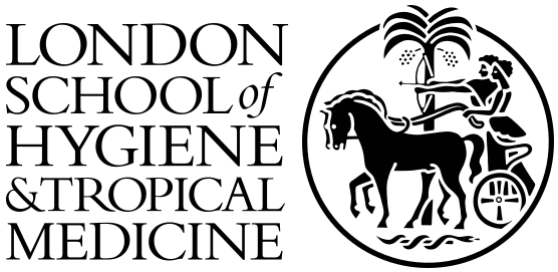

Pre-natal and early life risk factors for diabetes, cryptorchidism and inguinal hernia in children

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Abstract

Findings are presented from matched case-control studies of risk factors for diabetes, cryptorchidism and inguinal hernia in children using routine data collected by the Oxford Record Linkage Study since 1965.

There were 315 cases born 1965–85 in the diabetes study, 947 and 1449 cases in studies of cryptorchidism diagnosed at birth and at orchidopexy respectively, and 1701 male and 347 female cases in the study of inguinal hernia. Each case was individually matched with up to eight controls on sex, year, and hospital or place of birth.

A potential bias caused by differential migration of cases and controls was identified. A sample of 753 controls born in Oxfordshire was checked against the Oxfordshire Family Health Services Authority register to determine migration out of the study area in relation to perinatal risk factors. A general procedure was developed to estimate the strength of the migration bias.

Pre-eclampsia was identified as a significant pre-natal risk factor for diabetes. The studies of cryptorchidism identified significantly raised risks with low birth weight, low social class and breech presentation. The results suggested that asymmetric growth retardation in the third trimester may be involved in the aetiology of undescended testes that do not spontaneously descend in later life. Analysis of risk factors among siblings of cases and controls suggested that permanent changes to the mother may occur around the time of the pregnancy involving the affected child.

Low birth weight, short gestation and smoking during pregnancy were associated with significantly raised risks of inguinal hernia among boys. Among girls the results were similar, suggesting that mechanisms independent of the sex of the child may be important in the aetiology of this condition. Estimates of disease risk in siblings showed a strong familial aggregation, especially among girls.

To my parents,
who have always supported me in whatever I have wanted to do.

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Abbreviations

ORLS	Oxford Record Linkage Study
LSHTM	London School of Hygiene & Tropical Medicine
NHS	National Health Service
NHSCR	National Health Service Central Register
FHSA	Family Health Services Authority
OPCS	Office of Population Censuses and Surveys
ICD	International Classification of Diseases
CSO	Classification of Surgical Operations
n.e.c.	not elsewhere classified
LRS[n]	Log-likelihood Ratio Statistic with n degrees of freedom
OR	Odds Ratio
95% CI	95% Confidence Interval
IDDM	Insulin Dependent Diabetes Mellitus
LGA	Large for Gestational Age
AGA	Appropriate for Gestational Age
SGA	Small for Gestational Age

Part I

Study Design

Chapter 1

Introduction

1.1 Prenatal and early life origins for disease in later life

During the most critical stage of human development, while *in-utero*, adverse exposures may initiate a disease process which takes many years to reach clinical significance, or may predispose one to disease in later life [1, 2]. Chemical, viral and exposures to ionising radiation are known to have adverse effects on foetal development [3] and although many of the effects of these exposures are observable at birth, as congenital malformations, others may only become apparent in later life. For example: (a) it is now accepted that exposure to diethylstilboestrol (DES) during the first trimester of pregnancy can cause adenocarcinoma of the lower genital tract in female offspring some 10–30 years later [4]; (b) the congenital rubella syndrome is strongly associated with diabetes, but the clinical onset of disease may not appear until 10–30 years after birth [5]; and (c) there is a well established association, probably causal, between prenatal exposure to diagnostic x-rays and an increased risk of cancer in childhood [6].

There is increasing evidence that prenatal exposures may be involved in the development of a wide range of diseases in man. For example, recent studies suggest that the *in-utero* environment may be important in the aetiology of the sudden infant death syndrome [7], childhood cancers [8, 9], testicular cancer [10], ovarian germ cell cancer [11], breast cancer [12], Crohn's disease [13], insulin dependent diabetes [14], schizophrenia [15], and epilepsy [16]. The intrauterine environment may also influence blood pressure [17] and lung function [18] in children and susceptibility to hypertension [19, 20], cardiovascular disease [21] and non-insulin dependent diabetes in adults [1]. It is, however, difficult to study risk factors for diseases diagnosed several years after birth or in adolescence and adulthood. In such studies markers for *in-utero* exposures may be highly misclassified, potentially with

recall bias, when cases or their mothers are interviewed years after the birth. In addition, many cases may not know their own exposure history, and sometimes the mothers cannot be traced or may have died. Routine data provides a potentially useful source of information on perinatal exposures. Information from obstetric case notes, if available, can be used to avoid recall bias and reduce misclassification errors. The Oxford Record Linkage Study (ORLS) is one such accumulation of routinely collected medical records that makes such studies possible.

1.2 Specific aims and goals

The major aim of this study was to examine prenatal and early life risk factors for insulin dependent diabetes, cryptorchidism and inguinal hernia in children. Each disease raises specific issues which will be considered in detail later, but the general approach was to estimate the increase in risk of disease that was associated with prenatal or early life exposures.

A more general aim of this study was to investigate the usefulness of routine data for studying prenatal risk factors for disease in later life. In particular, problems associated with incomplete follow-up and migration (i.e. selecting controls at birth) were considered.

Chapter 2

Study Design

2.1 Rationale for a nested case-control study

An ideal prospective cohort study of prenatal risk factors for disease in later life would explicitly measure prenatal exposures and monitor subjects for specific diseases that develop in later life. Such studies are usually not feasible for rare conditions or for diseases that develop years after birth because such a study would need to run for many years or decades before a sufficient number of subjects developed the disease of interest. Historic birth cohorts can be followed up to the present day to ascertain all cases of the disease under study but these studies are limited to relatively common diseases [1] because of the logistical difficulties in following up the large number of people that are needed to ensure a sufficient number of affected subjects in the cohort. The nested case-control study design provides an efficient alternative to the retrospective cohort study. The main advantage of nested case control studies over cohort studies is that only for a fraction of the population do exposure data need to be obtained.

The usual design involves the following: (a) selecting all cases of the disease under study, usually from a defined geographical area; (b) finding the obstetric notes or delivery records for those cases who were born within the area; (c) comparing these to all, or a sample of, births occurring at the same time in the same area. This design has been used to investigate prenatal and early life risk factors for pyloric stenosis [22], the sudden infant death syndrome [7], spastic cerebral palsy [23], cryptorchidism [24], testicular cancer [25], insulin dependent diabetes [14], inflammatory bowel disease [26], schizophrenia [27, 28], childhood cancers [8, 9, 29, 30], neuroblastoma [31, 32] and leukaemia [33].

Studies based around routine case notes, however, still require a large amount of work, first to identify the cases and controls, and then to find their delivery and their mother's

maternity notes. Once found trained personnel would need to abstract and code relevant data items from the case notes. Record linkage systems, in particular the Oxford Record Linkage Study (ORLS), offer a potentially less expensive option. The ORLS is described in appendix A. Within limits the ORLS currently provides an exceptional opportunity to examine prenatal and early life risk factors for selected diseases in later life.

2.2 Diseases and conditions to be studied

The diseases and conditions selected for study were insulin dependent diabetes mellitus (type I diabetes), cryptorchidism and inguinal hernia. Cases were identified by searching the ORLS delivery and general hospital files for specific discharge diagnoses or operation codes. Appendices B and C describe in detail the methods used to identify cases. The epidemiology of these diseases and conditions, with emphasis on possible pre-natal origins, will be discussed in chapters 5, 6 and 9.

2.3 Sample size considerations

To detect an odds ratio of 2.0 or greater for a dichotomous exposure of moderate prevalence (10% of controls exposed, 5% significance level, and 80% power) requires 223 cases each with two matched controls [34]. The sample size should be increased by about 10% if a confounding variable is to be included in the analysis [34]. Missing records or unrecorded data items and prior exclusions will result in a reduction of the actual number of subjects entering the analysis. In addition, analyses usually extend beyond simple relative risks for dichotomous exposures: polychotomous exposures, sub-groups and interactions are often analysed, and multivariate models are used to summarise the results. These considerations imply a minimum sample size of 250–300 expected cases is needed.

The number of cases that might be expected to occur in the ORLS population was estimated from published Hospital In-Patient Enquiry (HIPE) data [35]. It became clear that, of the diseases or conditions that might have prenatal origins, a hospital diagnosis of diabetes or an operation to correct an undescended testis or inguinal hernia would provide a reasonable number of cases for study. The actual number of affected people identified by the ORLS was 330, 1571 and 2809 respectively, although after exclusions the actual number of people available for analysis was less than the above. To get over 300 cases the diabetes study had to include cases born 1965–86, but to ensure sufficient numbers the other two studies only needed to include cases born 1970–86.

2.4 Brief overview of the study design

The study was designed as a series of nested matched case-control studies with diseased individuals identified from ORLS records. Section B.1 and C.1 in the appendices lists the diagnostic or operation codes used to select cases. Since 1963, the ORLS have collected information on births, deaths and hospital events in such a way that all records relating to one individual can easily be traced and linked together. The details of the case selection are described in detail appendix B (section B.2) for the diabetes study, and appendix C for the studies of cryptorchidism and inguinal hernia.

Diseased individuals were linked to a summary of their delivery notes. If they did not have a delivery record (i.e. were not born under ORLS coverage) they were not included in the study. Up to eight controls were selected at random from livebirths of the same sex, born in the same hospital, during the same year as the case. Several complex linkages between different ORLS files and a computer program written and run at the London School of Hygiene were required to select the controls. The details of the control selection procedure are described in appendix B.

