

## Birth Defects and Parental Consanguinity in Norway

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The study compares frequencies of birth defects between immigrant groups and the rest of the Norwegian population in Norway and estimates the influence of consanguinity and socioeconomic factors on these frequencies. The authors studied all 1.56 million births in Norway from 1967 to 1993. Of these, 7,494 children had two Pakistani parents, 84,688 had one Norwegian and one immigrant parent, and 25,891 had two immigrant parents from countries other than Pakistan. The risk of birth defects relative to the Norwegian group was 0.98 (95% confidence interval 0.92–1.03) in the group with one foreign and one Norwegian parent, 1.39 (95% confidence interval 1.22–1.60) in the group with two Pakistani parents, and 1.04 (95% confidence interval 0.95–1.14) in the group with two parents from other foreign countries; 0.1% of the Norwegian and 30.1% of the Pakistani children had parents who were first cousins. There was no difference in risk between children of nonconsanguineous Pakistani parents and the other groups. The relative risk of birth defects among children whose parents were first cousins was about 2 in all groups. Among the Pakistani, 28% of all birth defects could be attributed to consanguinity. Low paternal educational level was associated with a slightly increased risk in the Norwegian group, while independent effects of parental educational levels were not found in any other groups. *Am J Epidemiol* 1997;145:439–48.

abnormalities; consanguinity; education; ethnic groups; genetics; social class

Clear associations between mortality and social class have been demonstrated in studies on early mortality in Norway, Pakistan, and several other countries regardless of considerable differences in absolute mortality among these countries (1–3). However, the relation between birth defects and social class is not clear.

Consanguineous marriages are widely accepted and practiced globally (4–18). Bittles et al. (4) estimated that 20–50 percent of all marriages in many regions of Asia and Africa are between first cousins. Marriages between close relatives serve important social, cultural, and economic functions (4, 19) and may have both positive and negative biologic consequences. Children born to parents who are closely related are at considerably higher risk of illness and death from rare recessive diseases and at moderately higher risk of suffering from conditions with multifactorial etiologies and a continuously distributed liability (8). Many

studies on consanguinity and health do not have adequate information on social and economic factors, and there are controversies about the effects of consanguinity on morbidity and mortality after proper adjustment for social class (4, 5, 20).

Ethnically and socioeconomically, Norway has been a relatively homogeneous society. Since about 1970, there has been a slow development toward a more multiethnic society, although Norwegians without a recent immigrant background still constitute the overwhelming majority of the population. Approximately half of the immigrants in Norway come from other European and North American countries (120,179 of 204,810 persons born in foreign countries as of January 1, 1993) (21). Pakistani immigrants and their children constitute the largest non-Scandinavian immigrant group and are the focus of the present study. About 11,000 people are immigrants from Pakistan, and more than 8,000 children have been born in Norway to two parents who are immigrants from Pakistan (21). This is the largest group of children born in Norway since 1967 by immigrant parents from a single country. People with Pakistani origin and some other immigrant groups form relatively well-defined ethnic minorities, largely because nearly all of them marry within their own population. In addition, an increasing number of ethnic Norwegians have children with immigrant partners. These children do not belong

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Abbreviations: *F*, coefficient of inbreeding (the proportion of autosomal loci predicted from pedigree analysis to be homozygous through inheritance of identical genes from common ancestors); ICD-8, *International Classification of Diseases*, Eighth Revision.

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to well-defined cultural or ethnic groups. Genetically, they belong to a heterogeneous, biologically outbred group that, theoretically, has a lower risk of recessive diseases and birth defects than the groups with two parents from the same ethnic background (8).

In order to understand better the effects of social class and consanguinity on birth defects, we have compared the risk of birth defects in ethnic minority groups with the risk in the ethnic majority of the Norwegian population and estimated the association among birth defects, consanguinity, and parental educational levels.

The study comprises all births in Norway between 1967 and 1993 and is an unusual opportunity to compare different ethnic groups and social classes. It represents the largest study of consanguinity and birth defects among people with Pakistani origin outside Pakistan.

## MATERIALS AND METHODS

### Study population

The Medical Birth Registry of Norway comprises all births from 1967 and onward (22). All 1,566,839 birth records from 1967 to 1993 were updated with information from the Norwegian Central Bureau of Statistics on country of origin and parental educational levels attained by 1990. The analyses were based on an anonymous file.

