A Case-Control Investigation of Perinatal Risk Factors for Childhood IDDM in Northern Ireland and Scotland

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OBJECTIVE — To identify perinatal risk factors for childhood insulin-dependent diabetes mellitus (IDDM) and determine if they differ between early-onset and late-onset disease.

RESEARCH DESIGN AND METHODS — We selected 258 diabetic children in Northern Ireland and 271 diabetic children in Scotland from population-based registers. For each diabetic child, five matched control subjects were drawn from the same population. All perinatal data were recorded routinely at birth. Odds ratios (ORs) were estimated for parental age, social class, breast-feeding, deprivation measures, and other perinatal variables.

RESULTS — Scottish data indicated an increased risk among children born to older mothers (OR = 2.43, 95% confidence interval [CI] 1.49–3.97 for mothers ≥35 years of age relative to those <25 years of age). Northern Ireland data showed no such effect. Only Northern Ireland data showed an excess risk in children of professional or managerial families (OR = 1.51, 95% CI 1.11–2.04). A small but nonsignificant reduction in risk among breast-fed children was observed only after adjustment for social class (OR = 0.76, 95% CI 0.54–1.07). Deprivation measures were associated with reductions in risk. Children delivered by cesarean section were at increased risk in both Northern Ireland (OR = 1.66, 95% CI 1.10–2.50) and Scottish (OR = 1.70, 95% CI 1.12–2.59) data. In Northern Ireland data only, children of first pregnancies were at increased risk (OR = 1.41, 95% CI 1.03–1.93). Both data sets indicated that a first pregnancy was a more important risk factor for early-onset disease than for late-onset disease.

CONCLUSIONS — Many reported risk factors are weak and show inconsistencies between studies. They may be secondary to more direct, as-yet-undiscovered risk factors. Although irrelevant in the majority of cases, the increased risk associated with delivery by cesarean section deserves further study.

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IDDM, insulin-dependent diabetes mellitus; OR, odds ratio; CI, confidence interval; RR, relative risk.

Environmental factors remain to be identified in childhood insulin-dependent diabetes mellitus (IDDM) (1). Perinatal risk factors such as maternal age, failure to breast-feed, and high socioeconomic status have been described, but published studies are contradictory. One reason some studies are difficult to interpret is that they have unsatisfactory control groups and non–population-based case series. This investigation used data collected routinely at birth to compare sociodemographic, obstetric, and neonatal factors in two population-based series of diabetic children and matched control children. A similar study (2) identified stressful perinatal events such as preeclamptic toxemia, cesarean section, and maternal-child blood-group incompatibility as risk factors, but these findings require confirmation.

There is evidence for two subtypes of IDDM in childhood (3,4), which are characterized in part by age at onset. A minor peak in the distribution of age at onset in the preschool years (5,6) and an absence of seasonal variation among children <5 years of age (5,7) have also been noted. These reports prompted us to compare risk factors in two subgroups defined by age at onset. If perinatal factors are important, their influence is likely to be greatest among early-onset cases.

RESEARCH DESIGN AND METHODS

Northern Ireland data

A prospective register of IDDM occurring in children <15 years of age has been maintained since 1989 (8). Details of earlier cases were assembled retrospectively, using information from pediatricians, nurses specializing in diabetes, summer camps, and the School Health Service.

Perinatal data were obtained from the Child Health System, which includes 99% of live births. Obstetric data were derived from birth notifications; and sociodemographic, parental disease history, and breast-feeding information were recorded by a health visitor during the first

Table 1—*Distribution of parental age at the time of birth in diabetic children and control subjects*

