Risk factors for congenital anomaly in a multiethnic birth cohort: an analysis of the Born in Bradford study

Eamonn Sheridan, John Wright, Neil Small, Peter C Corry, Sam Oddie, Catherine Whibley, Emily S Petherick, Teena Malik, Nicole Pawson, Patricia A McKinney, Roger C Parslow

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Bradford Institute for Health Research, Bradford Royal Infirmary, Bradford, UK (E Sheridan MBChB, Prof J Wright MBChB, P C Corry MBBCh, S Oddie MBChB, E S Petherick PhD, N Pawson PhD)**; Department of Genetics, Wellcome Trust Brenner Building, St James's University Hospital, Leeds, UK** (E Sheridan)**; School of Health Studies, Horton A Building, University of Bradford, Bradford, UK** (Prof N Small PhD)**; Paediatric Epidemiology Group, Division of Epidemiology and Biostatistics, Leeds Institute of Genetics Therapeutics and Health, University of Leeds, Leeds, UK** (C Whibley PhD, Prof P A McKinney PhD, R C Parslow PhD)**; and Yorkshire Regional Genetics Service, Chapel Allerton Hospital, Leeds, UK** (T Malik RGN)

Correspondence to: Dr Eamonn Sheridan, Leeds Institute of Biomedical & Clinical Sciences, Section of Genetics, Wellcome Trust Brenner Building, St James's University Hospital, Beckett Street, Leeds LS9 7TF, UK **medesh@leeds.ac.uk**

Summary

Background Congenital anomalies are a leading cause of infant death and disability and their incidence varies between ethnic groups in the UK. Rates of infant death are highest in children of Pakistani origin, and congenital anomalies are the most common cause of death in children younger than 12 in this ethnic group. We investigated the incidence of congenital anomalies in a large multiethnic birth cohort to identify the causes of the excess of congenital anomalies in this community.

Methods We obtained questionnaire data from the mothers of children with one or more anomalies from the Born in Bradford study, a prospective birth cohort study of 13 776 babies and their families in which recruitment was undertaken between 2007 and 2011. Details of anomalies were prospectively reported to the study and we cross checked these details against medical records. We linked data for anomalies to maternal questionnaire and clinical data gathered as part of the Born in Bradford study. We calculated univariate and multivariate risk ratios (RRs) with 95% CIs for various maternal risk factors.

Findings Of 11 396 babies for whom questionnaire data were available, 386 (3%) had a congenital anomaly. Rates for congenital anomaly were 305·74 per 10 000 livebirths, compared with a national rate of 165·90 per 10 000. The risk was greater for mothers of Pakistani origin than for those of white British origin (univariate RR 1·96, 95% CI 1·56–2·46). Overall, 2013 (18%) babies were the offspring of first-cousin unions. These babies were mainly of Pakistani origin—1922 (37%) of 5127 babies of Pakistani origin had parents in first-cousin unions. Consanguinity was associated with a doubling of risk for congenital anomaly (multivariate RR 2·19, 95% CI 1·67–2·85); we noted no association with increasing deprivation. 31% of all anomalies in children of Pakistani origin could be attributed to consanguinity. We noted a similar increase in risk for mothers of white British origin older than 34 years (multivariate RR 1·83, 95% CI 1·14–3·00). Maternal education to degree level was protective (0·53, 95% CI 0·38–0·75), irrespective of ethnic origin.

Interpretation Consanguinity is a major risk factor for congenital anomaly. The risk remains even after adjustment for deprivation, and accounts for almost a third of anomalies in babies of Pakistani origin. High levels of educational attainment are associated with reduced risk in all ethnic groups. Our findings will be valuable in health promotion and public health, and to those commissioning antenatal, paediatric, and clinical genetic services. Sensitive advice about the risks should be provided to communities at increased risk, and to couples in consanguineous unions, to assist in reproductive decision making.

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Introduction

Infant mortality varies substantially between ethnic groups in the UK, with the highest rates noted in babies of Pakistani origin.[1] Overall, the most common causes of infant mortality are immaturity-related disorders;[1] however, in babies of Pakistani origin, the most common cause is congenital anomaly.[1] Every year, about 90 extra deaths occur because of congenital anomalies in infants born to Pakistani mothers in England and Wales than would have been expected in this group if they had the same mortality rate as infants born to white British mothers.[2] Causes of this excess are unclear.

Findings from a UK study in 1993 suggested that consanguineous unions were the cause of the excess in congenital anomalies in babies of Pakistani origin,[3] but no adjustments were made for deprivation, which has been associated with increased risk.[2] Although women of Pakistani origin are more likely to live in regions of high deprivation and to earn less than their white British counterparts,[4] the disparity in risk of congenital anomaly cannot be wholly explained by socioeconomic differences between groups. For example, parents of infants of Bangladeshi origin have a similar socioeconomic profile to those of infants of Pakistani origin, but the risk of congenital anomalies is much lower.[2] Causes of the excess risk in babies of Pakistani origin continue to be debated in the UK by the Chief Medical Officer,[5] in the medical literature,[6–8] and often heatedly in the public press.[9,10] However data to clarify the issue are scarce.

Bradford is an ethnically diverse city in the north of England where levels of deprivation are high. Infant mortality in Bradford has been consistently above the

national average, peaking at 9·4 deaths per 1000 livebirths in 2003, when the national average was 5·5 deaths per 1000 livebirths.[11] Levels of congenital anomalies and childhood disability in Bradford are among the highest in the UK,[12–14] and an excess of deaths occur in babies of Pakistani origin because of such anomalies.[11] We analysed the Born in Bradford dataset, and a separate substudy of babies born with anomalies, to investigate the causes for the excess of congenital anomalies in this community.