The mothers of the cases and controls were identified, and for the studies of undescended testis and inguinal hernia, so too were the siblings of cases and controls. Selected data items from general hospital, delivery, maternity and death records were extracted for cases and controls, and for the cryptorchidism and inguinal hernia studies, also for the siblings and mothers of cases and controls. Data extraction from the ORLS files is described in more detail in appendix B, section B.4.

2.4.1 Matching

The prevalence of certain procedures, use of diagnostic tests and the quality of writing-up case notes may differ between hospitals and over time. For example, the study area included a large teaching hospital where protocols might differ from that in a small cottage hospital. To ensure that the delivery records of cases and controls were comparable controls were matched to cases on year and hospital of birth, or if domiciliary to another domiciliary delivery during the same year. A matched design and analysis ensured that any confounding effects due to the above matching variables were controlled for in the analysis. Cases were also matched to controls on sex because sex is known to be related to obstetric variables (e.g. birth weight, incidence of congenital malformations) and for undescended testes and inguinal hernia sex is a prerequisite or strong risk factor for disease. Up to eight controls were selected for each case.

Chapter 3

Migration Bias

3.1 Introduction

One of the disadvantages of the study design described in section 2.4 was that migration of subjects out of the study area may introduce a potential bias into the study. The cases, by the way in which they were identified, are individuals who were born in the study area and were still living there at diagnosis. In comparison, the controls, although also born in the study area may at any time subsequently have died or migrated from the area. If mortality or migration rates were related to the prenatal risk factors under investigation this could lead to a biased estimate of the relative risk [36].

To investigate this bias data from the case-control study of insulin dependent diabetes (described in chapter 5) were used to determine the relation between prenatal variables and subsequent migration. The amount by which the relative risk was biased by migration and death of controls was calculated for a range of general situations. The result of this work has also been published elsewhere [37].

3.2 Methods

The controls, from the diabetes case-control study, were used to describe the pattern of migration in relation to perinatal variables. Only controls born to parents resident in Oxfordshire were used because information on migration status was only collected for these controls.

3.2.1 Linkage with the Oxfordshire FHSA

In order to assess whether controls had migrated out of Oxfordshire the register of the Oxfordshire Family Health Services Authority (FHSA) was searched in March 1994. The Oxfordshire FHSA keep a list of all people who are enrolled with National Health Service (NHS) doctors in Oxfordshire or have been enrolled there at any time since 1987. Virtually all individuals of the ages covered by this study and resident in Oxfordshire will be registered with the NHS, which was verified as described later.

The search of the Oxfordshire FHSA was made using NHS number [38], which is a unique personal identifier, first and last names, sex and date of birth of the controls, as extracted from Oxford Record Linkage Study (ORLS) records. Anyone not found by this method was assumed to have died or migrated out of the Oxfordshire FHSA area before 1987. For five controls the link to an FHSA record was not certain: two were classified as not linked and three as linked. To validate negative linkage, records for 10 males and 10 females who did not link with a record on the FHSA were checked against the NHS Central Register (NHSCR). The NHSCR includes all people who are or have been registered with the NHS in England and Wales. It indicates in which FHSA subjects are currently enrolled, or their reason for removal. Eighteen of the 20 people not linked to records on the Oxfordshire FHSA were confirmed as currently registered outside of Oxfordshire, one had been removed from the Oxfordshire FHSA in 1981 and one was matched to a person still registered in Oxfordshire. This person was one of the five uncertain matches and was re-classified as a positive match. In order to check whether positive linkages with the Oxfordshire FHSA represented individuals truly present in the area, diabetic cases with a recent hospital admission in Oxfordshire were checked against the Oxfordshire FHSA. During the five years 1983–87 there were 122 diabetics among the case group who had a general hospital admission where their area of residence was recorded as Oxfordshire. Of these, only two were not linked to records on the Oxfordshire FHSA, and both known to have died during 1986 (i.e. they were correctly not registered on the Oxfordshire FHSA from 1987 onward).

3.2.2 Analysis

In the following analyses information collected on the control group was used to estimate the strength of the association between migration and potential prenatal and early life risk factors for disease in later life. Odds ratios for migration were calculated by unconditional logistic regression using the computer package Stata [39]. The expected size of the bias due

Table 3.1: Odds ratios for migration out of Oxfordshire for sex, year of birth, place of birth, and social class, 1965–1986

Risk factor	Migrated: Yes (total=219) number	Migrated: Yes (total=219) percent	Migrated: No (total=534) number	Migrated: No (total=534) percent	Odds* ratio	95% confidence interval	p-value
Sex*							
Male	113	51.6	278	52.1	1.00	baseline	
Female	106	48.4	256	47.9	0.98	0.71–1.36	0.900
†LRS[1]=0.02, p=0.900							
Year of birth*							
1965–69	57	26.0	104	19.5	1.00	baseline	
1970–74	91	41.6	220	41.2	0.73	0.48–1.12	0.154
1975–79	47	21.5	128	24.0	0.67	0.41–1.10	0.114
1980–85	24	11.0	82	15.4	0.57	0.32–1.03	0.062
LRS[3]=4.19, p=0.242; trend LRS[1]=3.72, p=0.054							
Place of birth*							
Oxford district hospitals	140	63.9	384	71.9	1.00	baseline	
Banbury district hospitals	72	32.9	132	24.7	1.37	0.96–1.97	0.086
Domiciliary	7	3.2	18	3.4	0.77	0.30–1.99	0.586
LRS[2]=3.66, p=0.161							
Social class of parents*							
I	29	13.2	37	6.9	2.93	1.65–5.20	<0.001
II	30	13.7	62	11.6	2.04	1.20–3.49	0.009
III	58	26.5	218	40.8	1.00	baseline	
IV	13	5.9	73	13.7	0.66	0.34–1.29	0.226
V	4	1.8	35	6.6	0.44	0.15–1.29	0.134
Other occupations	42	19.2	23	4.3	7.35	4.05–13.34	<0.001
Missing	43	19.6	86	0.16	2.24	1.36–3.70	0.002
LRS[4]=27.71, p<0.001; trend LRS[1]=27.04, p<0.001 (groups I to V only) LRS[6]=73.07, p<0.001 (all groups included)							

* Odds ratios adjusted for sex, year of birth and place of birth
† LRS[n] = Log-likelihood Ratio Statistics on n degrees of freedom

to migration and death was derived for a general instance, assuming different proportions of the population lost to follow-up. Mathematical details are contained in appendix E.

3.3 Results

There were 218 cases and 753 controls born to parents resident in Oxfordshire during 1965-86. Eight of the controls had died before 1987. Five-hundred and thirty-four (70.9%) of the controls were linked with records on the Oxfordshire FHSA register. In total, therefore, 219 out of 753 (29.1%) controls had migrated out of Oxfordshire or died during 1965–87, an average rate of 2.53 per 100 person-years. Hereafter, references to 'migration' denote people who were not linked to a record on the Oxfordshire FHSA, including people who have died. The annual migration rate was similar for males (2.53 per 100 person-years) and females (2.52 per 100 person-years).

There was no difference in the odds of migration between males and females, as seen in table 3.1. Persons born in the earlier time periods were more likely to have migrated than those born in the later periods. There was a strong relationship between migration and social class, with a statistically significant trend ($p<0.001$) across groups I to V. (Up to 1972 social class was defined as father's social class; from 1973 it was defined as bread-winner's social class.) The group most likely to have migrated were born into the social class group classified as 'other occupations' (students, armed forces, and, after 1972, housewives). Those classified to social class group 'unoccupied and not known', which included the unemployed, were also more likely to have migrated than the baseline group.

Table 3.2 shows the relation between obstetric variables and migration. There was little change in the odds ratio across birth weight groups, except that those with the lowest birth weights were more likely to have migrated than those in the baseline group (odds ratio (OR): 1.65; 95% confidence interval (95% CI): 0.76–3.59). This result was little changed when subjects who had died were removed from the analysis (OR :1.57; 95% CI: 0.71–3.49). Risk of migration was reduced for children with the longest gestation, but this observation was based on small numbers and did not reach statistical significance. Maternal parity (before this birth) was strongly related to migration, with risk decreasing with parity up to two, but not decreasing thereafter. There was weak evidence that children born to younger mothers were more likely to migrate than those born to older mothers, but this disappeared after adjusting for maternal parity.

Results for selected perinatal factors are presented in table 3.3 and 3.4. Raised maternal systolic and diastolic blood pressure were associated with a reduced risk of migration, the former significantly so, as was maternal blood group 'AB', but this observation was based on small numbers. Pre-eclampsia, excessive vomiting during pregnancy, x-ray, maternal body mass index and smoking during pregnancy were not strongly related to migration. Neither

Table 3.2: Odds ratios for migration out of Oxfordshire for birth weight, gestation, maternal parity and age

Risk factor	Migrated: Yes (total=219) number	Yes percent	Migrated: No (total=534) number	No percent	Odds* ratio	95% confidence interval	p-value
Birth weight (kg)							
≤2.4	12	5.6	19	3.6	1.65	0.76–3.59	0.210
2.5–2.9	35	16.3	78	14.8	1.15	0.71–1.86	0.569
3.0–3.4	78	36.3	197	37.4	1.00	baseline	
3.5–3.9	63	29.3	167	31.7	0.92	0.62–1.36	0.674
4.0 or more	27	12.6	66	12.5	0.99	0.59–1.69	0.985
missing§	4		7				
†LRS[4]=2.41, p=0.661; trend LRS[1]=1.39, p=0.239							
Gestation (completed weeks from date of last menstrual period)							
≤36	12	6.5	29	6.1	0.98	0.48–2.01	0.963
37–39	55	29.9	173	36.5	0.73	0.50–1.07	0.109
40–42	111	60.3	247	52.1	1.00	baseline	
43 or more	6	3.3	25	5.3	0.55	0.21–1.38	0.201
missing	35		60				
LRS[3]=3.90, p=0.272; trend LRS[1]=0.18, p=0.673							
Maternal parity (before this birth)							
0	102	4.7	195	36.7	1.00	baseline	
1	73	33.6	192	36.1	0.73	0.51–1.05	0.090
2	25	11.5	91	17.1	0.54	0.33–0.90	0.019
3 or more	17	7.8	54	10.2	0.59	0.32–1.08	0.085
missing	2		2				
LRS[3]=7.87, p=0.049; trend LRS[1]=6.93, p=0.008							
Maternal age (years)							
≤19	29	13.3	54	10.1	1.23	0.72–2.10	0.447
20–24	75	34.4	169	31.7	1.00	0.68–1.47	0.995
25–29	75	34.4	180	33.8	1.00	baseline	
30–34	27	12.4	98	18.4	0.64	0.39–1.06	0.086
35 or over	12	5.5	32	6.0	0.85	0.41–1.76	0.669
missing	1		1				
LRS[4]=5.03, p=0.284; trend LRS[1]=3.11, p=0.078							

* Odds ratios adjusted for sex, period and place of birth
† LRS[n] = Log-likelihood Ratio Statistics on n degrees of freedom

were Rhesus blood group, Rhesus incompatibility, mother receiving a blood transfusion, albuminuria, duration of labour, episiotomy, Apgar score, oxygen or resuscitation at birth, or size of baby's head (not shown in the tables). When the eight subjects who had died were removed from the analyses the results remained essentially the same.