	Diabetic children *n* (%)	Control subjects *n* (%)	OR (95% CI)
Northern Ireland			
n	258	1,290	
Maternal age (year)			
<25	74 (28.7)	404 (31.3)	1.00
25–29	80 (31.0)	420 (32.6)	1.04 (0.73–1.46)
30–34	69 (26.7)	276 (21.4)	1.36 (0.95–1.96)
≥35	35 (13.6)	190 (14.7)	1.00 (0.65–1.56)
Mean ± SD	28.2 ± 5.5	27.9 ± 5.7	
Paternal age (year)			
<25	36 (14.9)	237 (20.3)	1.00
25–29	74 (30.6)	370 (31.8)	1.27 (0.82–1.97)
30–34	73 (30.2)	298 (25.6)	1.58 (1.02–2.46)
≥35	59 (24.4)	260 (22.3)	1.52 (0.96–2.39)
Unknown	16	125	
Mean ± SD	30.7 ± 6.1	30.1 ± 6.2	
Scotland			
n	271	1,355	
Maternal age (year)			
<25	96 (35.4)	627 (46.3)	1.00
25–29	98 (36.2)	459 (33.9)	1.40 (1.03–1.90)
30–34	50 (18.5)	197 (14.5)	1.68 (1.15–2.46)
≥35	27 (10.0)	72 (5.3)	2.43 (1.49–3.97)
Mean ± SD	26.9 ± 5.2	25.5 ± 5.2	

postnatal visit, when the infant was ~2 weeks old. Data were available for the period 1979–1987.

Of 272 children with diabetes born in this period, 258 (95%) were identified in the Child Health System. For each child with diabetes, five control subjects were randomly selected from children of the same sex born the same day whose mothers lived in the same health board.

Scotland data

Computerized hospital discharges have been monitored since 1968 to identify children whose diagnoses include diabetes (7). By December 1988, 321 children born during the period 1975–1976 and coded as Scottish residents had been identified. An additional 21 cases were obtained from a register maintained by Scottish clinicians (9).

Record linkage (10) was used to match these children to Scottish maternal discharge records using surname, date of birth, sex, and postal code. These records supplied sociodemographic, obstetric, and perinatal information for 95% of births in 1975–1976 (11). Of the 342 cases, 271 (79%) provided good matches and were included in the study. For each case, five control subjects were randomly selected from deliveries of the same sex on the same day at hospitals in the same health board. Multiple pregnancies were excluded because of difficulties in distinguishing between details of the neonates.

Statistical analysis

Analysis was conducted using the conditional logistic model (12,13), which takes account of case-control matching and provides odds ratios (ORs) that approximate relative risks (RRs). Variables that showed association with a risk factor (and therefore could potentially confound the relationship between the factor and the disease) were controlled for by including them in the logistic model. The interaction between age at onset (coded as <5 years or ≥5 years) and a risk factor provided a test for differences in RRs between children with early and late onset. Likelihood-ratio statistics were referred to the χ^2 distribution.

RESULTS

Parental age

Distributions of maternal age and paternal age (in Northern Ireland only) at birth are shown in Table 1. Northern Ireland data showed little evidence that older maternal age was associated with increased risk of diabetes. Although children born to fathers ≥30 years of age had an ~50% increase in risk compared with those born to fathers <25 years of age, this finding could largely be explained by the confounding effect of social class. By contrast, Scottish data showed evidence of increasing risk with advancing maternal age, and this finding was not attributable to the potential confounding effects of social class or parity.

Social class

Estimates of RR by social class grouping are shown in Table 2. Compared with those whose fathers were in professional or managerial occupations, Northern Ireland children with fathers in other occupations were at significantly decreased risk. In contrast, the corresponding estimates for Scottish children suggested a slight, but nonsignificant, increase in risk. Neither result was altered much by adjustments for maternal age or parity. In both sets of data, children with fathers whose occupation was not classified (students, armed forces, or not known) were at reduced risk.

Breast-feeding

Patterns of feeding among the Northern Ireland children at ~2 weeks of age are summarized in Table 3. The risk among children who were breast-fed was very similar to the risk for those who were not.