Methods

Born in Bradford cohort

The Born in Bradford study is an ongoing prospective birth cohort study that recruited 12 453 women with 13 776 pregnancies between 2007 and 2011, and monitors them, their infants, and their partners.[15] The dataset contains information about demographics (including deprivation) and clinical outcomes and risk factors. To be eligible for the study, women had to attend the antenatal service in Bradford between March, 2007, and December, 2010, and be booked to give birth in Bradford. Full details of the study methods have been previously reported.[15] All women booked for delivery in Bradford were offered a 75 g oral glucose tolerance test (OGTT) at about 26–28 weeks' gestation. Women who attended the test completed an interviewer-administered questionnaire and had their height and weight measured. Interviews were done in English and a range of south Asian languages (including Mirpuri, Bengali, and Punjabi). A smaller group of women were recruited at the time of the birth of their baby; these women were less likely to complete a questionnaire than were those recruited at the time of the OGTT.

Ethics approval for the study was provided by Bradford Local Research Ethics Committee (reference 06/Q1202/48). Women were provided with information about the study at their fist antenatal appointment. At the time of the OGTT, women were approached to participate in the study. They were provided with written information about the study and were able to discuss it with a research coordinator. Women whose first language was not English were offered the opportunity to discuss the study with a native speaker of their own language. English, Urdu, Punjabi, and Mirpuri speaking coordinators were available at all times.

Case ascertainment and coding methods

All individuals were confirmed as participants of the Born in Bradford study before clinical data acquisition. Babies with congenital anomalies, including metabolic disorders, were prospectively identified by clinicians working at Bradford Teaching Hospitals Foundation Trust (BTHFT), with use of a standardised notification system. Systematic case-note review was done independently by a community paediatrician (PCC), a neonatologist (SO), and a clinical geneticist (ES) to confirm all cases by examination of patient notes after an anomaly was reported. Investigators also obtained information about babies born to mothers participating in the Born in Bradford study who delivered outside BTHFT.

We coded anomalies according to the International Classification of Diseases version 10. We categorised anomalies by congenital anomaly group (the organ system affected), subtype (the individual disorder) and syndrome (when applicable) according to EUROCAT guidelines.[16] We excluded babies with minor anomalies in accordance with the EUROCAT classification scheme (appendix). Cases were reviewed and assigned with a hierarchical classification system, with modification to include data for the metabolic disorders collected. We used six categories for classification of anomalies: single anomalies, including various anomalies for which secondary anomalies were attributable to one primary anomaly; several anomalies within the same anomaly group (eg, more than one heart anomaly); metabolic disorders; syndromal associations; chromosomal syndromes; and more than one unrelated anomaly.

See **Online** for appendix

For more on the **Born in Bradford study** see www.borninbradford.nhs.uk

Risk factors

We investigated a range of risk factors: ethnic origin (white British, Pakistani, other); age of mother (<20, 20–34, >34 years); educational attainment (less than five General Certificate of Secondary Education [GCSE] equivalents; five or more GCSE equivalents at grades A–C, two Advanced Level equivalents; diploma, degree, or higher degrees; other; unknown; foreign unknown); socioeconomic status (Index of Multiple Deprivation 2010 [IMD][17]); smoking (number of cigarettes per day smoked during pregnancy or during the 3 months before pregnancy [none, one to five, six to ten, 11–20, >20]); alcohol consumption (drank alcohol during pregnancy or the 3 months before pregnancy [yes or no]); and consanguinity (first cousin, other blood relation [less than first cousin], or non-consanguineous). We categorised results for body-mass index (BMI) and OGTT in accordance with WHO guidelines.[18,19]

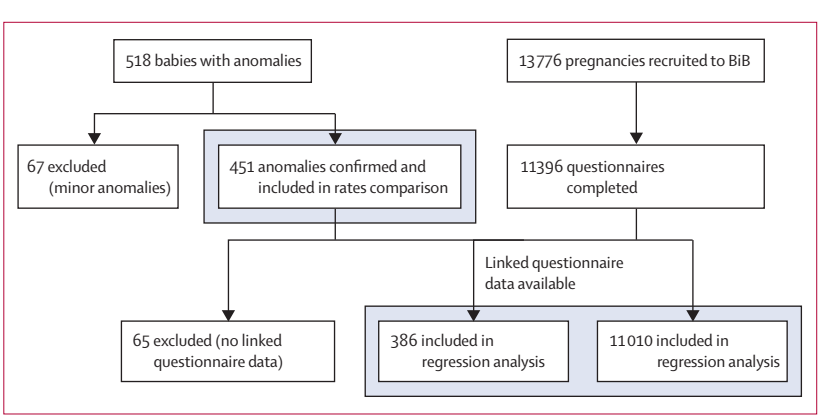

Figure: **Flow diagram of steps in analysis**
BiB=Born in Bradford.

Statistical analysis

For risk factors, we estimated univariate risk ratios (RRs) and 95% CIs for the occurrence of an anomaly with Poisson regression with robust error variance.[20] We calculated risks for all ethnic groups and separately for white British, Pakistani, and other groups. We included risk factors in the multivariate analysis to estimate adjusted RRs with the exception of the BMI test results, which were not significantly associated with the occurrence of anomalies in the univariate analyses. We did a test for interaction to investigate the association between consanguinity and IMD score, which was treated as a continuous variable. We did analyses with Stata (version 12).

We calculated the population attributable risk (PAR) for the offspring of first-cousin parents in the Pakistani community as:

$$\mathrm{PAR} = \frac{r(\mathrm{RR}-1)}{1+r(\mathrm{RR}-1)}$$

where r is proportion of population exposed and RR is the adjusted risk ratio.