Table 3.3: Odds ratios for migration out of Oxfordshire for maximum blood pressure, maternal blood group and pre-eclampsia

Risk factor	Migrated: Yes (total=219) number	Migrated: Yes (total=219) percent	Migrated: No (total=534) number	Migrated: No (total=534) percent	Odds* ratio	95% confidence interval	p-value
Maximum systolic blood pressure (mmHg)							
≤119	5	6.8	14	6.2	0.90	0.30–2.69	0.853
120–139	57	78.1	148	65.2	1.00	baseline	
140 or more	11	15.1	65	28.6	0.42	0.20–0.87	0.019
Missing	35		36				
Not collected	111		271				
†LRS[2]=6.16, p=0.046;trend LRS[1]=4.18, p=0.041							
Maximum diastolic blood pressure (mmHg)							
≤79	22	30.1	59	26.0	1.08	0.58–2.03	0.807
80–89	37	50.7	106	46.7	1.00	baseline	
90 or more	14	19.2	62	27.3	0.63	0.31–1.27	0.194
Missing	35		36				
Not collected	111		271				
LRS[2]=2.30, p=0.316; trend LRS[1]=1.81, 0.178							
Maternal blood group							
O	92	47.7	207	43.4	1.00	baseline	
A	75	38.9	204	42.8	0.81	0.56–1.17	0.260
B	23	11.9	40	8.4	1.33	0.75–2.37	0.329
AB	3	1.6	26	5.5	0.27	0.08–0.92	0.036
Missing	11		22				
Not collected	15		35				
LRS[3]=8.67, p=0.034							
Pre-eclampsia or eclampsia							
No mention	184	84.0	449	84.1	1.00	baseline	
Any mention	35	16.0	85	15.9	1.03	0.67–1.60	0.886
LRS[1]=0.02, p=0.886							

* Odds ratios adjusted for sex, period and place of birth
† LRS[n] = Log-likelihood Ratio Statistics on n degrees of freedom

Table 3.4: Odds ratios for migration out of Oxfordshire for vomiting during pregnancy, x-ray, body mass index and smoking

Risk factor	Migrated				Odds* ratio	95% confidence interval	p-value
	Yes (total=219)		No (total=534)				
	number	percent	number	percent			
Vomiting during pregnancy							
No mention	204	93.2	497	93.1	1.00	baseline	
Any mention	15	6.8	37	6.9	1.33	0.68–2.61	0.404
†LRS[1]=0.68, p=0.410							
X-ray during pregnancy							
No	196	96.6	478	96.2	1.00	baseline	
Yes	7	3.4	19	3.8	1.05	0.42–2.60	0.919
Missing	0		1				
Not collected	16		36				
LRS[1]=0.01, p=0.919							
Body mass index (kg/m^2)							
<22	6	15.8	40	27.4	0.46	0.17–1.24	0.124
22–25.9	21	55.3	62	42.5	1.00	baseline	
26 or more	11	28.9	44	30.1	0.68	0.29–1.59	0.376
Missing	7		8				
Not collected	174		380				
LRS[2]=2.73, p=0.256							
Smoking during pregnancy							
No	34	79.1	111	75.5	1.00	baseline	
Yes	9	20.9	36	24.5	0.83	0.36–1.91	0.659
Missing	8		12				
Not collected	168		375				
LRS[1]=0.20, p=0.656							

* Odds ratios adjusted for sex, period and place of birth
† LRS[n] = Log-likelihood Ratio Statistics on n degrees of freedom

3.3.1 Theoretical treatment of migration

The previous section demonstrated that some perinatal risk factors may be related to subsequent migration, and hence, may lead to a bias due to migration. To give generally applicable information about the impact of migration bias on the relative risk for disease in studies of prenatal or early life risk factors a hypothetical study was considered where controls are selected at birth from a single birth cohort and cases are selected as they are diagnosed in later life, from the same birth cohort. By assuming a constant migration rate in the exposed group and a different but constant migration rate in the unexposed group it was possible to determine how much bias was introduced into the estimate of the disease-exposure relative risk by differential migration. Mathematical details are given in appendix E. Table 3.5 shows the amount of bias in the apparent relative risk in a study that used controls selected at birth, compared to the true relative risk, for different values of cumulative migration, and different degrees to which migration is associated with the study variable. In table 3.5 the 'odds ratio for migration in relation to exposure' is a measure of the difference in migration rate between the exposed and baseline groups (for examples of actual values see tables 3.1, 3.2, 3.3 and 3.4). The 'percentage of population exposed at start of study' refers to the percentage in the exposure group under consideration relative to the baseline group, ignoring the numbers of people in the other exposure groups. For example, in table 3.1, approximately 19% of subjects were in social class I relative to social class III (the baseline). The 'percentage of population that migrated from the study by the end of the study period' is the number of controls lost from the study area by the end of the study period relative to the number that were selected at the start of the study period.

Table 3.5 was constructed using a migration rate of 2.5 per 100 person-years (i.e. 2.5% per year), a disease rate of 10 per 100,000 person-years and a true disease-exposure relative risk of 1.00. In sensitivity analyses one parameter was varied and the others held at the values given above and it was found that for migration rates between 0.5 per 100 and 10 per 100 person-years, or disease rates between 0.1 per 100,000 and 100 per 100,000 person-years, or true relative risks between 0.25 and 4.00 the results in the table held to plus or minus one percentage point. For certain extreme combinations of these values or for values outside the given ranges the bias may differ from that given in the table by more than plus or minus one percentage point.

As an example of the use of table 3.5, consider if there was no true association between a disease and, say, social class (i.e. all true relative risks were 1.00). If, during a study which used controls selected at birth, (a) 25% of controls migrate out of the study area, (b) there

were equal numbers of controls in each social class at the start of the study period (i.e. 50% exposed relative to baseline) and (c) the exposure-migration odds ratios were 3.00, 2.00, 1.00, 0.75 and 0.50 for social classes I to V respectively, then as a result of migration the observed relative risks for disease would be 0.88, 0.92, 1.00, 1.03 and 1.08. Although the bias in each stratum is small, taken together the results might easily be mistaken for a trend.

As another example, consider a risk factor where 10% of the controls are exposed relative to the baseline, and the migration-exposure odds ratio for the risk factor is 0.50 (this is similar to the actual figure for high parity versus nulliparity in Oxfordshire). If the true disease-exposure relative risk was 3.00 and a large proportion, say 50%, of the controls selected at birth had migrated by the end of the study period, the biased relative risk would be 3.45. If 25% of the controls had migrated the relative risk would be 3.21, and if 10% of the controls had migrated the relative risk would be 3.09.

It should be noted that the bias caused by migration is not always towards the null value of no association. If a risk factor is positively associated with disease but negatively associated with migration the relative risk will be biased upward and away from 1.0. Conversely, if a risk factor is negatively associated with disease but positively associated with migration the relative risk will be biased downward and away from 1.0.

Table 3.5: Percentage bias (relative risk with migration disregarded ÷ true relative risk × 100) in a case-control study in which controls are selected at birth but subsequently migrate out of the study area

Odds ratio for migration in relation to exposure	Percentage of population exposed at start of study								
	10			50			90		
	Percentage of population that migrated from the study by the end of the study period								
	10	25	50	10	25	50	10	25	50
0.125	105	114	135	108	124	157	121	148	176
0.25	104	111	126	106	117	136	111	126	144
0.50	103	107	115	103	108	117	104	110	119
0.75	101	103	106	101	103	107	102	104	107
1.00	100	100	100	100	100	100	100	100	100
1.50	98	95	91	98	95	91	98	96	92
2.00	96	91	84	97	92	86	97	93	87
3.00	93	84	76	95	88	79	96	91	82
4.00	90	79	70	94	86	74	96	90	79
8.00	83	67	57	92	81	64	95	88	74

Table derived using: migration rate $ID_{(0,\cdot)}$=2.5 per 100 person-years; disease rate $ID_{(1,\cdot)}$=10 per 100,000 person-years; and true disease relative risk RR_{true}=1.00. See appendix E for definition of $ID_{(0,\cdot)}$, $ID_{(1,\cdot)}$, and RR_{true}. Table holds to ±1 percentage point for true relative risks in the range 0.25–4.00, or migration rates in the range 0.5–10.0 per 100 person-year, or disease rates in the range 0.1–100 per 100,000 person-years. At extreme combinations of these values the percentage bias will differ from that given in the table by more than ±1 percentage point.