Table 2—*Comparison of social class distribution at birth between diabetic children and control subjects*

	Diabetic children *n* (%)	Control subjects *n* (%)	OR (95% CI)
Northern Ireland			
n	258	1,290	
Professional or managerial (I, II)	73 (28.3)	245 (19.0)	1.00
Skilled manual or nonmanual (III)	114 (44.2)	598 (46.4)	0.65 (0.47–0.89)
Semi- or unskilled manual (IV, V)	57 (22.1)	278 (21.6)	0.70 (0.48–1.03)
Armed forces, students, or not known	14 (5.4)	169 (13.1)	0.27 (0.14–0.49)
Scotland			
n	271	1,355	
Professional or managerial (I, II)	48 (17.7)	271 (20.0)	1.00
Skilled manual or nonmanual (III)	131 (48.3)	587 (43.3)	1.27 (0.88–1.82)
Semi- or unskilled manual (IV, V)	72 (26.6)	311 (23.0)	1.32 (0.88–1.97)
Armed forces, students, or not known	20 (7.4)	186 (13.7)	0.61 (0.35–1.05)

For children who were exclusively breast-fed (no artificial feeds), the risk was only slightly reduced. When these risks were adjusted for the confounding influence of social class, the resulting estimates were 0.76 (95% CI 0.54–1.07) and 0.73 (95% CI 0.50–1.05), respectively. Adjustment for other potential confounding variables (maternal age and parity) did not alter these estimates.

Material deprivation

Several deprivation measures were available in the Northern Ireland data (Table 4). Children born to unmarried mothers were at significantly lower risk. Those born into homes with six or more residents were at slightly, but not significantly, reduced risk. Taking size of house into account by calculating the number of residents per bedroom, those born into overcrowded households (more than two people per bedroom) were at three quarters of the risk of other children. However, this was significant only when residents per bedroom was analyzed as a continuous variable ($P = 0.03$). There is a high proportion of missing data for these variables because numbers of residents were not recorded in the final years of the period. Nonavailability of a bathroom was associated with a much reduced risk, as was the health visitor's subjective assessment of unsatisfactory home conditions. Sharing the home with another family (excluding unmarried mothers still living at home) was also associated with a marked but nonsignificant risk reduction.

Obstetric, neonatal, and family history data

Analyses of other variables are summarized in Table 5. Prematurity, low or high birthweight, being small for gestational age, low 5-minute Apgar score, multiple (twin) pregnancies, maternal height, pre-eclamptic toxemia, prolonged duration of labor, and assisted delivery (e.g., use of forceps or vacuum extraction) were not associated with any significant difference in risk. However, both sets of data indicated that babies born by cesarean section are at significantly increased risk. Adjustment for parity, birthweight, and breast-feeding practice in the Northern Ireland data did not alter this finding. In the Scottish data, where it was possible to distinguish between elective and emergency sections, the increase was most evident for elective section (OR = 2.08, 95% CI 1.28–3.41 relative to normal deliveries). Children of first pregnancies were at significantly increased risk only in the Northern Ireland data. Allowance for the confounding effects of maternal age gave adjusted risks of 1.66 (95% CI 1.18–2.35) in the Northern Ireland data and 1.01 (95% CI 0.75–1.36) in the Scottish data. Additional adjustment for social class and breast-feeding practice (Northern Ireland data only) did not alter these risks.

Both data sources recorded maternal history of diabetes (IDDM or non-insulin-dependent diabetes mellitus) before pregnancy, although ascertainment of history may have been incomplete. Significant increases in risk were observed in children of diabetic mothers. Northern Ireland data also showed significantly increased risks for paternal history and paternal family history.

Comparisons of RRs by age at onset

When RRs were estimated in two subgroups defined by age at onset of diabetes (<5 years and ≥5 years), they did not

Table 3—*Comparison of infant-feeding practice at 2 weeks between diabetic children and control subjects in Northern Ireland*

	Diabetic children *n* (%)	Control subjects *n* (%)	OR (95% CI)
n	258	1,290	
Breast-feeding			
No	186 (74.4)	895 (73.2)	1.00
Yes	64 (25.6)	327 (26.8)	0.93 (0.67–1.28)
Unknown	8	68	
Artificial feeds			
Yes	202 (80.8)	995 (79.3)	1.00
No	48 (19.2)	260 (20.7)	0.89 (0.63–1.26)
Unknown	8	35	

Table 4—*Comparison between diabetic children and control subjects of measures of material deprivation recorded at the time of birth in Northern Ireland*