Role of the funding source

The sponsor of the study had no role in study design; data collection, analysis, or interpretation; or writing of the report. ES, RCP, CW, JW, and ESP had full access to all the data in the study and all authors had final responsibility for the decision to submit for publication.

Results

The figure shows a flow diagram for inclusion of cases. 518 babies were reported with an anomaly (figure). The appendix provides details of recorded anomalies. Comparison of rates with other regional registers was based on 740 anomalies noted in the 451 babies remaining after exclusion of those with a minor anomaly (figure). We based all other analyses on the 386 cases for whom Born in Bradford questionnaire data were available. The comparison group were the 11 010 pregnancies for which questionnaire data were available but the resulting babies had no anomaly (figure).

Congenital anomalies were identified in 386 (3%) of 11 396 cases for whom questionnaire data were available (figure). Table 1 compares prevalence of anomalies in Bradford with national data reported by the British Isles Network of Congenital Anomaly Registers (BINOCAR). In 2010, BINOCAR reported a prevalence (based on 2009 data) for congenital anomalies, excluding chromosomal disorders, of 165·90 per 10 000 livebirths (table 1). We report a rate of 305·74 per 10 000 that specifically excludes babies with chromosomal or metabolic disorders reported to the register (table 1).[21] BINOCAR registers babies with metabolic disorders only if they also have a structural anomaly. The total prevalence reported by the Born in Bradford register includes infants diagnosed with chromosomal defects and those with metabolic disorders, whether they had a structural anomaly or not (table 1). BINOCAR registrations include terminations of pregnancy for fetal anomaly and miscarriages with fetal anomalies. Because recruitment to the Born in Bradford study is at 26–28 weeks' gestation,

	All livebirths in the BiB cohort (n=13 776)		BINOCAR data			
	Total*	Total excluding chromosomal and metabolic anomalies*	Total†	Livebirths only (n=201 902)	Livebirths and stillbirths (n=202 945)	Total excluding chromosomal anomalies†
All (BINOCAR classified) reported anomalies	399·42	305·74	205·70	153·44	156·94	165·90
Nervous system	50·84	43·57	23·80	7·33	8·28	21·60
Congenital heart disease	132·17	100·94	54·60	45·81	46·91	45·90
Respiratory	9·44	7·26	5·80	3·91	4·24	5·40
Orofacial clefts	19·61	18·16	15·00	13·08	13·16	13·80
Digestive system	25·42	21·06	16·60	13·82	14·24	14·90
Abdominal wall defects	<2	<2	9·30	5·65	5·86	8·00
Urinary	22·51	20·33	25·40	20·85	21·04	24·20
Genital	19·61	16·70	15·00	14·21	14·24	14·80
Limb	34·13	30·50	30·30	24·91	25·47	28·50
Musculoskeletal	12·35	11·62	6·70	3·62	4·04	6·60
Chromosomal	31·95	0·00	39·80	16·79	18·13	0·00

Prevalence per 10 000 births. BiB=Born in Bradford. BINOCAR=British Isles Network Of Congenital Anomalies Register. *Includes metabolic disorders not collected by BINOCAR; these are excluded from the total excluding chromosomal anomalies to allow comparison with BINOCAR. †Includes livebirths, stillbirths, miscarriages, and terminations of pregnancy.

Table 1: **Comparison of prevalence of congenital anomalies in the BiB and BINOCAR datasets**

these cases would not be reported to the study's congenital anomaly register.

Table 2 shows characteristics of mothers in the Born in Bradford study who gave birth to children with or without a congenital anomaly. Table 3 shows the univariate and multivariate analyses of the risk factors detailed in table 2. Inclusion of gestational age and twinning as covariates did not change point estimates of the other variables in the multivariate models. To address possible issues of multiple testing we re-ran the analyses with 99·9% CIs; all the main effects remained significant (data not shown). The cohort were multiethnic (39% were white British, 45% were Pakistani, and 15% were classed as other—43 recorded different ethnic origins; table 2). The proportion of babies with anomalies that was born to Pakistani mothers was higher than that born to mothers in the cohort overall (60% *vs* 45%). In the white British subgroup, significantly more babies with an anomaly were born to mothers older than 34 years than to those