3.4 Discussion

Markers for prenatal exposures, like parental social class and maternal parity, were shown to be strongly related to subsequent migration. This in turn may lead to bias in the estimate of the disease-exposure relative risk for these variables. Other variables such as birth weight, gestation and maternal age were not strongly associated with migration, and this would lead to little or no bias in the relative risk. The relationships between the exposures and migration in this study, however, were specific to Oxfordshire and it will need studies elsewhere to determine whether these associations are similar in other Western populations and under different social and economic conditions. Nonetheless it seems reasonable that high social class and low parity, at least, should be strongly associated with potential for migration in Western countries.

FHSA registers have provided sampling frames for population based studies [40], especially for those among children [41] where the electoral roll and telephone directories are not suitable. Migration was assessed by linkage of ORLS records to entries on the Oxfordshire FHSA register, but the accuracy of this linkage was high: in a sample of 122 diabetic cases known to be recently resident in Oxfordshire, all 120 who were alive after 1986 were recorded on the Oxfordshire FHSA in 1987 or later, i.e. there was no misclassification. In a sample of 20 people who did not link with an Oxfordshire record, 19 were confirmed by the NHSCR as not registered in Oxfordshire. The twentieth person was unusual because she was one of five uncertain linkages. Since there were only four other uncertain linkages out of 753 control subjects, changing their classification would have made virtually no difference to the overall results.

The results presented in tables 3.1, 3.2, 3.3, and 3.4 relate to migration out of an English county and may show smaller effects than for a US county or state where migration rates may well be greater. On the other hand, in studies with national coverage the cumulative effect of migration is likely to be smaller than for county or state based studies. For example, in 1981 among 0–14 year olds, the migration rate out of Oxfordshire to the rest of Britain was 3.0% [42, 43], whereas the migration rate out of the country was only 0.3% [44]. Furthermore, the pattern of migration in relation to prenatal risk factors may be different for international migration than for inter-county or inter-state migration, so that these results may not apply to studies at the national level.

In case-control studies using controls selected at birth calculations showed that if appreciably less than 25% of the population migrate, bias will only exceed 10% if the migration-exposure odds ratio is large, say greater than 4.00 or less than 0.25. Only one of the observed

odds ratios was this extreme. This indicates that, with few exceptions, when the proportion of controls that migrate is small, bias caused by migration is unimportant so long as the associations detected are found to be approximately of the same strength in future studies.

If 25% or more of the population leave the study area, however, migration may cause appreciable bias even with more modest migration-exposure odds ratios. In Oxfordshire 29.1% of the controls had migrated by 1987, the end of the study period, when their average age was only 13 years. For a disease where the average age of onset is later in life, a longer interval from birth to disease will be required to ensure that a sufficient number of cases have occurred. The cumulative effect of migration may then result in more than 50% of the control group eventually migrating by the end of the study period, even if migration rates are not as high as those in Oxfordshire. Bias caused by migration, therefore, is likely to be important for case-control studies of diseases in adolescence (e.g. insulin dependent diabetes) or young adults (e.g. testicular cancer) especially in populations which are highly mobile (e.g. the USA, where in 1990–91, 2.9% of Americans had moved to a different state [45] compared to Britain where 2.1% had moved to a different county [46]). Furthermore, the potential effects of bias caused by migration will be even greater when investigating the role of prenatal factors in the aetiology of diseases of middle age and beyond, such as non-insulin dependent diabetes and heart disease [1].

3.4.1 Conclusions

A case-control study ideally needs to select controls who were known to be present in the study area at the time the case was diagnosed. This information is not usually available for studies of prenatal risk factors when the controls are selected from birth records. If the migration status of each control can be ascertained at the end of the study period the potential effect of migration bias for any given exposure can be determined in the same way as shown here, but it is often not be feasible to collect such information. The results here suggest, however, that if the investigator knows that appreciably less than 25% of the controls are likely to have migrated or died by the end of the study period then migration bias will be unimportant, unless the association between exposure and migration is large. If more than 25% of the controls have migrated or died, as is likely for state or county based studies of adolescent or adult diseases, then the bias caused by migration may be appreciable for certain risk factors. Such studies need to consider the impact of migration bias on their results and conclusions.

Part II

Insulin Dependent Diabetes Mellitus

Chapter 4

Brief Review of the IDDM Literature

4.1 Introduction

Insulin dependent diabetes mellitus (IDDM) is one of the commonest chronic diseases of childhood. The cumulative incidence of IDDM in British children to age 14 years was 0.2% in 1988 [47], which at that time was similar to all childhood cancers [48]. The consequences for the individual include acute complications and increased long term mortality and morbidity rates [49]. Genetic and environmental factors are known to play an important part in the pathogenesis of this disease, but to date the exact causes remain unknown.

4.1.1 Classification of diabetes mellitus

Diabetes mellitus is a disease that is characterised by hyperglycaemia. The hyperglycaemia is caused by an absolute or relative deficiency of insulin, or resistance to the effects of insulin, or both. Diabetes mellitus may be sub-divided into four types based on aetiology, natural history, clinical features and the need for insulin [50, 51].

- Insulin Dependent Diabetes Mellitus (IDDM) patients require exogenous insulin for survival, otherwise extreme hyperglycaemia, ketosis and death occur. These patients have little or no endogenous capacity to secrete insulin, hence the insulin dependence. Clinical onset of disease is rapid and usually occurs before 30 years of age.

- Non-Insulin Dependent Diabetes (NIDDM) usually occurs after 40 years of age but can occur in children. These patients may be treated with insulin to correct symptomatic

or persistent hyperglycaemia but they do not spontaneously develop ketosis if insulin is withdrawn.

- Malnutrition-related diabetes mellitus is of importance in developing countries and is frequently associated with malnutrition in infancy and childhood.

- Other types of diabetes mellitus are secondary to certain diseases and conditions. For example, chronic pancreatitis, cystic fibrosis, or haemochromatosis may lead to diabetes. Diabetes may also be induced by drugs or chemicals, or be caused by genetic syndromes, or abnormalities of hormones and insulin receptors. These causes of diabetes, however, are rare when compared to cases of unknown aetiology.

There are two other conditions related to diabetes mellitus that complete the spectrum of this disease: impaired glucose tolerance (IGT) and gestational diabetes mellitus (GDM) [50, 51]. IGT may represent a transient stage during the development of NIDDM [51], but not all who exhibit IGT become diabetic. GDM is diabetes or IGT that first occurs when a woman becomes pregnant. After parturition GDM may recede, or be re-classified to full diabetes or IGT. The remainder of this chapter concentrates on diabetes that occurs in childhood or young adult life in developed countries; this is usually the insulin dependent type of diabetes, i.e. IDDM.

4.1.2 IDDM and type I diabetes

In the literature the labels IDDM and type I (or type 1) diabetes are often used synonymously, although the term type I diabetes sometimes refers specifically to a particular disease process. The proposed mechanism of pathogenesis in type I diabetes is an autoimmune process leading to destruction of the pancreatic β-cells, which are essential to the production of insulin [52, 53]. The majority of the reports cited below refer to childhood onset diabetes which, within Caucasian populations, is usually insulin dependent and is thought to have a type I mechanism of pathogenesis.

4.2 Incidence

4.2.1 International comparison of incidence rates

The sudden onset of the clinical symptoms in childhood or young adult life, the ease of diagnosis, the necessity for specific life-long medical treatment with insulin, and, in developed countries, the relatively few deaths that occur at onset, make IDDM a disease suitable

for epidemiological register-based study. The Diabetes Epidemiology Research International Group (DERIG) [54] and the World Health Organization Project, the Multinational Project for Childhood Diabetes (DIAMOND) [55], helped establish childhood diabetes registers in many parts of the world. Standardization of data collection and analysis has enabled incidence to be compared between countries. Worldwide, in the late 1980s, the annual incidence of IDDM under 15 years of age ranged from a low of 0.6 per 100,000 in Korea and Mexico, through 13.5 per 100,000 in the United Kingdom, to a high of 35.3 per 100,000 in Finland [55]. Within Europe, rates were high in Scandinavia and Scotland, and lower in southern and eastern Europe [56], with the exception of Sardinia in Italy where the rates were unexpectedly high. In the United States rates were reported to be lower in blacks than whites [55, 57] and in Hispanics than non-Hispanics [55], although in Philadelphia the Puerto Rican Hispanics' rate was higher than that of the white and black populations [57]. The large variation seen between countries, and between ethnic groups within the same country, suggest that genetic susceptibility may play an important part in the aetiology of IDDM.

4.2.2 Age-sex specific rates of IDDM

There is a characteristic rise of incidence with age until around 12 years and then incidence falls in adolescence, with few cases of IDDM diagnosed after 35 years of age [58]. At older ages the incidence of IDDM is poorly documented, but a recent population based study from Denmark suggested that after 30 years of age the incidence of IDDM was approximately constant [59].

The evidence for sex differences in incidence is inconsistent; within Europe some registries have reported a small excess of boys, many reported no differences and some a slight excess of girls [56]. The excess of cases of one sex over the other may be related to the overall incidence rate; boys show an excess if the overall rate is high [60, 61]. There are also reports of male or female excesses at specific ages [58] but usually rates are aggregated by five-year age group and such detail is obscured in most published reports.

4.2.3 Time trends

During the 1960–80s, where data were available, there was no temporal variation in incidence in areas of the United States and Canada [55], but in Scandinavia and the UK the incidence of the disease in childhood was increasing [55] by 3% to 12% per year [54]. It has been suggested that cumulative lifetime incidence is not changing, but in those susceptible clinical

disease is occurring at an earlier age [62].

A well described temporal characteristic of IDDM incidence is the relative excess of cases diagnosed in winter months [47,58]. Peaks in incidence, or 'epidemics', have also been reported [63] and these two features suggest that IDDM may have a viral cause or trigger [64].