The births were categorized as children with two ethnic Norwegian parents ( $n = 1,448,766$ ), children with one ethnic Norwegian and one immigrant parent ( $n = 84,688$ ), children with two immigrant parents from Pakistan ( $n = 7,494$ ), and children with two parents who have emigrated from foreign countries other than Pakistan ( $n = 25,891$ ). Henceforth, these groups will be referred to as "Norwegian," "mixed," "Pakistani," and "other" regardless of citizenship. The categorization was based on codes indicating immigration status and country of origin of the parents.

**Birth defects.** Physicians diagnose birth defects during the first days of life. These defects are then coded at the Medical Birth Registry according to the *International Classification of Diseases*, Eighth Revision (ICD-8). All birth defects were included (umbilical hernia, ICD-8 code 551.1; ventral hernia, ICD-8 code 551.2; and congenital anomalies, ICD-8 codes 740.0–759.9) (22), except those for which diagnoses had low reliability due to large differences in diagnostic procedures among hospitals (other anomalies of the nose, ICD-8 code 748.1; congenital hydrocele testis, ICD-8 code 752.4; clubfoot, ICD-8 codes 754.0–754.9; congenital dislocation of the hip, ICD-8 code 755.6; and other specified anomalies of muscle,

tendon, and fascia, ICD-8 code 756.8). The presence of any birth defect was used as the dependent variable, except in an attempt to estimate effects of consanguinity in separate birth defect categories. There were 1,986 children in the Norwegian group, 26 in the Pakistani group, and 46 in the other group who had multiple birth defects. These children were assigned to the category of "other syndromes" (ICD-8 codes 759.0–759.9).

**Consanguinity.** The blood relationship between parents was categorized as not consanguineous, first cousin or closer, more distant than first cousin and unspecified, or missing (table 1).

**Educational level.** The mother's and father's levels of education were obtained from a census conducted by the Norwegian Central Bureau of Statistics in 1990. The educational level is registered as the number of years of education completed by 1990. Years of education were categorized as 0–9 years, 10–12 years, more than 12 years, and missing (23). Years of education for both parents were chosen as the best available indicators of social class (24–28).

**Parity.** The condition of having given birth to an infant or infants was categorized as primiparous, multiparous, or unknown.

**Maternal age.** The mother's age at delivery was divided into four categories: younger than 25, 25–29, 30–34, and 35 years or older.

**Year of birth.** The birth year was assigned to one of three 9-year periods: 1967–1975, 1976–1984, and 1985–1993. The period of birth was included in the analyses in order to allow for secular changes, both within and between the population groups, and for possible changes in diagnostic routines.

**Place of birth.** Hospitals and all other locations of birth (i.e., home, during transportation) were categorized into two groups: 1) three large hospitals in the Oslo area and 2) all other locations. This division was necessary because a large proportion (70 percent) of children with Pakistani parents were delivered at the Aker and Ullevaal hospitals in Oslo and the Central Hospital of Akershus. These three hospitals registered 12.9 percent of all births and reported birth defects in 2.3 percent of the newborns, while all other locations of birth together reported less than 1.4 percent (table 2). Thus, the place of birth could be a confounder. Consequently, the estimated relative risks were adjusted for place of birth when necessary.

### Statistical methods

Contingency table analysis and multivariate logistic regressions were performed using SPSS software (29). Relative risks were approximated by odds ratios. Measures of uncertainty were computed as 95 percent

confidence intervals for proportions and odds ratios (30). The population attributable risk (AR) was calculated based on the following formula (31):

$$AR = (r(RR - 1)) / (r(RR - 1) + 1)$$

where  $r$  is the exposed proportion of the population, and RR is the relative risk for birth defects (measured as the prevalence odds ratio in this study).

## RESULTS

In the Pakistani group, 40 percent of the children had parents who were consanguineously related, and 30 percent had parents who were first cousins. For six children, the biologic relationship of the parents was closer than that of first cousins. About 4 percent were related in the group where both parents were from foreign countries other than Pakistan. A large proportion of these consanguineous parents came from Turkey and Morocco. In the Norwegian group, 1 percent

had related parents, and 0.1 percent were first cousins or more closely related (table 1).