	All		White British		Pakistani		Other	
	No anomaly	Anomaly	No anomaly	Anomaly	No anomaly	Anomaly	No anomaly	Anomaly
Ethnic origin*	11 010 (97%)	386 (3%)	4384 (98%)	104 (2%)	4894 (96%)	233 (5%)	1683 (97%)	49 (3%)
Age (years)								
20–34	8894 (81%)	307 (80%)	3298 (75%)	76 (73%)	4172 (85%)	196 (84%)	1386 (82%)	35 (71%)
<20	795 (7%)	22 (6%)	551 (13%)	8 (8%)	150 (3%)	8 (3%)	89 (5%)	6 (12%)
>34	1299 (12%)	57 (15%)	525 (12%)	20 (19%)	563 (12%)	29 (13%)	206 (12%)	8 (16%)
Missing	22 (<1%)	0	10 (<1%)	0	9 (<1%)	0	2 (<1%)	0
Education†								
<5 GCSE equivalents	2347 (21%)	106 (28%)	873 (20%)	23 (22%)	1251 (26%)	72 (31%)	211 (13%)	11 (23%)
≥5 GCSE equivalents at grades A–C	3360 (31%)	128 (33%)	1494 (34%)	37 (35%)	1517 (31%)	79 (34%)	339 (20%)	12 (25%)
2 Advanced Level equivalents	1594 (15%)	50 (13%)	744 (17%)	18 (17%)	613 (13%)	30 (13%)	233 (14%)	2 (4%)
Diploma, degree, or higher degrees	2846 (26%)	66 (17%)	846 (19%)	15 (14%)	1291 (26%)	38 (16%)	694 (41%)	13 (27%)
Other	603 (6%)	23 (6%)	378 (9%)	9 (9%)	149 (3%)	11 (5%)	76 (5%)	3 (6%)
Not known	123 (1%)	5 (1%)	43 (1%)	1 (1%)	55 (1%)	2 (<1%)	24 (1%)	2 (4%)
Foreign unknown	109 (1%)	6 (2%)	3 (<1%)	0	6 (<1%)	0	97 (6%)	6 (12%)
Missing	28 (<1%)	2 (<1%)	3 (<1%)	1 (1%)	12 (<1%)	1 (<1%)	9 (<1%)	0
IMD 2010 score‡ (fifths)								
1 (most deprived)	7289 (66%)	278 (72%)	2233 (51%)	53 (51%)	3883 (79%)	188 (81%)	1136 (68%)	37 (76%)
2	1990 (18%)	62 (16%)	945 (22%)	23 (22%)	698 (14%)	33 (14%)	339 (20%)	6 (12%)
3	1222 (11%)	28 (7%)	773 (18%)	17 (16%)	279 (6%)	8 (3%)	167 (10%)	3 (6%)
4	325 (3%)	9 (2%)	276 (6%)	5 (5%)	24 (<1%)	2 (<1%)	24 (1%)	2 (4%)
5 (least deprived)	181 (2%)	9 (2%)	155 (4%)	6 (6%)	9 (<1%)	2 (<1%)	17 (1%)	1 (2%)
Missing	3 (<1%)	0	2 (<1%)	0	1 (<1%)	0	0	0
Smoking§								
None	8768 (80%)	332 (86%)	2609 (60%)	69 (66%)	4659 (95%)	224 (96%)	1469 (87%)	39 (80%)
1–5 a day	721 (7%)	21 (5%)	526 (12%)	14 (14%)	103 (2%)	4 (2%)	86 (5%)	3 (6%)
6–10 a day	625 (6%)	18 (5%)	541 (12%)	13 (13%)	39 (<1%)	1 (<1%)	44 (3%)	4 (8%)
11–20 a day	323 (3%)	4 (1%)	291 (7%)	3 (3%)	6 (<1%)	0	24 (1%)	1 (2%)
>20 a day	60 (<1%)	1 (<1%)	57 (1%)	1 (1%)	2 (<1%)	0	1 (<1%)	0
Not known	513 (5%)	10 (3%)	360 (8%)	4 (4%)	85 (2%)	4 (2%)	59 (4%)	2 (4%)
Alcohol¶								
Yes	3398 (31%)	83 (22%)	2954 (67%)	71 (68%)	15 (<1%)	0	414 (25%)	12 (25%)
No	7581 (69%)	301 (78%)	1423 (33%)	33 (32%)	4864 (99%)	232 (100%)	1264 (75%)	36 (74%)
Do not remember	7 (<1%)	0	5 (<1%)	0	0	0	2 (<1%)	0
Missing	24 (<1%)	2 (<1%)	2 (<1%)	0	15 (<1%)	1 (<1%)	3 (<1%)	1 (2%)
Consanguinity‖								
Non-consanguineous	8020 (73%)	201 (52%)	4379 (100%)	104 (100%)	2035 (42%)	54 (23%)	1562 (93%)	43 (88%)
First cousin	1890 (18%)	123 (32%)	2 (<1%)	0	1802 (37%)	120 (52%)	84 (5%)	3 (6%)
Other blood	1100 (10%)	62 (16%)	3 (<1%)	0	1057 (22%)	59 (25%)	37 (2%)	3 (6%)

(Continues on next page)

	All		White British		Pakistani		Other	
	No anomaly	Anomaly	No anomaly	Anomaly	No anomaly	Anomaly	No anomaly	Anomaly
(Continued from previous page)								
BMI**								
Normal	4470 (41%)	156 (40%)	1703 (39%)	34 (33%)	1999 (41%)	99 (43%)	743 (44%)	23 (47%)
Overweight	2811 (26%)	104 (27%)	1105 (25%)	22 (21%)	1318 (27%)	67 (29%)	383 (23%)	15 (31%)
Obese	2097 (19%)	59 (15%)	985 (23%)	24 (23%)	838 (17%)	28 (12%)	266 (16%)	7 (14%)
Underweight	428 (4%)	15 (4%)	99 (2%)	3 (3%)	252 (5%)	12 (5%)	75 (5%)	0
Missing	1204 (11%)	52 (14%)	492 (11%)	21 (20%)	487 (10%)	27 (12%)	216 (13%)	4 (8%)
OGTT††								
Normal	9653 (88%)	339 (88%)	3972 (91%)	92 (89%)	4178 (85%)	204 (88%)	1461 (87%)	43 (88%)
Impaired fasting glucose	34 (<1%)	1 (<1%)	6 (<1%)	1 (1%)	19 (<1%)	0	8 (<1%)	0
Impaired glucose tolerance	787 (7%)	31 (8%)	196 (5%)	8 (8%)	467 (10%)	19 (8%)	120 (7%)	4 (8%)
Diabetes	508 (5%)	14 (4%)	206 (5%)	3 (3%)	213 (4%)	9 (4%)	87 (5%)	2 (4%)
Missing	28 (<1%)	1 (<1%)	4 (<1%)	0	17 (<1%)	1 (<1%)	7 (<1%)	0