4.3 Family and genetic associations

There are strong familial associations in IDDM. The cumulative risk to age 30 years to parents, siblings or children of a diabetic proband is 3-10% [65], which is much greater than that in unrelated individuals. The risk to siblings appears to be greater than that for parents and children [65–67], and is increased with the number of shared haplotypes [68]. Most interesting is the observation that fathers with IDDM confer a greater risk to offspring than mothers with IDDM [69].

The HLA (human leukocyte antigen) alleles DR3, DR4, or both together, have high Sensitivity ~~specificity~~ for IDDM being present in over 90% of cases, however they have low Specificity ~~sensitivity~~ because their frequency in the general population is over 50% [68]. In Caucasians the HLA-DR2 is associated with a protective influence [68] but no simple model of inheritance fits the observed genetic associations [70]. More recently discovered are specific alterations to single amino acids, within the HLA region on the DQα and DQβ chain, that identify subjects at very high risk of IDDM [71–73]. Other alterations may exist on chromosome 6 or on other chromosomes, but at present there is much about the genetics of IDDM that remains to be discovered.

Studies of identical twins show that the concordance rate for IDDM is 30–40% [74–76], which suggests that genetic factors may be necessary but are not sufficient to cause IDDM. Apart from genetic factors, however, no other determinants have been confirmed as playing a major role in the aetiology of IDDM.

4.4 Autoimmunity and IDDM

Islet cell antibodies (ICAs) are a feature of IDDM [77,78], present in around 50%–80% of recently diagnosed cases [79]. Insulin autoantibodies (IAAs) are also found before treatment with insulin begins [80] and their presence is associated with rapid progression to IDDM [81]. Autoantibodies to glutamic acid decarboxylase (GADab) are found in a large proportion of first degree relatives of subjects with IDDM who eventually develop IDDM

themselves [82]. In addition the HLA-D genes partly control immune response and several autoimmune conditions have HLA susceptibility alleles in common with IDDM [75]. These observations strongly suggest that the pathogenesis of IDDM may have a strong autoimmune component [53].

In first-degree relatives ICA status is a sensitive marker of future IDDM [83, 84]; depending on cut-off criteria, sensitivity can be over 80% with specificity over 95% for predicting risk in first degree relatives. The risk of developing IDDM also increases with increasing ICA concentration [85]. First degree relatives who exhibit raised levels of ICA do not always develop IDDM in the near future [86]. Indeed, the identical co-twin of a diabetic proband may exhibit ICA but remain non-diabetic for at least ten years after the proband was diagnosed [87]. After ten years of being discordant for diabetes the risk of the co-twin developing IDDM is small, around 3% [87].

IDDM, however, exhibits some unusual features for a purely autoimmune disease: usual age at onset is in childhood and males are equally affected as females. In addition, among newly diagnosed patients presence of ICA appears to be transient, although some high titres persist for years after diagnosis [77]. IDDM can also be caused by ingestion of a rodenticide, and in some cases ICAs are reported even though the mechanism of pathogenesis is chemical [88]. Furthermore, immunosupression of newly diagnosed subjects has failed to result in long term remission of insulin dependency [89]. The autoimmune nature of IDDM, therefore, is complicated.

4.5 Viruses and IDDM

Anecdotal reports of recent viral infection preceding clinical onset of IDDM and presence of specific IgM antibodies in newly diagnosed subjects suggest a role for viruses in the aetiology of IDDM [5, 64]. In animal studies viruses have been shown to induce diabetes [64], and at autopsy pancreatic tissue from recently diagnosed cases shows lymphocytic infiltration [90]. Viruses may act by directly infecting and destroying pancreatic β-cells, or they may trigger or contribute to the autoimmune destruction of β-cells [64]. IDDM, however, is thought to have a long pre-clinical period, such that the beginning of pathogenesis may occur several years before diagnosis [91], perhaps even in infancy [92]. Furthermore the virtual elimination of mumps seen after the nationwide use of mumps-measles-rubella vaccination in Finnish children did not cause major changes in the incidence of childhood diabetes [93], nor were there changes in incidence associated with use of mumps and rubella vaccination in the USA [94]. The role of viruses, therefore, may be to so stress the body that slowly

progressing sub-clinical diabetes becomes clinically apparent, during or soon after an infection. Alternatively an infection may trigger the final stages of an autoimmune process that eventually leads to β-cell destruction [95].

In-utero infection has also been associated with IDDM. One of the consequences of the congenital rubella syndrome (CRS) is diabetes mellitus in later life [96]. Although the CRS is also associated with other defects like deafness, mental retardation, cataracts and congenital heart disease, it was found that patients at risk for IDDM had the same genetic features seen in classic IDDM, namely HLA-DR3 and the absence of HLA-DR2 [97]. A cluster of cases of diabetes has been reported among subjects exposed to mumps in-utero [98], and entrovirus infection during, or possibly before, pregnancy was found to be associated with an increased risk of IDDM in offspring [99]. Conversely, it has been speculated that infection or immune stimulation may also reduce the risk of diabetes [64]. Viral infections, therefore, play a role in at least some cases of IDDM, although the mechanisms involved are as yet unclear.

4.6 Risk factors

A variety of environmental exposures have also been documented as risk factors for IDDM but their significance is uncertain. Rainfall and temperature has been correlated with IDDM [100]. Local peaks in incidence around ages four to eight have been observed [58, 101]. Risk was increased if the father had a non-manual occupation [102, 103]. Solid foods rich in protein or carbohydrate have been implicated [104], and so too has living in an area of low population density [105]. Occurrence of IDDM is also associated with stressful life events [106], but like viruses this may merely precipitate the clinical onset of the disease.

Animal studies show that diet can be modified to change the incidence of diabetes in mice [107] and rats [108], with the critical period being just after weaning [109]. Since breast-feeding was first hypothesised as being protective against IDDM [110], subsequent ecological [111] and analytical [112–115] studies have strengthened the observation. Animal studies support the hypothesis that cow's milk can cause diabetes [116]. The discovery of antibodies against bovine serum albumin [117] in nearly all newly diagnosed IDDM patients led to the hypothesis that developing a 'memory' in the immune system, to a protein in cow's-milk, is the initial step in the aetiology of IDDM [117–119]. In later childhood the immune system, perhaps while fighting off an infection, may incidentally attack the pancreas.

Not all studies, however, find a significant protective influence of breast-feeding [120],

and the association between antibodies to bovine serum albumin and diabetes may not be specific to this disease. A study that also included patients with other autoimmune diseases found that antibodies to bovine serum albumin in IDDM may be associated with a predisposition to autoimmunity rather than immunity specific to β-cells.

To further complicate matters two recent epidemiological meta-analyses of breast-feeding and IDDM, based on studies found from comprehensive searches of the literature, came to different conclusions. The first study [121] concluded that early exposure to cow's milk was associated with a risk significantly increased by about 1.5 times for subsequent diabetes. The second study [122], which cites the earlier one, concluded that the weak association between infant diet and diabetes may have a methodological explanation; studies that used existing records showed little association compared to those that relied on maternal recall, and differences in case and control participation rates may have biased the results of these earlier studies.

4.6.1 Prenatal risk factors

Older maternal age is associated with an increased risk of a child developing IDDM [14, 102, 103, 123, 124], but the association is reversed for children of mothers with diabetes [125]. High birth weight [102] has been identified as being associated with increased risk of IDDM, as too has greater than average weight gain in infancy [126, 127]. High birth order has been implicated as a risk factor [123, 128], and so too has being first born [103].

Other risk factors point to pre-natal origins. For example, association with consumption of smoked foods at the time of conception [129], mother smoking during pregnancy [14], caesarean section [14, 103], maternal enteroviral infection [99], seasonality of births [130] and the congenital rubella syndrome [96] suggest the prenatal period may be important. Pre-eclampsia [14] and maternal-child blood group incompatibility between mother and child [14] may also be associated with increased risk of IDDM, perhaps because of an early immunological disturbance.

4.7 Summary

Recent advances in understanding the pathogenesis of IDDM now make it possible to identify children at high risk of developing IDDM, with the eventual hope of primary prevention [51, 131]. It is, however, still not known what factors initiate and control the pathogenesis of IDDM but a genetic predisposition and environmental factors are clearly involved.

The initiation of pathogenesis may precede the abrupt clinical onset of IDDM by several years, even in children [91, 92]. Although the peak in incidence is about 12 years of age, cases can occur within the first year of life [58] suggesting that the predisposing events that eventually lead to IDDM may have occurred *in-utero*.

Chapter 5

The Diabetes Study

5.1 Introduction

Since 1963 the Oxford Record Linkage Study (ORLS) has assembled information to link birth, death and hospital records for individuals living in a defined area in and around Oxfordshire, England. The original ORLS area was Oxford city and county, with a population of about 340,000 persons. From 1966 the coverage was extended to Oxfordshire and West Berkshire: a population of about 800,000 persons with about 14,000 births each year. Details of the pregnancy, labour and delivery, and subsequent morbidity of mother and infant were abstracted from hospital case notes by trained clerks. For domiciliary deliveries the midwife who delivered the infant sent her notes to the ORLS where clerks abstracted relevant information. Data was obtained from the ORLS on all cases of diabetes discharged from an ORLS hospital during 1965–1986 who were born to parents resident in Oxfordshire or West Berkshire during the same period. Appendix A describes the ORLS in more detail.

For cases born during 1970–1986 up to eight controls for each case were selected, at random, from all livebirths in the ORLS area. Controls were individually matched to cases on sex, year and hospital of delivery, or if domiciliary to another domiciliary delivery. Controls born in hospital had to have been discharged alive from that hospital. Maternity and delivery information was extracted from ORLS computer files. For cases born before 1970 it was not possible to match on hospital of delivery because of the way data had been stored. Instead two controls for each case were chosen, matched on sex, year and place of delivery, which was either at home or in hospital. The maternity and delivery information for these subjects was extracted from ORLS microfilm files. Appendix B describes the control selection and data extraction in more detail.