Information on the educational level was missing for a large proportion of the Pakistani group and for the parents from other foreign countries (table 1). Among those with information on the duration of maternal education, 20 percent in the Norwegian, 34 percent in the mixed, 13 percent in the Pakistani, and 33 percent in the other group had completed more than 12 years of education. The pattern was similar for paternal education.

The overall distribution of maternal age was relatively similar in all groups, while the Pakistani group had a higher proportion of multiparous mothers than did the other groups (table 1). Few children with Pakistani parents (4.4 percent) or with parents from other foreign countries (9.1 percent) were born in the first 9-year period. About 70 percent of the children with Pakistani parents were born in the three major hospitals in Oslo and Akershus while, in the other

TABLE 1. Births in Norway during 1967–1993 by parental consanguinity, years of education, maternal age, and parity according to ethnic origin of the parents

	Children with two Norwegian parents ( <i>n</i> = 1,448,766)		Children with one Norwegian and one foreign parent ( <i>n</i> = 84,688)		Children with two Pakistani parents ( <i>n</i> = 7,494)		Children with both parents from other foreign countries ( <i>n</i> = 25,891)	
	No.	%	No.	%	No.	%	No.	%
Parental consanguinity								
Not consanguineous	1,420,087	98.0	83,796	98.9	4,344	58.0	24,111	93.1
First cousins or more closely related*	1,992	0.1			2,268	30.3	657	2.5
Other consanguineous relations	13,731	0.9			685	9.1	423	1.6
Missing	12,956	0.9	892	1.1	197	2.6	700	2.7
Mother's education (years)								
<10	317,589	21.9	12,612	14.9	1,515	20.2	3,746	14.5
10–12	817,765	56.4	35,699	42.2	873	11.6	4,980	19.2
>12	279,110	19.3	24,623	29.1	365	4.9	4,355	16.8
Missing	34,302	2.4	11,754	13.9	4,741	63.3	12,810	49.5
Father's education (years)								
<10	466,241	32.2	23,391	27.6	2,052	27.4	13,031	50.3
10–12	674,312	46.5	29,810	35.2	1,839	24.5	4,855	18.8
>12	297,879	20.6	25,420	30.0	645	8.6	4,038	15.6
Missing	10,334	0.7	6,067	7.2	2,958	39.5	3,967	15.3
Maternal age (years)								
<25	529,603	36.6	22,777	26.9	2,494	33.3	6,429	24.8
25–29	507,981	35.1	30,586	36.1	2,616	34.9	9,296	35.9
30–34	283,801	19.6	21,526	25.4	1,536	20.5	7,042	27.2
>34	127,381	8.8	9,799	11.6	848	11.3	3,124	12.1
Parity								
1	600,616	41.5	37,801	44.6	1,930	25.8	10,573	40.8
≥2	842,896	58.2	46,545	55.0	5,518	73.6	15,187	58.7
Missing	5,254	0.4	342	0.4	46	0.6	131	0.5

\* For 104 children, parental relationships were noted as closer than first cousin: 94 in the Norwegian group, six in the Pakistani group, and four in the group of children with parents from other foreign countries.

population groups, a large majority (67–88 percent) of the children were born elsewhere.

Low educational levels were associated with higher frequencies of consanguineous marriage in all three of the population groups studied. In the Pakistani group, 46 percent of the children who had mothers with the lowest educational level were offspring of consanguineous parents, while this was the case for 29 percent of those whose mothers had 10–12 years of education and for 23 percent of those whose mothers had the highest educational levels. The proportion of consanguineous parents among those whose mothers' educational level was unknown was close to the proportion of those with the lowest educational levels (41 percent).

### Birth defects

The proportion of birth defects among children of nonconsanguineous parents was quite similar in all population groups when the place of birth was taken into consideration (table 2). In all groups, the proportion of birth defects was higher among children whose parents were first cousins or closer.

*Specified birth defects.* The number of children in each birth defect category with relative risks for parental consanguinity is shown in table 3. No clear pattern of elevated risks was found for those with related parents, except possibly for hydrocephalus and "other syndromes."

*Analysis within each population group.* After adjustment for other variables, the relative risk of birth defects in the offspring of parents who were first cousins or closer was approximately 2 in the three population groups where consanguinity occurred (table 4). The effect of other kinds of consanguinity varied among the groups. There was no effect in either the Norwegian group or the group from foreign countries other than Pakistan, while the risk in the Pakistani group of parents with unspecified or other degrees of consanguinity was equal to that found among first cousins (table 4).