	Diabetic children *n* (%)	Control subjects *n* (%)	OR (95% CI)
n	258	1,290	
Marital status			
Unmarried	3 (1.2)	56 (4.4)	0.25 (0.08–0.80)*
Married	252 (98.8)	1209 (95.6)	1.00
Unknown	3	25	
Household size			
≥6 residents	41 (19.8)	244 (23.6)	0.80 (0.55–1.17)
<6 residents	166 (80.2)	791 (76.4)	1.00
Unknown	51	255	
Overcrowding			
>2 persons/bedroom	25 (12.1)	160 (15.5)	0.73 (0.46–1.16)
≤2 persons/bedroom	182 (87.9)	871 (84.5)	1.00
Unknown	51	259	
Bathroom available			
No	3 (1.2)	56 (4.4)	0.27 (0.08–0.85)*
Yes	251 (98.8)	1215 (95.6)	1.00
Unknown	4	19	
Condition of home			
Unsatisfactory	1 (0.4)	33 (2.6)	0.15 (0.00–0.90)†
Satisfactory	252 (99.6)	1236 (97.4)	1.00
Unknown	5	21	
Home shared			
Yes	17 (6.7)	130 (10.2)	0.63 (0.37–1.07)
No	238 (93.3)	1143 (89.8)	1.00
Unknown	3	17	

* $P < 0.01$. † $P < 0.05$.

differ significantly for most variables. However, in both sets of data, the RR for children of first pregnancies was significantly greater in the younger-onset subgroup. In the Northern Ireland data, this risk was 2.27 (95% CI 1.28–4.04); in the Scottish data, it was 1.33 (95% CI 0.80–2.22). The latter risk was 1.67 (95% CI 0.97–2.90) after adjustment for maternal age.

CONCLUSIONS — Both of our case series are population-based, and matched control subjects have been selected from the same population. An important advantage of using data recorded contemporaneously, before disease onset, is that many of the possible biases (14) in retrospective case-control studies do not apply. Neither is control nonresponse a problem in our study. However, the potential unreliability of routinely collected data recorded by many observers needs to be considered. This unreliability produces nondifferential misclassification (15), which typically results in conservative estimation of risks.

Other potential sources of bias remain. Scottish diabetic children whose families had changed addresses are less likely to succeed in the record linkage. This could produce a social class bias were certain classes to be more mobile, but available data suggest that any such effect is minimal (16). A similar bias might apply to marital status in the Northern Ireland data. The birth records of some diabetic children born to unmarried mothers could be difficult to match to their diabetic register details because subsequent marriage could lead to a change of surname and address. In both sets of data, increased mobility of students and armed forces personnel could contribute to the reduced risk among those whose social class was not ascertained, because cases of diabetes in their offspring are less likely to be registered because of emigration.

Flood et al. (17) concluded that older maternal age was a risk factor after they compared the distribution of mother's age in Boston patients with national data for a single year. The observation was repeated in a similar analysis from Turin (18), but temporal and geographical variations in maternal age cannot be discounted. The potential bias in studies that compare mother's age at the time of birth of her diabetic and nondiabetic children makes them difficult to interpret (19,20). Of studies using the conventional case-control design, most have supported the finding (2,21,22), although one has not (23). Our results suggest that maternal age may not be relevant in every population.

The higher risk to Northern Ireland children with fathers in professional or managerial occupations, although not supported by the Scottish data, concurs with the majority of previous studies. Higher rates have been noted in children living in areas with higher average income (24,25) and in children from high-income families (23). A Scottish study reported lower risks in materially deprived urban areas (26), but another from England showed higher risks in deprived areas (27). Another study reported that a greater proportion of diabetic children's fathers were manual workers (21). Our Northern Ireland data suggests that deprivation offers some protection against childhood diabetes.