Findings are for participants for whom questionnaire data were available. GCSE=General Certificate of Secondary Education. IMD=Index of Multiple Deprivation. BMI=body-mass index. OGTT=oral glucose tolerance test.*49 individuals did not report origin. †Five or more GCSEs at grades A*–C equates to Level 2 attainment defined by the 2011 revision of the International Standard Classification of Education; 2 or more Advanced Levels or equivalent qualifications equate to Level 3 educational attainment. ‡English Indices of Deprivation 2010. §Number of cigarettes per day smoked during pregnancy or the 3 months before pregnancy. ¶Drank alcohol during pregnancy or the 3 months before pregnancy. ||How mother is related to father: non-consanguineous (not related), first cousin, other blood (blood relation, but more distant than first cousin). **Normal: 18·5–24·9 kg/m^2; overweight: 25–29·9 kg/m^2; obese: ≥30 kg/m^2; underweight: <18·5 kg/m^2. ††OGTT test criteria: impaired fasting glucose (fasting glucose 6·1–6·9 mmol/L); impaired glucose tolerance (fasting plasma glucose ≥7·0 mmoL and venous plasma glucose 2 h after 75 g oral glucose load ≥7·8 mmol/L and <11·1 mmol/L; diabetes (fasting plasma glucose ≥7·0 mmol/L or venous plasma glucose 2 h after 75 g oral glucose load ≥11·1 mmol/L).

Table 2: **Demographic, lifestyle, and clinical characteristics of Born in Bradford mothers who gave birth to children with or without a congenital anomaly**

aged 20–34 years or younger (table 3). The point estimate for the adjusted rates was slightly higher than that for the unadjusted rates (table 3). In the univariate analysis, mothers with a diploma, degree, or other high level of education were less likely to have babies with an anomaly than were mothers of other educational levels (table 3). The adjusted rates for high education confirm its protective effect in the cohort overall (table 3). We noted this effect in both white British and Pakistani mothers (table 3).

More than two-thirds of the Born in Bradford cohort who had completed questionnaires lived in areas defined by the IMD as the most deprived fifth of the population of England (table 2). The adjusted rates showed an excess risk to babies born to mothers in the least deprived fifth overall, but the numbers were very small and this finding should be treated with caution (table 3). 18% of mothers had partners who were their first cousins (table 2). Less than 1% of babies of white British origin were the offspring of first-cousin unions compared with 38% of those in the Pakistani subgroup and 5% of those in the other subgroup (table 2). 6% of the offspring of first-cousin unions and 5% of those of more distantly related parents had an anomaly (table 2). Mothers in first-cousin unions were more than twice as likely to have a baby with an anomaly than were their counterparts in non-consanguineous unions (table 3). The adjusted rates confirmed this observation (table 3). The proportion of babies with an anomaly who were the product of non-consanguineous unions did not differ significantly between ethnic groups (tables 2, 3).

We identified no significant effect of interaction between IMD score and consanguinity on risk of congenital anomaly (interaction RR 0·99, 95% CI 0·97–1·01). We noted no independent effect overall of IMD score when this interaction was modelled (data not shown). Impaired fasting glucose in women of white British origin was associated with an increased risk of having a baby with an anomaly (table 3). The adjusted rates confirmed this observation, but the 95% CI was very wide (table 3). We noted no other significant associations overall.

Consanguinity was the most significant risk factor for congenital anomaly in this study (table 3). However, consanguinity was not evenly distributed between the ethnic groups—it was common in the Pakistani community and very rare in the white British community (table 2). With the equation for population attributable risk for the offspring of first-cousin parents in the Pakistani population, we calculated the risk as 30·7%, where r was 1922/5127 and RR was 2·18.

Discussion

This is the largest report of contemporary congenital anomaly data for the offspring of consanguineous unions in the UK. Our findings show that consanguinity was a major risk factor for congenital anomaly, independent of deprivation, and accounted for almost a third of anomalies in babies of Pakistani origin. High levels of educational attainment were associated with reduced risk in all ethnic groups, and advanced maternal age was associated with increased risk. The frequency of consanguinity reported here is similar to that reported