5.2 Children with a hospital diagnosis of diabetes

The ORLS identified 330 children, from general hospital files, who had a diagnosis of diabetes during 1965-87 and had been born during 1965–85. Children with cystic fibrosis, major congenital anomalies or who were part of twin or higher order deliveries were excluded from the analyses. Appendix F describes the exclusions and the case series in more detail. In total there were 315 cases selected into the study (160 boys; 155 girls), each individually matched with up to eight controls on sex, year and hospital or place of delivery. The were 1525 controls.

5.3 Identifying risk factors

The following univariate analyses present relative risks for diabetes as defined by a general hospital diagnosis in relation to routinely collected perinatal exposures. For some variables there was a considerable proportion of subjects for whom data was not collected. This is different to data that should have been collected but was missing because, for certain hospitals during certain periods, it was not expected that such data items should have been collected.

A potential bias caused by migration may have affected the results of this study. This bias was discussed in detail in chapter 3, where a theoretical development led to a procedure to estimate the size of this bias and, hence, the ability to adjust results for the effect of the bias.

5.3.1 Birth weight and gestation

Table 5.1 shows relative risks for birth weight, gestational age and birth weight for gestational age. A baby was defined as small, appropriate or large for gestational age (SGA, AGA or LGA) if its sex-specific birth weight was lower than the 10th or higher than the 90th percentile of a reference birth weight distribution for a given gestational age. The reference distribution used here was based upon a large series of neonatal discharge records (form SMR11) covering 70–75% of all babies born in Scottish hospitals during 1973–79 [132]. This series of births was used in preference to a commonly used standard based upon births in Aberdeen, 1948–64 [133], because the former series was more recent, over three times larger and covered a wider range of gestational ages.

There were no significant associations between subsequent risk of diabetes and birth weight, gestational age or birth weight for gestational age. It was shown previously, in

Table 5.1: Relative risk for diabetes: birth weight, gestational age and birth weight for gestational age

Risk factor	Cases (total=315) number	percent	Controls (total=1525) number	percent	Relative risk	95% confidence interval	p-value
Birth weight (kg)							
≤2.4	9	2.9	45	3.0	0.97	0.45 – 2.08	0.934
2.5–2.9	42	13.6	231	15.3	0.85	0.58 – 1.27	0.433
3.0–3.4	115	37.3	574	38.1	1.00	baseline	
3.5–3.9	103	33.4	480	31.9	1.00	0.74 – 1.36	0.992
4.0 or more	39	12.7	177	11.7	1.15	0.76 – 1.75	0.515
Not known	7		18				
* LRS[4]= 1.39, p= 0.846; Trend LRS[1]= 0.94, p= 0.333							
Gestation (completed weeks from date of last menstrual period)							
≤36	9	3.1	63	4.7	0.54	0.25 – 1.15	0.111
37–38	46	15.9	199	14.8	0.97	0.66 – 1.42	0.862
39–40	161	55.5	690	51.4	1.00	baseline	
41–42	59	20.3	332	24.7	0.72	0.51 – 1.02	0.067
43 or more	15	5.2	58	4.3	0.88	0.46 – 1.66	0.684
Not known	25		183				
LRS[4]= 5.79, p= 0.216; Trend LRS[1]= 0.14, p= 0.710							
† Birth weight for gestational age							
LGA	31	10.7	160	11.9	0.91	0.59 – 1.40	0.669
AGA	215	74.4	1025	76.4	1.00	baseline	
SGA	43	14.9	156	11.6	1.04	0.67 – 1.63	0.861
Not known	26		184				
LRS[2]= 0.23, p= 0.890; Trend LRS[1]= 0.21, p= 0.650							

* LRS[n]: Log-likelihood Ratio Statistic with n degrees of freedom
† LGA: Large for Gestational Age (above 90th percentile for birth weight)
† AGA: Appropriate for Gestational Age (between 10th and 90th percentile for birth weight)
† SGA: Small for Gestational Age (below 10th percentile for birth weight)

chapter 3, that relative risks for birth weight and gestational age were not greatly influenced by the bias due to migration. For example, it was calculated that the bias due to migration would cause the relative risk for birth weight ≤2.4 kg to be 8% smaller than its true value. A better estimate of the relative risk, therefore, would then be 1.05 instead of the observed 0.97. For the other birth weight categories the change would be even smaller. These corrections were too small to change the overall interpretation of the results.

Table 5.2: Relative risk for diabetes: maternal age and parity

Risk factor	Cases (total=315) number	Cases (total=315) percent	Controls (total=1525) number	Controls (total=1525) percent	Relative risk	95% confidence interval	p-value
Maternal age (years)							
≤19	28	8.9	140	9.2	0.84	0.53 – 1.35	0.483
20–24	102	32.4	488	32.1	0.94	0.70 – 1.27	0.703
25–29	117	37.1	544	35.7	1.00	baseline	
30–34	49	15.6	266	17.5	0.87	0.60 – 1.25	0.445
35 or over	19	6.0	84	5.5	0.96	0.55 – 1.69	0.896
Not known	0		1				
Not collected	0		2				
* LRS[4]= 0.89, p= 0.926; Trend LRS[1]= 0.01, p= 0.903							
Parity (before this pregnancy)							
0	122	39.0	590	38.9	1.00	baseline	
1	111	35.5	586	38.6	0.98	0.73 – 1.32	0.897
2	48	15.3	218	14.4	1.14	0.78 – 1.67	0.502
3 or more	32	10.2	124	8.2	1.08	0.69 – 1.69	0.750
Not known	2		5				
Not collected	0		2				
LRS[3]= 0.70, p= 0.874; Trend LRS[1]= 0.33, p= 0.566							

* LRS[n]: Log-likelihood Ratio Statistic with n degrees of freedom

5.3.2 Maternal age and parity

Table 5.2 shows risk of diabetes in relation to maternal age and parity. There were no significant associations with risk of diabetes. Adjusting for birth weight made no material difference to these results, nor did adjusting for the effect of the migration bias.

5.3.3 Social class, feeding at discharge and smoking during pregnancy

As shown in table 5.3 cases were less likely than controls to belong to the group classified to 'other occupations', which was made up of students, armed forces personnel, and after 1972, housewives. Among groups I to V the lowest risk was in those children born in group I, although there was no statistical evidence for a trend (trend across groups I to V: p=0.566). The observed pattern of relative risks can partly be explained by the bias due to migration. Migration rates were high in social class group I and the group classified to 'other occupations', and this would cause the relative risks in these groups to be smaller than they should be (see chapter 3). An estimate of the relative risk for group I, allowing for the migration bias, would be 0.86 instead of 0.72, and for the 'other occupations' it would be 0.75 instead of 0.50. The other remaining relative risks would change by smaller

Table 5.3: Relative risk for diabetes: social class, breast feeding and smoking during pregnancy

Risk factor	Cases (total=315) number	percent	Controls (total=1525) number	percent	Relative risk	95% confidence interval	p-value
Social class							
I	23	7.9	134	10.1	0.72	0.43 – 1.21	0.215
II	52	17.9	239	18.1	1.11	0.76 – 1.62	0.601
III	139	47.9	604	45.7	1.00	baseline	
IV	47	16.2	167	12.6	1.13	0.76 – 1.68	0.546
V	19	6.6	83	6.3	1.01	0.58 – 1.75	0.982
Other occupations	10	3.4	96	7.3	0.50	0.25 – 1.02	0.057
Not known	16		149				
Not collected	9		53				
* LRS[5]= 7.32, p= 0.198							
Feeding at discharge							
Breast	63	55.8	371	65.5	1.00	baseline	
Artificial	46	40.7	181	32.0	1.29	0.83 – 2.00	0.253
Complement	4	3.5	14	2.5	1.25	0.37 – 4.29	0.720
Not known	0		11				
Not collected	202		948				
LRS[2]= 1.33, p= 0.514							
Smoking during pregnancy							
No	40	83.3	299	77.1	1.00	baseline	
Yes	8	16.7	89	22.9	0.66	0.30 – 1.47	0.310
Not known	10		54				
Not collected	257		1083				
LRS[1]= 1.11, p= 0.293							

* LRS[n]: Log-likelihood Ratio Statistic with n degrees of freedom

amounts. After allowing for the migration bias, therefore, there was even less evidence that social class at birth was related to risk of diabetes in childhood.

Table 5.3 also shows that there was a small, but not significant, raised risk of diabetes with not breast-feeding. Allowing for the bias due to migration would not change this result materially and adjusting for birth weight also made little difference. Feeding at discharge, however, was not available for a considerable proportion of the subjects and this would have reduced the power to detect a statistically significant association between not breast-feeding and diabetes in later life.

Smoking during pregnancy was associated with a lower risk of diabetes in offspring. The number of mothers for whom smoking data were available was, however, small and the result was not statistically significant.

5.3.4 Pre-eclampsia

Table 5.4 shows relative risks in relation to pre-eclampsia and eclampsia, and its two main components, albuminuria and raised blood pressure. The maximum blood pressure measurements must be interpreted with caution. After 1975 it was the highest recorded systolic and highest diastolic readings that were collected; readings taken during labour were not recorded and the two readings need not have been taken at the same time. Up to 1975 it was uncertain which blood pressure measurements were collected. The distribution of blood pressure readings before and after 1975 were examined; they were similar and, therefore, it was assumed that the readings were comparable.

Pre-eclampsia and eclampsia was associated with a significantly increased risk of diabetes in offspring. There was no significant association with raised levels of albuminuria. There was a significant association with maximum systolic blood pressure, with a significant trend towards greater risk if the mother had a high maximum blood pressure. The pattern with maximum diastolic blood pressure was less clear, with risk rising at low and high blood pressures.

5.3.5 Maternal diabetes

The mothers of three cases and three controls had diabetes recorded during pregnancy (relative risk: 5.87; 95% CI (0.90–38.33)). With so few affected mothers it was not possible to explore this in more detail.