Our limited infant-feeding data did not confirm previous reports of a protective effect for breast-feeding (23,28, 29). Other studies have failed to detect any such effect (21,30). The breast-feeding hypothesis is, nevertheless, supported by the identification of a cow's milk protein that may trigger the disease (31). Additional detailed studies into infant-feeding practices of the kind reported from Finland (32) and Pittsburgh (33) are re-

Table 5—*Comparison of obstetric, neonatal, and family history data between diabetic children and control subjects*

	Northern Ireland			Scotland		
	Diabetic children %	Control subjects %	OR (95% CI)	Diabetic children %	Control subjects %	OR (95% CI)
n	258	1,290		271	1,355	
Gestation <38 weeks	8.6	10.0	0.83 (0.51–1.35)	7.9	8.1	0.93 (0.57–1.51)
Birthweight <2.5 kg	5.1	5.2	0.97 (0.53–1.79)	4.1	6.2	0.66 (0.34–1.26)
Birthweight ≥4.0 kg	12.6	11.3	1.14 (0.75–1.74)	9.2	8.1	1.15 (0.72–1.83)
Small for gestation	3.9	5.7	0.67 (0.32–1.36)	7.6	9.2	0.82 (0.48–1.37)
Apgar 5 min ≤7	—	—	—	7.8	7.9	0.99 (0.60–1.65)
Multiple pregnancy	2.3	1.9	1.28 (0.50–3.27)	—	—	—
Mother's height <1.55 m	—	—	—	21.2	19.3	1.06 (0.76–1.49)
Mother's height ≥1.65 m	—	—	—	19.3	21.4	0.87 (0.61–1.23)
Preeclamptic toxemia	3.5	3.7	0.94 (0.42–2.01)	—	—	—
Labor duration ≥10 h	12.4	10.8	1.15 (0.75–1.76)	22.8	25.2	0.92 (0.66–1.27)
Assisted delivery	10.9	8.3	1.46 (0.93–2.28)	15.4	14.0	1.21 (0.83–1.77)
Cesarean section	13.6	9.0	1.66 (1.10–2.50)*	12.8	8.4	1.70 (1.12–2.59)*
First pregnancy	34.5	28.1	1.41 (1.03–1.93)*	32.6	36.6	0.84 (0.63–1.11)
Maternal history	1.6	0.2	6.7 (1.5–29.8)*	2.6	0.4	7.0 (2.2–22.1)†
Paternal history	1.9	0.2	11.2 (2.2–58.6)†	—	—	—
Maternal family history	10.5	7.9	1.37 (0.87–2.14)	—	—	—
Paternal family history	8.1	4.7	1.80 (1.07–3.02)*	—	—	—

Birthweight ≥ 4.0 kg excludes children with mothers known to have diabetes. * $P < 0.05$. † $P < 0.01$.

quired, but the avoidance of recall bias is problematic.

In contrast with our findings, two studies have reported an increased risk among children in crowded households in early childhood (34,35).

Many of the analyses of risk factors in Table 5 are exploratory, and any statistically significant findings must be interpreted cautiously. Our negative findings for birthweight and gestation concur with one study (21) but contrast with others that suggested that high birthweight (22,36) and gestation of <38 weeks (2) are risk factors. A previous study has reported firstborn children to be at increased risk (20), but another did not (22). Our results indicate that this increased risk may be restricted to early childhood and may be confounded by maternal age. An increased risk among children delivered by cesarean section was apparent in both our studies. As a consequence, this finding is persuasive, and it strongly supports an earlier report (2). However, we were unable to confirm the increase in risk associated with maternal preeclamptic toxemia also reported in that study. The greater relevance of paternal rather than maternal history of diabetes observed in our data has been reported previously (37).

With the exception of birth order, our analyses did not distinguish any consistent differences in risk factors between diabetes in early and late childhood. If childhood diabetes has two subtypes, they appear to share a similar pattern of perinatal risk factors.

The level of agreement both within our sets of data and between our data and previous work is disappointing. It is tempting to speculate that, from one country to another, different environmental exposures are responsible for the development of diabetes in genetically susceptible individuals. An alternative explanation is that the nonspecific risk factors so far identified are proxy variables for stronger, unknown factors that may show different associations with maternal age, breast-feeding, social class, etc. in different countries. Additional properly conducted case-control studies are needed to clarify the picture.

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