	Univariate analyses								Multivariate analyses							
	All		White British		Pakistani		Other		All		White British		Pakistani		Other	
	RR (95% CI)	p	RR (95% CI)	p	RR (95% CI)	p	RR (95% CI)	p	RR (95% CI)	p	RR (95% CI)	p	RR (95% CI)	p	RR (95% CI)	p
Ethnic origin*	..	..	1·00	..	1·96 (1·56–2·46)	<0·001	1·22 (0·87–1·71)	0·24	..	..	..	..	..	..	..	..
Age (years)														..		..
20–34	1·00	..	1·00	..	1·00	..	1·00	..	1·00	..	1·00	..	1·00	..	1·00	..
<20	0·81 (0·53–1·24)	0·33	0·64 (0·31–1·31)	0·22	1·13 (0·57–2·25)	0·73	2·56 (1·11–5·95)	0·0282	0·92 (0·59–1·43)	0·71	0·58 (0·29–1·23)	0·16	1·19 (0·56–2·23)	0·75	1·72 (0·74–4·03)	0·21
>34	1·26 (0·96–1·66)	0·10	1·63 (1·00–2·64)	0·0482	1·09 (0·75–1·6)	0·65	1·52 (0·71–3·23)	0·28	1·28 (0·96–1·71)	0·09	1·83 (1·14–3·00)	0·0169	1·08 (0·73–1·60)	0·71	1·50 (0·65–3·45)	0·34
Education†																
<5 GCSE equivalents	1·18 (0·92–1·52)	0·20	1·06 (0·64–1·78)	0·82	1·10 (0·81–1·5)	0·55	1·45 (0·65–3·23)	0·36	0·91 (0·71–1·18)	0·49	0·84 (0·49–1·43)	0·52	0·93 (0·68–1·27)	0·64	0·74 (0·33–1·66)	0·47
≥5 GCSE equivalents	1·00	..	1·00	..	1·00	..	1·00	..	1·00	..	1·00	..	1·00	..	1·00	..
Advanced Level equivalent	0·82 (0·6–1·14)	0·25	0·98 (0·56–1·71)	0·94	0·94 (0·63–1·42)	0·78	0·25 (0·06–1·10)	0·07	0·83 (0·59–1·17)	0·30	0·77 (0·41–1·46)	0·43	0·95 (0·62–1·45)	0·81	0·21 (0·05–0·95)	0·0432
Diploma, degree, or higher degrees	0·62 (0·46–0·83)	0·0013	0·72 (0·40–1·31)	0·28	0·58 (0·40–0·84)	0·0046	0·54 (0·25–1·17)	0·12	0·53 (0·38–0·75)	0·0002	0·42 (0·20–0·91)	0·0286	0·56 (0·38–0·84)	0·056	0·44 (0·19–1·01)	0·053
Other	1·00 (0·65–1·55)	1·00	0·96 (0·47–1·98)	0·92	1·39 (0·76–2·55)	0·29	1·11 (0·32–3·85)	0·87	1·07 (0·68–1·67)	0·78	0·76 (0·35–1·64)	0·48	1·33 (0·72–2·46)	0·37	0·98 (0·27–3·62)	0·98
Not known	1·06 (0·44–2·56)	0·89	0·94 (0·13–6·70)	0·95	0·71 (0·18–2·81)	0·63	2·25 0·53–9·53)	0·27	0·94 (0·39–2·28)	0·90	0·87 (0·19–6·40)	0·89	0·61 (0·15–2·51)	0·5	2·05 (0·47–8·99)	0·34
Foreign unknown	1·42 (0·65–3·16)	0·39	0·00 (0·00–0·00)	0·98	0·00	0·98	1·70 (0·66–4·43)	0·27	1·68 (0·74–3·78)	0·21	0·00	<0·0001	0·00	<0·0001	1·60 (0·61–4·25)	0·34
IMD 2010 score‡																
1 (most deprived)	1·00	..	1·00	..	1·00	..	1·00	..	1·00	..	1·00	..	1·00	..	1·00	..
2	0·82 (0·63–1·08)	0·16	1·03 (0·63–1·66)	0·92	0·98 (0·68–1·4)	0·90	0·55 (0·24–1·30)	0·17	1·02 (0·77–1·35)	0·91	1·02 (0·63–1·65)	0·95	1·11 (0·77–1·61)	0·57	0·63 (0·26–1·52)	0·31
3	0·61 (0·42–0·9)	0·0116	0·93 (0·54–1·59)	0·79	0·60 (0·3–1·21)	0·15	0·56 (0·17–1·79)	0·33	0·81 (0·54–1·22)	0·33	0·90 (0·51–1·58)	0·71	0·76 (0·38–1·54)	0·45	0·48 (0·11–2·05)	0·32
4	0·73 (0·38–1·41)	0·35	0·77 (0·31–1·90)	0·57	1·67 (0·44–6·35)	0·46	2·44 (0·62–9·59)	0·20	1·23 (0·62–2·43)	0·56	0·83 (0·33–2·13)	0·7	2·86 (0·78–10·46)	0·11	2·96 (0·8–10·95)	0·10
5 (least deprived)	1·29 (0·67–2·47)	0·44	1·61 (0·70–3·68)	0·26	3·94 (1·12–13·9)	0·0332	1·76 (0·26–12·15)	0·57	2·10 (1·04–4·26)	0·0395	1·80 (0·78–4·16)	0·17	6·19 (1·57–24·38)	0·09	0·00	<0·0001
Smoking§																
None	1·00	..	1·00	..	1·00	..	1·00	..	1·00	..	1·00	..	1·00	..	1·00	..
1–5 a day	0·78 (0·50–1·20)	0·25	1·01 (0·57–1·77)	0·98	0·82 (0·31–2·15)	0·68	1·30 (0·41–4·14)	0·65	0·95 (0·60–1·51)	0·83	1·00 (0·55–1·82)	0·99	0·85 (0·31–2·33)	0·76	1·08 (0·31–3·71)	0·91
6–10 a day	0·77 (0·48–1·23)	0·27	0·91 (0·51–1·64)	0·75	0·55 (0·08–3·79)	0·54	3·22 (1·20–8·66)	0·0203	0·99 (0·61–1·62)	0·98	0·86 (0·46–1·61)	0·64	0·65 (0·09–4·47)	0·66	2·80 (1·08–7·28)	0·0345

(Continues on next page)