Maternal educational level was not significantly associated with birth defects in any group ( $p < 0.01$ ), while a low paternal educational level was associated with a slightly increased risk of birth defects in the Norwegian group (table 5). Among the other three population groups, there were no significant effects of paternal education.

*Comparisons among population groups.* When adjusted for period and place of birth, the risk of birth defects did not differ significantly among the Norwegian, the mixed, and the other group. In the Pakistani group, the risk was 1.4 times higher than in the Norwegian group (table 6). Adjusted for consanguinity in

TABLE 2. Proportion of births with birth defects in four population groups by parental consanguinity and place of birth, Norway, 1967–1993

Parental consanguinity	Children with two Norwegian parents (n = 1,448,766)				Children with one Norwegian and one foreign parent (n = 84,666)				Children with two Pakistani parents (n = 7,494)				Children with both parents from other foreign countries (n = 25,881)			
	SAU* (n = 170,028)		Other places (n = 1,278,738)		SAU (n = 18,406)		Other places (n = 66,262)		SAU (n = 5,245)		Other places (n = 2,249)		SAU (n = 8,666)		Other places (n = 17,225)	
	OR*	95% CI*	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Not consanguineous	2.2	2.2–2.3	1.4	1.4–1.4	2.6	2.4–2.8	1.3	1.2–1.4	2.4	1.9–3.1	1.4	0.9–2.2	2.7	2.3–3.0	1.4	1.3–1.6
First cousins or closer	4.8	2.1–9.3	3.2	2.5–4.1					5.0	4.0–6.1	3.2	1.9–5.0	3.5	1.8–6.0	4.2	2.3–7.1
Other kinds of consanguinity	2.6	1.5–4.1	1.5	1.3–1.7					3.7	2.2–5.8	4.1	1.8–7.9	3.9	1.6–7.9	0.8	0.1–2.9
Missing	2.3	1.6–3.2	2.1	1.9–2.4	2.4	0.5–6.7	0.9	0.4–1.9	5.9	1.2–12.4	1.1	0.0–5.7	4.3	1.7–8.6	3.2	1.9–5.0
All	2.3	2.2–2.3	1.4	1.4–1.4	2.6	2.4–2.8	1.3	1.2–1.4	3.5	3.0–3.9	2.1	1.5–2.8	2.8	2.4–3.1	1.5	1.4–1.7
	%	95% CI	No. of births with birth defects		%	95% CI	No. of births with birth defects		%	95% CI	No. of births with birth defects		%	95% CI	No. of births with birth defects	
All places	1.5	1.5–1.5	22,005	1.6	1.5–1.7	1,349	3.0	2.7–3.4	228	1.9	1.8–2.1	504				

\* SAU, Central Hospital of Akershus, Aker Hospital, and Ullevaal Hospital in Oslo; OR, odds ratio; CI, confidence interval.

TABLE 3. Crude odds ratios for specified birth defects by parental consanguinity in three groups of births classified according to ethnic origin of the parents, Norway, 1967-1993

