control of different genetic mechanisms during the millenia since the groups diverged, or if being heterozygous at a high proportion of gene loci was protective.[22]

Our findings for NTD match much other evidence that these defects are more common in people of British descent than in those whose ancestors came from sub-Saharal Africa, and more common still in those of Irish origin.[23] These observations cannot be due to ethnic differences in the extent to which antenatal diagnosis and induced abortion of fetuses with NTD are practised, since the data were collected largely when the impact of these practices on birth prevalence was negligible. In Birmingham, although this impact had become very marked by the last year of the study (1984), it was imperceptible before 1979.[4] Births in 1979 onwards were not included in our comparison of subjects of British and Irish origin. The difference reported above between subjects

of Caribbean and European descent was based on all births in 1960–84, but the pattern was the same in 1960–78 (when 1·05/1000 Caribbeans and 3·90/1000 Europeans were affected by NTD) as in the whole study period.

After migration between areas with different risks of NTD, published studies suggest that birth prevalence in the migrants' descendents eventually becomes more like that in their Caucasoid neighbours if the migrants are themselves Caucasoid, but not if they are Negroid.[1] This pattern led one of us to suggest that the variation in birth prevalence between different Caucasoid populations was due at least in part to environmental differences, but that genetic factors were largely responsible for NTD being less common in Negroids than in English and US Caucasoids.[24] The present study has reinforced these suggestions. Among its findings, the difference between Europeans and Caribbeans seems more likely to have arisen from variations in the genotype of the conceptus than from environmental differences, since p_1 is much greater than p_2. The reverse is true for our finding of a higher risk to Irish than to British subjects.

CONCLUSION

Some caution is needed in interpreting data on the offspring of matings between parents from different ethnic groups, since one cannot totally exclude the possibility that these parents are selected for attributes which influence the risk of malformations in their offspring. Despite this reservation, it seems reasonable to regard our findings in these offspring as useful evidence, firstly that factors in the intrauterine environment may be responsible for the high birth prevalence of NTD in subjects of Irish descent, and secondly that differences in genotype betwen concepti are more likely to account for subjects of European origin being more liable than Caribbeans to NTD, cleft lip, hip dislocation, hypospadias, and syndactyly and less liable to polydactyly. These suggestions are strengthened by their consistency with the other epidemiological evidence as to the relative importance of genotype and environment that is available for NTD and cleft lip (the defects for which we have most evidence of this kind).

Our data on subjects of mixed ethnicity provide less ground for speculation about the sources of variation in birth prevalence between Europeans and South Asians, firstly because there were fewer matings between these groups than between the others examined, and secondly because of the high level of consanguinity among the Pakistanis in the South Asian group. This does not extend to mixed matings, and complicates the interpretation of variations between the offspring of these matings and their parental groups.

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