	Univariate analyses								Multivariate analyses							
	All		White British		Pakistani		Other		All		White British		Pakistani		Other	
	RR (95% CI)	p	RR (95% CI)	p	RR (95% CI)	p	RR (95% CI)	p	RR (95% CI)	p	RR (95% CI)	p	RR (95% CI)	p	RR (95% CI)	p
(Continued from previous page)																
11–20 a day	0·34 (0·13–0·89)	0·0288	0·40 (0·13–1·25)	0·11	0·00	0·98	1·55 (0·22–10·82)	0·66	0·42 (0·15–1·14)	0·09	0·36 (0·11–1·19)	0·09	0·00	<0·0001	1·19 (0·15–9·59)	0·87
>20 a day	0·45 (0·06–3·15)	0·42	0·67 (0·10–4·74)	0·69	0·00	0·99	0·00	0·99	0·57 (0·08–4·05)	0·58	0·59 (0·08–4·10)	0·59	0·00	<0·0001	0·00	<0·0001
Alcohol¶																
No	1·00	..	1·00	..	1·00	..	1·00	..	1·00	..	1·00	..	1·00	..	1·00	..
Yes	0·62 (0·49–0·79)	<0·0001	1·03 (0·69–1·56)	0·87	0·00	0·99	1·02 (0·53–1·94)	0·96	0·96 (0·71–1·29)	0·78	1·06 (0·70–1·61)	0·79	0·00	<0·0001	1·03 (0·48–2·19)	0·95
Consanguinity‖																
Non-consanguineous	1·00	..	1·00	..	1·00	..	1·00	..	1·00	..	1·00	..	1·00	..	1·00	..
First cousin	2·50 (2·01–3·11)	<0·0001	0·00	..	2·42 (1·76–3·31)	<0·0001	1·29 (0·41–4·10)	0·67	2·19 (1·67–2·85)	<0·0001	0·00	<0·0001	2·18 (1·57–3·02)	<0·0001	1·22 (0·38–3·94)	0·74
Other blood	2·18 (1·65–2·88)	<0·0001	0·00	..	2·05 (1·42–2·94)	<0·0001	2·80 (0·91–8·65)	0·07	1·99 (1·45–2·72)	<0·0001	0·00	<0·0001	1·87 (1·3–2·71)	0·0009	2·91 (0·97–8·76)	0·06
OGTT**																
Normal	1·00	..	1·00	..	1·00	..	1·00	..	1·00	..	1·00	..	1·00	..	1·00	..
Impaired fasting glucose	0·67 (0·97–4·69)	0·69	6·31 (1·02–39·18)	0·048	0·00	<0·0001	0·00	<0·0001	0·79 (0·11–5·70)	0·81	11·41 (1·70–76·71)	0·0122	0·00	<0·0001	0·00	<0·0001
Impaired glucose tolerance	1·07 (0·75–1·5)	0·72	1·73 (0·85–3·52)	0·13	0·84 (0·53–1·33)	0·46	1·13 (0·41–3·09)	0·81	0·99 (0·68–1·43)	0·95	1·69 (0·83–3·47)	0·15	0·81 (0·51–1·29)	0·37	1·25 (0·43–3·63)	0·69
Diabetes	0·87 (0·63–1·19)	0·38	0·63 (0·2–1·99)	0·43	0·87 (0·45–1·68)	0·68	0·79 (0·19–3·19)	0·74	0·77 (0·45–1·33)	0·35	0·70 (0·22–2·18)	0·54	0·81 (0·40–1·64)	0·56	0·79 (0·20–3·19)	0·74
BMI††																
Normal	1·00	..	1·00	..	1·00	..	1·00	..	..	..	..	..	..	..	..	..
Overweight	1·06 (0·83–1·35)	0·65	1·00 (0·59–1·70)	0·99	1·03 (0·76–1·39)	0·87	1·26 (0·66–2·38)	0·49	..	..	..	..	..	..	..	..
Obese	0·81 (0·60–1·09)	0·17	1·22 (0·73–2·04)	0·46	0·69 (0·45–1·03)	0·07	0·85 (0·37–1·97)	0·71	..	..	..	..	..	..	..	..
Underweight	1·00 (0·60–1·69)	1·00	1·50 (0·47–4·81)	0·49	0·96 (0·54–1·73)	0·96	0·00	0·99	..	..	..	..	..	..	..	..

RR=risk ratio. GCSE=General Certificate of Secondary Education. IMD=Index of Multiple Deprivation. BMI=body-mass index. OGTT=glucose tolerance test.*49 individuals did not report origin. †Five or more GCSEs at grades A*–C equates to Level 2 attainment defined by the 2011 revision of the International Standard Classification of Education; 2 or more Advanced Levels or equivalent qualifications equate to Level 3 educational attainment. ‡English Indices of Deprivation 2010. §Number of cigarettes per day smoked during pregnancy or the 3 months before pregnancy. ¶Drank alcohol during pregnancy or the 3 months before pregnancy. ‖How mother is related to father: non-consanguineous (not related), first cousin, other blood (blood relation, but more distant than first cousin). **OGTT test criteria: impaired fasting glucose (fasting glucose 6·1–6·9 mmol/L); impaired glucose tolerance (fasting plasma glucose ≥7·0 mmoL and venous plasma glucose 2 h after 75 g oral glucose load ≥7·8 mmol/L and <11·1 mmol/L; diabetes (fasting plasma glucose ≥7·0 mmol/L or venous plasma glucose 2 h after 75 g oral glucose load ≥11·1 mmol/L). ††Normal: 18·5–24·9 kg/m^2; overweight: 25–29·9 kg/m^2; obese: ≥30 kg/m^2; underweight: <18·5 kg/m^2.

Table 3: **Univariate and multivariate RRs for the risk of congenital anomaly related to demographic, lifestyle, and clinical risk factors in the Born in Bradford cohort, by ethnic group**

20 years ago for families of Pakistani origin in the UK.[3] A Norwegian study analysed data for 2268 infants of Pakistani origin from consanguineous unions, with maternal education as a proxy for deprivation.[22] However, the data were not contemporary, with recruits born over a 26 year period, and case diagnoses were unvalidated. We noted rates of congenital anomalies that were almost twice that of nationally reported data. The largest groups

of disorders were congenital heart disease and anomalies of the nervous system, a finding similar to that from previous reports.[21] The excess rates for these disorders were the major reason for the overall excess reported to the Born in Bradford register.

In our study, the highest risks were in the offspring of first cousins. The proportion of congenital anomalies in children of Pakistani origin born to first cousins in this study that could be attributed to consanguinity is similar to that from the Norwegian study (28%).[22] That study reported an adjusted RR for congenital anomaly of 2·15 for children of Pakistani origin who were the product of a first cousin union, similar to that reported here. Similar results were reported from studies in Israel.[23–25] Two-thirds of the babies in the present study were from the most deprived fifth of the UK population. The increased risk associated with consanguinity was still apparent in the rates adjusted for deprivation: deprivation in mothers in consanguineous unions did not explain the increased rates of congenital anomaly in offspring.