Birth defect	ICD-8† code	Children with two Norwegian parents by parental consanguinity						Children with two Pakistani parents by parental consanguinity						Children with both parents from other foreign countries by parental consanguinity					
		Not consanguineous (n = 1,420,087)		First cousins or closer (n = 1,992)		Other kinds of consanguinity (n = 13,731)		Not consanguineous (n = 4,344)		First cousins or closer (n = 2,268)		Other kinds of consanguinity (n = 685)		Not consanguineous (n = 24,111)		First cousins or closer (n = 657)		Other kinds of consanguinity (n = 423)	
		No.	Refer-ence	No.	OR†	No.	OR	No.	Refer-ence	No.	OR	No.	OR	No.	Refer-ence	No.	OR	No.	OR
Abdominal wall	551	544	1.0	0	0.0	6	1.1	2	1.0	0	0.0	0	0.0	11	1.0	1	3.3	0	0.0
Anencephaly	740	431	1.0	0	0.0	2	0.5	1	1.0	3	5.8	0	0.0	13	1.0	0	0.0	0	0.0
Spina bifida	741	553	1.0	0	0.0	6	1.1	1	1.0	2	3.8	2	12.7*	8	1.0	1	4.6	0	0.0
Hydrocephalus	742	445	1.0	4	6.4**	6	1.4	1	1.0	8	15.4**	2	12.7*	7	1.0	1	5.2	1	8.2*
Other central nervous system	743	150	1.0	1	4.7	3	2.1	2	1.0	3	2.9	0	0.0	1	1.0	1	36.8*	0	0.0
Eye	744	169	1.0	0	0.0	0	0.0	3	1.0	3	1.9	1	2.1	6	1.0	0	0.0	0	0.0
Ear, face, neck	745	563	1.0	1	1.3	5	0.9	2	1.0	1	1.0	0	0.0	19	1.0	0	0.0	0	0.0
Heart	746	2,234	1.0	3	1.0	20	0.9	13	1.0	18	2.7**	2	1.0	57	1.0	6	3.9**	0	0.0
Circulatory	747	248	1.0	2	5.8*	5	2.1	3	1.0	2	1.3	0	0.0	9	1.0	0	0.0	0	0.0
Respiratory	748	194	1.0	0	0.0	0	0.0	1	1.0	1	1.9	0	0.0	7	1.0	1	5.2	0	0.0
Cleft lip and palate	749	2,411	1.0	6	1.8	20	0.9	2	1.0	6	5.8*	1	3.2	23	1.0	1	1.6	0	0.0
Mouth, esophageal	750	319	1.0	1	2.2	3	1.0	1	1.0	0	0.0	0	0.0	8	1.0	0	0.0	0	0.0
Digestive, anal	751	479	1.0	2	3.0	2	0.4	1	1.0	3	5.7	1	6.3	13	1.0	1	2.8	0	0.0
Genital	752	3,845	1.0	7	1.3	32	0.9	24	1.0	24	1.9*	5	1.3	76	1.0	5	2.4	2	1.5
Renal	753	558	1.0	1	1.3	4	0.7	5	1.0	1	0.4	0	0.0	21	1.0	0	0.0	0	0.0
Limb defects	755	3,076	1.0	12	2.8**	37	1.2	11	1.0	11	1.9	1	0.6	54	1.0	5	3.4**	1	1.1
Axial	756	593	1.0	0	0.0	12	2.1*	2	1.0	4	3.8	1	3.2	11	1.0	0	0.0	0	0.0
Skin, hair, nail	757	802	1.0	2	1.8	7	0.9	4	1.0	1	0.5	1	1.6	17	1.0	0	0.0	0	0.0
Other defects	758	83	1.0	0	0.0	2	2.5	1	1.0	1	1.9	0	0.0	1	1.0	0	0.0	0	0.0
Other syndromes	759	3,750	1.0	25	4.8**	42	1.2	12	1.0	11	1.8	8	4.8**	84	1.0	2	0.9	5	3.4**

\* p < 0.05; \*\* p < 0.01.

† ICD-8, International Classification of Diseases, Eighth Revision, OR, crude odds ratio. A separate analysis was conducted within each population group. Children with missing information on parental consanguinity were excluded.

**TABLE 4. Crude and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) for birth defects by parental consanguinity in three groups of births classified according to ethnic origin of the parents, Norway, 1967–1993**

Parental consanguinity	Children with two Norwegian parents		Children with two Pakistani parents		Children with both parents from other foreign countries	
	OR	95% CI	OR	95% CI	OR	95% CI
Not consanguineous	1.00	Reference	1.00	Reference	1.00	Reference
First cousins or closer						
Crude OR	2.28**	1.79–2.91	2.19**	1.64–2.91	2.03**	1.33–3.08
Adjusted OR†	2.32**	1.82–2.96	2.15**	1.60–2.87	1.84**	1.20–2.82
Other consanguineous relations						
Crude OR	1.03	0.90–1.18	1.83**	1.18–2.85	1.17	0.60–2.28
Adjusted OR†	1.09	0.95–1.24	1.84**	1.18–2.87	1.13	0.58–2.21

\*  $p < 0.05$ ; \*\*  $p < 0.01$ .

† Odds ratios adjusted for mother's and father's years of education, maternal age, parity, period, and place of birth. A separate analysis was conducted within each group. Births with missing information on parity or consanguinity were excluded from the analyses.