5.3.6 Other selected risk factors

Certain other selected risk factors deserve a mention because they have either been reported in the literature as risk factors for diabetes, or there is reason to believe that they might be associated with diabetes in later life.

Maternal infections

There was no mention of Cocksackie infection, measles, mumps or chickenpox recorded on the maternity record for mothers of cases or controls. The mother of one control had a mention of rubella and another had a mention of herpes. Infectious mononucleous was mentioned for the mother of one case and eight controls (relative risk: 0.98; 95% CI: (0.10–9.52)). The mother of one case and the mothers of nine controls had a mention of an 'other virus' (relative risk: 0.67; 95% CI: (0.07–6.12)). With so few mentions of infections during pregnancy it was not possible to explore this further with the available data.

Table 5.4: Relative risk for diabetes: maternal pre-eclampsia, albuminuria and maximum blood pressure

Risk factor	Cases (total=315) number	percent	Controls (total=1525) number	percent	Relative risk	95% confidence interval	p-value
Pre-eclampsia and eclampsia							
No mention	259	82.2	1326	87.0	1.00	baseline	
Yes	56	17.8	199	13.0	1.48	1.05 – 2.10	0.027
* LRS[1]= 4.70, p= 0.030							
Albuminuria							
No trace	186	84.9	1017	85.5	1.00	baseline	
Trace only	27	12.3	127	10.7	1.11	0.67 – 1.84	0.697
More than trace	6	2.7	46	3.9	0.80	0.33 – 1.95	0.627
Not known	28		173				
Not collected	68		162				
LRS[2]= 0.45, p= 0.800; Trend LRS[1]= 0.02, p= 0.884							
Maximum systolic blood pressure (mmHg)							
≤119	27	12.7	145	12.6	1.15	0.70 – 1.90	0.588
120–139	110	51.6	685	59.4	1.00	baseline	
140–159	60	28.2	280	24.3	1.41	0.99 – 2.02	0.059
160 or more	16	7.5	43	3.7	2.66	1.39 – 5.07	0.003
Not known	34		210				
Not collected	68		162				
LRS[3]= 9.93, p= 0.019; Trend LRS[1]= 6.27, p= 0.012							
Maximum diastolic blood pressure (mmHg)							
≤69	12	4.7	50	4.1	1.57	0.77 – 3.20	0.219
70–79	80	31.4	370	30.2	1.33	0.94 – 1.88	0.110
80–89	98	38.4	544	44.4	1.00	baseline	
90–99	47	18.4	184	15.0	1.45	0.94 – 2.21	0.090
100 or more	18	7.1	78	6.4	1.58	0.86 – 2.88	0.139
Not known	54		253				
Not collected	6		46				
LRS[4]= 5.41, p= 0.247; Trend LRS[1]= 0.02, p= 0.888							

* LRS[n]: Log-likelihood Ratio Statistic with n degrees of freedom

Rhesus incompatibility between mother and child

There was no evidence for an increased risk with rhesus incompatibility between mother and child (relative risk: 0.92; 95% CI: (0.47–1.80)).

Caesarean section

There was a raised risk with caesarean section delivery (relative risk: 1.28; 95% CI: (0.76–2.17)), but only 19 mothers of cases had caesarean section and the association was not

Table 5.5: Relative risk for diabetes by month of birth

Risk factor	Cases (total=315) number	percent	Controls (total=1525) number	percent	Relative risk	95% confidence interval	p-value
Month of birth							
January	31	9.8	120	7.9	1.00	baseline	
February	21	6.7	123	8.1	0.71	0.39 – 1.32	0.286
March	27	8.6	138	9.0	0.80	0.44 – 1.45	0.457
April	27	8.6	131	8.6	0.84	0.46 – 1.51	0.551
May	29	9.2	132	8.7	1.04	0.58 – 1.84	0.897
June	29	9.2	133	8.7	0.96	0.54 – 1.72	0.889
July	22	7.0	126	8.3	0.89	0.48 – 1.66	0.713
August	38	12.1	144	9.4	1.18	0.68 – 2.05	0.560
September	23	7.3	126	8.3	0.73	0.40 – 1.35	0.318
October	25	7.9	124	8.1	0.93	0.51 – 1.70	0.803
November	19	6.0	110	7.2	0.71	0.37 – 1.38	0.315
December	24	7.6	118	7.7	0.84	0.46 – 1.55	0.575
Heterogeneity * LRS[11]= 5.78, p= 0.888							
Sinusoidal seasonality LRS[2]= 1.22, p= 0.543							

* LRS[n]: Log-likelihood Ratio Statistic with n degrees of freedom

statistically significant.

Seasonal pattern of births

There was no indication of heterogeneity in the risk of diabetes by month of birth, nor was there evidence for a sinusoidal pattern of seasonality, as shown in table 5.5.

5.3.7 Analysis by age at diagnosis

Risk factors were also examined by age at diagnosis of the cases (0–4, 5–9, and 10–14 years), but the small number of cases in each group and the rarity of some exposures limited the usefulness of these analyses.

Table 5.6 shows relative risks for pre-eclampsia and eclampsia, and maximum blood pressure for three groups based upon age at diagnosis. The relative risk for pre-eclampsia and eclampsia was elevated in all three age groups. There was no evidence for an interaction with age (p=0.946).

The pattern of risk with mother's maximum blood pressure was more complicated. For cases diagnosed at 10–14 years of age there was a significant increase in risk of diabetes with greater maximum systolic blood pressure. For cases diagnosed at ages 5–9 years the trend

Table 5.6: Relative risk for diabetes: maternal pre-eclampsia, albuminuria and maximum blood pressure, by age at diagnosis of diabetes

Risk factor	Age at diagnosis of diabetes			
	0–4 (77 cases)	5–9 (105 cases)	10–14 (93 cases)	0–14 (275 cases)
	Relative risk (95% CI)	Relative risk (95% CI)	Relative risk (95% CI)	Relative risk (95% CI)
Pre-eclampsia and eclampsia				
No mention	1.00 baseline	1.00 baseline	1.00 baseline	1.00 baseline
Yes	1.34 (0.65–2.77)	1.49 (0.83–2.69)	1.57 (0.83–2.98)	1.48 (1.02–2.14)
* LRS[1]	0.59 p= 0.443	1.69 p= 0.193	1.87 p= 0.172	4.04 p= 0.044
Maximum systolic blood pressure (mmHg)				
≤119	2.24 (1.01–4.98)	0.98 (0.42–2.29)	0.77 (0.28–2.17)	1.23 (0.74–2.04)
120–139	1.00 baseline	1.00 baseline	1.00 baseline	1.00 baseline
140–159	1.42 (0.75–2.69)	1.12 (0.60–2.10)	2.30 (1.18–4.48)	1.51 (1.04–2.18)
160 or more	2.54 (0.86–7.52)	1.84 (0.56–6.00)	7.56 (1.79–32.01)	2.87 1.46–5.66
LRS[3]	5.66 p= 0.129	1.00 p= 0.802	12.79 p= 0.005	11.22 p=0.011
Trend LRS[1]	0.18 p= 0.668	0.63 p=0.428	11.60 p= 0.001	6.47 p= 0.011
Maximum diastolic blood pressure (mmHg)				
≤79	1.59 (0.87–2.90)	1.18 (0.66–2.09)	1.38 (0.71–2.68)	1.37 (0.96–1.94)
80–89	1.00 baseline	1.00 baseline	1.00 baseline	1.00 baseline
90–99	0.84 (0.34–2.08)	1.45 (0.71–2.99)	2.66 (1.23–5.77)	1.49 (0.95–2.32
100 or more	1.19 (0.37–3.78)	0.37 (0.08–1.75)	5.12 (1.87–13.99)	1.59 (0.85–3.00)
LRS[4]	3.27 p= 0.351	3.57 p= 0.312	12.79 p= 0.005	5.32 p= 0.150
Trend LRS[1]	1.89 p= 0.169	0.36 p= 0.551	6.68 p= 0.001	0.12 p= 0.729

* LRS[n]: Log-likelihood Ratio Statistic with n degrees of freedom

was not statistically significant and at 0–4 years risk increased at high and low systolic blood pressures. There was, however, no strong evidence for an interaction with age (p=0.222).

Table 5.7: Relative risk for diabetes: maternal pre-eclampsia by sex of child with diabetes

Risk factor	Boys (160 cases) Relative risk (95% CI)	Girls (155 cases) Relative risk (95% CI)	Total (315 cases) Relative risk (95% CI)
Pre-eclampsia and eclampsia			
No mention	1.00 baseline	1.00 baseline	1.00 baseline
Yes	1.67 (1.04–2.68)	1.30 (0.77–2.17)	1.48 (1.05–2.10)
* LRS[1]	4.25 p= 0.039	0.94 p= 0.331	4.70 p=0.030

* LRS[n]: Log-likelihood Ratio Statistic with n degrees of freedom

All cells had five or more cases, except for the highest blood pressure group among 5–9 year olds where there were only four cases.

The pattern was less clear with maximum diastolic blood pressure, partly because some cells contained a small number of cases. The highest blood pressure group for 0–4 year olds only contained four cases, and in this group for 5–9 year olds there were only two cases. There was a significantly increased risk with increasing blood pressure for 10–14 year olds, and no clear pattern at younger ages. This was reflected in a statistically significant interaction with age (p=0.026).

5.3.8 Analysis by sex

Analyses were also carried out for boys and girls separately and table 5.7 shows relative risks for pre-eclampsia and eclampsia by sex to illustrate this type of analysis. Although the relative risk was higher among boys than girls the difference was not statistically significant (p=0.481). There were no other differences by sex that were noteworthy.

5.3.9 Other risk factors

A number of other risk factors were examined but none of the results were outstanding or statistically significant. The variables analysed included: size of baby's head; presentation at delivery; mother's blood group; mother's body mass index; co-habitation; episiotomy; duration of labour; and Apgar score.