Poor access to prenatal screening in pregnancy and low rates of termination of severely affected fetuses have been suggested as a cause of the excess of infant mortality due to congenital anomaly in babies of Pakistani origin.[26] Analysis of data for hospital activity for the period of the study showed that 132 terminations of pregnancy were done for fetal anomaly—59% in women of Pakistani origin and 32% in those of white British origin. The excess of anomalies in liveborn babies of Pakistani origin is not explained by low rates of termination. The risk of congenital anomaly was very similar for the offspring of first cousins and more distantly related parents. Similar observations were made in the Pakistani heritage community in Norway,[22] and in Israeli Arabs.[23] These communities have a longstanding tradition of consanguinity. The relationship coefficient between individuals from such communities might be higher than expected.[25] Furthermore, in the Pakistani heritage community, marriages are often done within substructures, termed *biraderi*, resulting in substantial population stratification.[27] Longstanding consanguinity and *biraderi* endogamy can both play a part in elevation of relationship coefficients greater than what might be expected from the simple parental relationship. This finding has been confirmed in the local Pakistani community by direct molecular analysis.[28] We did gather information about *biraderi*, but roughly a third of respondents did not know their *biraderi*, restricting the quality of analysis that could be done. We were therefore unable to control for this factor.

For couples in non-consanguineous unions, the risk of having a baby with an anomaly did not differ significantly between ethnic groups. The expected increase in risk in older mothers was noted in the white British group. An effect of similar magnitude was seen in mothers from the other ethnic group, albeit not significant. We did not record any such effect in mothers of Pakistani origin; this finding is because of the excess of babies with anomalies born to younger mothers (≤20–34 years) as a result of consanguinity. The protective effect of a high level of educational attainment was similar in women of Pakistani and white British origin, roughly halving the risk of having a baby with a congenital anomaly. For women of Pakistani origin, a complex association exists between education and consanguinity: a third of women in non-consanguineous unions in this study had attended higher education compared with only about a fifth of those in consanguineous unions. We identified an effect of similar size in white British women, suggesting that higher levels of education could be independently associated with reduced likelihood of having a baby with a congenital anomaly.

By contrast with other studies, maternal smoking,[29] alcohol consumption,[30] and obesity[31] were not identified as risk factors for congenital anomaly in this cohort. Pre-existing diabetes mellitus[32] and gestational diabetes mellitus[33] have both been associated with an increased risk of congenital anomalies, but neither explained the ethnic differences in anomalies in Bradford. The rate of gestational diabetes in the cohort overall is similar to reported rates,[33] and diabetes showed little variation by ethnic group, although the numbers were small.

The study has some limitations. Not all recruits to the Born in Bradford study completed a questionnaire, so

***Panel:* Research in context**

Systematic review

We did two searches of PubMed for papers in English published between April 1, 1965, and April 1, 2013. For the first search we used the MeSH terms "congenital abnormalities/epidemiology" AND "consanguinity." For the second search we used the MeSH terms "congenital abnormalities/etiology" AND "consanguinity." We filtered the search to human beings only. This search identified 219 relevant articles. Most of these articles assessed specific disorders in the context of consanguinity and not associations between congenital anomaly overall and maternal risk factors. 28 articles reporting primary data surveyed the risk of congenital anomaly associated with consanguinity. Most of these studies reported small numbers and were observational, with no corrections for other risk factors and no contemporary control groups. The Norwegian study,[22] UK study,[3] and three Israeli studies[23–25] had contemporary control groups and were of sufficient size to achieve significance in comparisons between the offspring of consanguineous and those of non-consanguineous unions.

Interpretation

Our study is the largest report of data for contemporary congenital anomalies in the offspring of first-cousin unions in the UK. Our findings confirm that the offspring of consanguineous unions have an increased risk for congenital anomalies, which is independent of deprivation. Couples contemplating such unions should be advised of these risks; however, advice should be given with sensitivity and cultural awareness. The public health implications are important. In regions with large communities that practise customary consanguineous unions, levels of congenital anomaly will be higher than average. Because most children with congenital anomaly survive, appropriate services should be commissioned to care for them and their families. Provision of paediatric, obstetric, and genetic care should be indicative of the increased needs of such communities.

some cases for which we received notifications were excluded, although the demographic profiles of the excluded cases were similar to those with available interview data.[15] Self-reporting of lifestyle factors might not be reliable, particularly for smoking and alcohol consumption. Information about consanguinity was also self reported, and rates in mothers of Pakistani origin were consistent with those previously reported.[3] We did not gather data for paternal age.

Antenatal counselling routinely covers the risks associated with advanced maternal age, medication and, alcohol consumption—all risk factors for congenital anomaly. Advice about the risks associated with consanguinity should be part of the consultation. In practice, the most useful technique is a thorough family history, which identifies couples at a particularly high risk (panel).[34,35] Clear and accessible information about the risks of consanguineous unions and congenital anomaly should be communicated to couples concerned and widely disseminated to local communities. The advice should be provided in a culturally sensitive way to promote discussion and improve awareness about the risks of congenital anomaly associated with consanguineous relationships. Health-care commissioners should be aware of the increased risks because these risks will result in an increased need for antenatal, paediatric, and genetic services.

Contributors

ES, JW, RCP, NS, and SO conceived the idea and designed the protocol, with advice from PAM. TM, CW, and NP supported the notification system and reporting. PCC, SO, and ES reviewed all anomaly notifications. EP, CW, and RCP did the statistical analysis, which was overseen by ES. All authors contributed to and have approved the final Article.

Conflicts of interest

We declare that we have no conflicts of interest.

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