**TABLE 5. Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) for birth defects by parental education, maternal age, and parity in four groups of births classified according to ethnic origin of the parents, Norway, 1967–1993**

	Children with two Norwegian parents		Children with one Norwegian and one foreign parent		Children with two Pakistani parents		Children with both parents from other foreign countries	
	Adjusted OR†	95% CI	Adjusted OR†	95% CI	Adjusted OR†	95% CI	Adjusted OR†	95% CI
<b>Mother's education (years)</b>								
<10	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
10–12	1.04*	1.01–1.08	0.98	0.83–1.16	1.17	0.69–2.01	0.81	0.59–1.11
>12	1.01	0.97–1.06	1.02	0.84–1.23	1.46	0.70–3.05	0.90	0.64–1.26
Missing	1.05	0.95–1.14	0.88	0.71–1.08	1.23	0.86–1.77	0.80	0.61–1.03
<b>Father's education (years)</b>								
<10	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
10–12	0.88**	0.85–0.91	1.02	0.89–1.18	1.19	0.81–1.75	0.96	0.74–1.24
>12	0.85**	0.82–0.89	0.95	0.81–1.11	0.66	0.33–1.31	0.90	0.67–1.21
Missing	1.04	0.89–1.20	1.00	0.80–1.25	1.21	0.86–1.71	1.04	0.80–1.35
<b>Maternal age (years)</b>								
<25	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
25–29	1.05**	1.01–1.08	1.00	0.87–1.17	1.00	0.70–1.44	0.95	0.74–1.23
30–34	1.12**	1.07–1.17	1.06	0.89–1.26	1.12	0.74–1.69	1.23	0.94–1.61
>34	1.47**	1.40–1.54	1.45**	1.19–1.76	1.36	0.85–2.17	1.49*	1.08–2.05
<b>Parity</b>								
1	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
≥2	0.89**	0.86–0.92	0.98	0.87–1.10	1.03	0.72–1.48	0.90	0.74–1.10

\*  $p < 0.05$ ; \*\*  $p < 0.01$ .

† Odds ratios adjusted for consanguinity, mother's and father's years of education, maternal age, parity, period, and place of birth. A separate analysis was conducted within each group. Births with missing information on parity or consanguinity were excluded from the analyses.

addition to period and place of birth, the risk of birth defects was almost equal in all four population groups (table 6). Adjustment for parity, maternal age, and mother's and father's years of education did not alter the risk of any of the groups relative to the risk in the Norwegian group (table 6). All models that included consanguinity yielded relative risks for the Pakistani group that were not significantly different from those in the other three groups. Results of models containing all possible combinations of the other variables (ex-

cluding consanguinity) indicated significantly higher relative risks for the Pakistani than for the other groups. In the mixed group, the risk was lower than in the Norwegian group, although the difference was not statistically significant.

#### Attributable risk

The population risk of birth defects that could be attributed to consanguinity was 28 percent in the

**TABLE 6. Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) for birth defects in four groups of births classified according to ethnic origin of the parents relative to births of two Norwegian parents, Norway, 1967–1993**

Multivariate logistic regression models†	Children with two Norwegian parents (reference group OR)	Children with one Norwegian and one foreign parent		Children with two Pakistani parents		Children with both parents from other foreign countries	
		OR	95% CI	OR	95% CI	OR	95% CI
1 (adjusted for year and place of birth)	1.00	0.98	0.92–1.03	1.39**	1.22–1.60	1.04	0.95–1.14
2 (adjusted for consanguinity, year, and place of birth)	1.00	0.98	0.92–1.03	1.03	0.87–1.20	1.01	0.92–1.11
3 (adjusted for parental educational level, year, and place of birth)	1.00	0.97	0.92–1.03	1.34**	1.15–1.55	1.00	0.90–1.10
4 (adjusted for maternal age, parity, year, and place of birth)	1.00	0.96	0.91–1.01	1.42**	1.24–1.63	1.03	0.94–1.13
5 (adjusted for consanguinity, parental educational level, maternal age, parity, year, and place of birth)	1.00	0.96	0.91–1.02	1.02	0.86–1.21	0.97	0.88–1.07

\*  $p < 0.05$ ; \*\*  $p < 0.01$ .

† All population groups were analyzed together in models 1–5. Births with missing information on parity or consanguinity were excluded from the analyses.

Pakistani group (attributable risk = 0.28,  $r = 0.394$ , relative risk = 2.00 for first cousins and other related parents combined), 0.09 percent in the Norwegian group (first cousins and closer), and 1.5 percent in the group with parents from foreign countries other than Pakistan (first cousins and closer).

**DISCUSSION**

This is a study with an emphasis on the epidemiologic, rather than the purely genetic, aspects of the associations between birth defects and consanguinity and social class. The focus is on the population risk and on the influence of socioeconomic factors versus genetic (consanguinity) factors. The strength of the study is that it covers a total population and that the data on birth defects, consanguinity, parental educational levels, and country of origin are collected in the same way for all the subgroups of the population.

**Main results**

The risk of birth defects is practically equal for all four groups of children with nonconsanguineous parents, independent of ethnic origin. The risk of birth defects was higher in the Pakistani population as a whole compared with the other groups. This difference is explained by the high frequency of consanguineous marriages in the Pakistani population. Social class, measured as mother’s and father’s years of education, was negatively associated with the frequency of consanguineous marriages but did not have any independent association with the risk of birth defects, except in the Norwegian group where there was a weak association between a low educational level among fathers and an increased risk of birth defects among the children.

**Data quality**

*Study population.* All stillbirths and livebirths with a gestational age of 16 weeks or more are included in the study. The proportion of pregnancies in each population group that were terminated on the basis of prenatal diagnosis of serious malformations is not known. Although this has not been investigated directly, the effect of consanguinity on birth defects was the same in all population groups, which makes it reasonable to assume that terminations because of malformations did not inflate the results in this study. A total of 3,266 (0.2 percent) children could not be categorized into one of the population groups with certainty. However, these were classified on the basis of information on either the mother’s or the father’s country of origin. Analysis with and without these births gave similar results.

*Birth defects.* Two main factors influencing the reliability of the birth defect diagnosis are identification of all cases and correct diagnosis. Birth defects noted in the Medical Birth Registry are diagnosed by physicians during the first days of life. Accordingly, only birth defects that are detectable immediately after birth can be included. Misdiagnosis is a problem in this analysis only when birth defects are diagnosed as something else. The birth defect variable used here is anatomically and etiologically heterogeneous, including both single gene disorders and polygenic and environmentally caused birth defects. In most cases, the etiology is unknown when the diagnosis is given and, in the present data set, it is not possible to separate diagnostic entities covering recessive disorders from those including birth defects with other etiologies, although table 3 may indicate categories of birth defects where recessive disorders have a larger contri-

bution.

**Consanguinity.** Consanguinity is routinely recorded in a standardized form when the mother undergoes her first pregnancy control, usually before 12 weeks of gestation. Only a small proportion of records in the Medical Birth Registry missed information on consanguinity (table 1). Underreporting of consanguinity is probable in all population groups and, consequently, estimates of relative risks will be deflated. Differential misclassification due to increased reporting of birth defects when consanguinity status is known may have occurred, and thereby the relative risk estimates within all population groups could be inflated.

**Categories of consanguineous relations.** The group of children with parents who were more closely related than first cousins was small ( $n = 104$ ) (table 1) and therefore included in the first cousin category. This did not alter the estimates calculated for the effect of first cousin relationships. The content of the category "other consanguinity" was heterogeneous and varied among the population groups. This probably reflects the fact that midwives and physicians had difficulties with the classification of the specific consanguineous relationships other than first cousins, particularly in the Pakistani group. The results infer that the group with nonspecified consanguineous relationships in the Pakistani population included relationships as close and closer than first cousins (table 4). The frequencies of first cousin marriages and other consanguineous relationships among Pakistani parents are lower in the present study than in studies among Pakistani immigrants in Great Britain and from Punjab in Pakistan (32–35). This may indicate underreporting rather than a real difference in the frequency of consanguineous relationships, because there does not appear to be a decrease in the frequency of consanguinity over time among Pakistani immigrant populations elsewhere (33). If this is the case, Pakistani children from nonconsanguineous marriages may have an even lower risk of birth defects than estimated here.

**Coefficients of inbreeding.** The present study does not allow use of estimated coefficients of inbreeding ( $F$ ) for types of consanguinity other than first cousins ( $F = 1/16$ ), because all other forms of close (second cousin and closer) relationships are either rare or not specified.

**Educational level.** A large proportion of parents in the Pakistani and the other groups have missing information on education. However, analysis without those with missing information on parental education gave results that were parallel to those presented in this study, although with less statistical power.

Education was used as an indicator of social class.

The negative relation between parental educational levels and frequency of consanguinity demonstrated in this study is consistent with findings from several other studies (10, 17, 36–39) and supports the use of parental educational levels as proxy measures of social class.

### Effects of consanguinity

In this study, the effects of consanguinity were estimated after adjusting for socioeconomic factors, maternal age, parity, year, and place of birth. There was a twofold increase in the proportion of children with birth defects among first-cousin parents in all three population groups considered. Evaluation of the results for the groups of children with mixed and other foreign parents was complicated because both of these population groups were heterogeneous, and their composition changed significantly over time. Although it should be interpreted with caution, the slightly lower risk in the mixed group is in accordance with the hypothesis of an outbreeding effect that can reduce the risk of birth defects by reducing the incidence of autosomal recessive disorders.

Birth defects tend to be etiologically heterogeneous, and analysis of parental consanguinity and specific birth defects may contribute to differentiation between recessive disorders and other etiologies. The relation between parental consanguinity and specified birth defects within each population group (table 3) may indicate which diagnostic categories include more recessive disorders. However, both the specificity and sensitivity of diagnosis in the first few days of life are low and, for many of the birth defect categories, the numbers are low.

Different studies report diverging conclusions as to the influence of parental consanguinity on rates of birth defects. Methodological issues related to studies of consanguinity and birth defects have been reviewed recently by Khlát and Khoury (5). Generally, the risk of early mortality in first cousin relationships tends to be approximately 2 relative to nonconsanguineous relationships (40). Although it is easier to compare the effects of consanguinity on mortality than on birth defects, an increased risk of birth defects within the same range as in the present study has been demonstrated previously (41, 42). Two Norwegian studies including subsamples of the present study have shown approximately the same risk of mortality and birth defects among offspring of first cousins compared with offspring of nonrelated parents (43, 44).

Only a minority of the children of consanguineous parents experience deleterious consequences of consanguinity on their health (40–45), although the cumulative effects of consanguinity on childhood mor-



bidity and mortality may be considerable. For example, a 5-year prospective study by Bunday and Alam (32) estimated that there was a threefold increase in postneonatal mortality and chronic severe childhood morbidity among children of consanguineous Pakistani parents compared with those with unrelated parents. By the age of 5 years, 10.2 percent (95 percent confidence interval 7.9–12.5) of the offspring of consanguineous parents were either dead or affected by a serious chronic condition, 50 percent of which was associated with mental retardation.

### Effects of socioeconomic conditions

There was no association between the educational levels of the parents and the proportion of children with reported birth defects, except in the Norwegian group where a very small effect was found for decreasing levels of paternal education. The absence of such an association in the Pakistani population suggests that parental education does not confound the risk estimates. The influence of social class on birth defect rates in the population groups considered here seems to act predominantly through the negative association between social class and the frequency of consanguinity.

This study does not include information on smoking, use of alcohol, diet, infectious diseases, or other factors that are, or may be, associated with both socioeconomic and cultural conditions and birth defects. Such factors may also interact with genes and thereby cause birth defects. Moreover, this study does not analyze the cultural, social, and economic conditions and values related to consanguinity. An exploration of these aspects of consanguinity is necessary in order to weigh the risks against the positive effects of consanguinity.

Based on a review of 31 studies, Khoury et al. (40) found that higher prereproductive mortality rates in a population were associated with lower effects of consanguinity. In addition, populations with high consanguinity rates had lower effects of consanguinity on mortality (40). Whether these observations are true also in the case of birth defects or prereproductive morbidity in general has not been evaluated. Mortality rates are declining in many of the countries where consanguinity is favored. Thus, there is probably a global increase in the number of people belonging to populations with very high rates of consanguinity (>20 percent of marriages between first cousins) combined with decreasing or low rates of mortality. The public health impact of consanguinity may therefore be increasing and more important than generally appreciated.

### Conclusions

The risk of birth defects is practically equal for all four groups of children with nonconsanguineous parents, independent of ethnic origin and social class. In the Pakistani group, consanguinity was a major risk factor for birth defects because of its high prevalence. Considering the high infant morbidity and mortality (3, 34, 45) in Pakistan and the socioeconomic differences between Pakistani immigrants and the rest of the Norwegian population (table 1), the results of this study revealed clear but moderate differences in the risk of birth defects among population groups in Norway.

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