5.4 Discussion

The preceding analyses identified pre-eclampsia and eclampsia, and maximum systolic blood pressure in the mother as significant risk factors for diabetes in offspring. Diabetes in the mother was also associated with a large increased risk in the offspring, as might be expect in a disease with a strong genetic component [68], although the numbers of affected mothers was small and the association was not statistically significant. The interpretation of the results presented here, however, depends on the usefulness of the routine data sources for ascertaining cases and providing exposure information.

5.4.1 Ascertainment of cases

Cases were diagnosed with diabetes from hospitals that formed part of the ORLS. The ORLS hospital reports covered patients admitted to National Health Service (NHS) care and private care, although the submission of data for the latter was somewhat inconsistent. In Britain, during the study period, only a small proportion of health care was provided by the private sector, and that was usually limited to minor conditions. The number of children with diabetes treated exclusively under private care, therefore, was likely to be small. Also outside the jurisdiction of the NHS were dependants and children of armed services personnel, who may be treated in 'military' hospitals, but the numbers are likely to be small too.

Eligible children, that is those born in Oxfordshire or West Berkshire who went on to develop diabetes, would also be missed if they were exclusively treated in hospitals in neighbouring health regions. Eighteen (5.7%) of the cases were diagnosed outside of Oxfordshire or West Berkshire. These cases were ascertained because in later years the ORLS general hospital coverage had expanded to include East Berkshire, Northampton, High Wycombe, Kettering, Aylesbury and Milton Keynes. It is not possible to say how many children resident within the ORLS area would be treated further afield, but the number of children missed are likely to be small.

Eligible children may also be lost to the study if they went to live outside of the ORLS area and were subsequently diagnosed with diabetes in their new district or country of residence. Chapter 3 discussed in detail the bias that may occur when the perinatal characteristics of those who migrate are different to those who remain in the region in which they were born. Corrections made for this migration bias did not materially change the results.

Even if children who develop diabetes remained resident in the ORLS area, not all newly diagnosed diabetic children would enter hospital. One report suggests that only 72% [134]

of patients were admitted to hospital at diagnosis, the remainder beginning insulin as out-patients. Children not entering hospital at onset of diabetes may preferentially be from higher social class families (i.e. their parents may be doctors) or from families that can afford the time and expense to stabilise the child on insulin at home (i.e. an only child). Children treated solely outside of hospital may also have had less severe symptoms at onset. Almost half the cases in this study were admitted to hospital a second time, with a mention of diabetes, so it is likely that some children who were initially treated outside of hospital were ascertained into the study at a later date.

Nevertheless it is probable that some eligible children with diabetes were not included in this study. A case who remained undiscovered might possibly be selected as a control, thus diluting the difference in exposures between cases and controls. For a rare disease, however, this would rarely happen, introducing little bias into the study. It is possible that the children with diabetes who were not selected into this study were different in some way from those who were, with respect to their disease or perinatal characteristics. It is unlikely, however, that the differences would be large enough to affect the results of this study.

5.4.2 Diagnosis of diabetes with routine data

The diagnosis of diabetes was taken from general hospital discharge summaries, and this diagnosis may have been in error. For a condition like insulin dependent diabetes, where treatment with insulin defines the condition, a misdiagnosis is unlikely. It is possible that 'diabetes' as recorded may refer to a type of diabetes that is not IDDM or type I, for example, the maturity onset diabetes of the young (MODY) which exhibits an autosomal dominant pattern of inheritance [50]. MODY, however, is rare and might only account for a few, if any, cases in this study.

The diabetes diagnosed in the subjects may have been secondary to some other condition. In fact, three children had diagnoses of cystic fibrosis which pre-dated the diagnosis of diabetes by many years. These three were excluded from the analysis because the aetiology of diabetes associated with cystic fibrosis may be different to that of IDDM. There was no mentions of other conditions that may cause diabetes, like chronic pancreatitis, haemochromatosis, or Cushing's disease. Conditions like these are rare and are unlikely to account for any of the cases of diabetes in this study. One boy did have a neoplasm of the 'other endocrine glands' and this could possibly have been related to his diabetes. The inclusion or exclusion of this one subject, however, was unlikely to change the interpretation of the results seen here.

Four cases were diagnosed with diabetes at birth, and seven in all before six months of age. These cases may have a transient neonatal form of diabetes which would be expected to resolve itself a few months after birth. Permanent diabetes would not usually develop. After excluding these seven cases from the main analyses there were no material differences in the results.

In support of the initial diagnosis of diabetes nearly half the cases had a subsequent hospital admission which mentioned diabetes. The majority (83.2%) of cases entered hospital as emergency admissions, which might be expected at first onset of diabetes. The conditions surrounding the index hospital event, described in appendix F, appear consistent with a diagnosis of diabetes in the majority of subjects. Although there was no verification of the insulin dependency of the cases, within the age group studied the type of diabetes would mostly be IDDM with a presumed type I, autoimmune mechanism of pathogenesis.

5.4.3 Use of routine data

Advantages

All perinatal exposure data used here were collected during pregnancy or shortly after birth, usually many years before the diagnosis of diabetes. One advantage of using routine data was that the study did not rely on mother's recall; the accuracy of some factors, like blood pressure or albuminuria, was likely to be greater than that achieved by recall alone, and there was no chance for recall bias to occur. Some other advantages of routine data were previously listed in section A.7.

The data for the controls were collected from the same source as that for cases, and those abstracting the data were unaware of the future disease status of the subjects. To make the exposure data more comparable controls were matched to cases on year and hospital of delivery where possible. This was done because the way diagnoses are made, and routine data recorded, in one hospital may not be comparable with diagnoses made, or recorded, in another hospital or at another time.

Need for special data handling skills

Extracting data from the ORLS, a large and complex set of datafiles, required special data handling skills. Without training and supervision access to the system was not possible, even if concerns regarding confidentiality were satisfied. Only in collaboration with staff at the ORLS, who had the special data handling skills and experience needed to extract the requested data, was this study possible.

Low cost of data extraction

Once a procedure for data extraction was set-up the cost of selecting extra cases and controls was minimal. It was first necessary, however, to gain an overview of the ORLS system and, in collaboration with staff at the ORLS, to carefully define a protocol for data extraction.

Comparison with ad hoc data collection studies

In ad hoc data collection studies, where the investigator organises and directs collection of data, the investigator has close contact with the data at its source. With routine data the investigator may be removed from the extraction of data from the computer system, and even further removed from the original form filling, collection, coding and entry of data. It was possible to view some of these processes as they occur now, but these may be different from those used in the past and methods must be reconstructed from existing documentation or oral history. It was vital, therefore, to cross-validate the data with itself and existing documentation until it was clear that it represented what was requested.

The routine data within the ORLS was collected over a long period of time data, and collection methods changed and coding schemes were revised. For example, a variable may have been vaguely defined at the start of data collection many decades ago, whereas now it may have a stricter definition. The comparability over time of data items like this needed to be considered, for example, by comparing ranges and distributions of before and after the possible change in definition. Sometimes a coding scheme was well defined but underwent revisions, like the International Classification of Diseases. It then become necessary to identify which revision was used for each record, and to bridge items across different revisions.

Disadvantages

A disadvantage of routinely collected information was that the study must be limited to those exposures that were recorded in sufficient detail to be useful in the analyses. The ORLS, however, collected a much wider range of exposure information than was usual in routine data systems.

It was possible, therefore, to use the routine data collected by the ORLS to look at pre-natal risk factors for diabetes, provided that there had been careful planning when extracting the data attention to detail when assembling and processing it.

5.4.4 Risk factors

Perinatal variables like raised birth weight [102], high social class [102, 103], being first born [103, 135], high maternal age [14, 102, 103, 123, 124] and caesarean section [14, 103] have previously been associated with diabetes, but in this study there was no strong evidence confirming this. The opposite, however, has also been reported in other studies, for example, low maternal age [135], high birth order [123, 128] and although not significant, lower birth weight [103, 127].

That these associations, when found, are usually weak and show inconsistencies, suggesting these risk factors may be secondary to more direct risk factors [103]. The associations between these underlying risk factors and, for example, birth weight, parity, and maternal age, may be different in different populations. Alternatively, but more unlikely, is that in different populations the environmental causes of diabetes are different.

There was a small, but not statistically significant, raised risk of IDDM with not breast-feeding at discharge. Intention to breast-feed, however, may differ from actual practice, and there was no information available on actual breast-feeding rates at, say, three months after delivery. Thus intention to breast-feed may be a crude measure of actual breast-feeding. Recently, however, it was suggested that studies which used existing records showed little association between IDDM and breast-feeding [122] and that methodological issues could have biased the positive results seen in other studies. Even if there is a real association between breast-feeding and IDDM the relative risk is weak, reported to be around 1.5 [121].

One consequence of not breast-feeding is the early introduction of dairy products into an infant's diet. The finding of antibodies against cow's milk albumin that are capable of reacting with β-cell specific surface protein [117] led to the hypothesis that cow's-milk may be involved in the initial stages of IDDM [117–119]. Further work is needed in this area because, unlike some of the other risk factors for IDDM, breast-feeding rates and infant diet are susceptible to beneficial change. The limitations of this and previous studies suggest that attention should be focused on IDDM in relation to duration of exclusive breast-feeding, and the age at which diary products were first introduced. Such measures have been looked at in the past, and protective associations have been found, albeit without a dose-respose relationship [115]. It would also be interesting to know the age at which antibodies to bovine serum albumin first appear and their relation to breast-feeding practice.

Pre-eclampsia

Pre-eclampsia and eclampsia was consistently found to increase risk of subsequent diabetes in male and female offspring and in young and later onset cases. This suggests the association was real. Recall bias could not have affected the association, because of the routine nature of the data, and migration bias was shown to have little effect in relation to pre-eclampsia. A similar association between pre-eclampsia and diabetes was seen in one other study [14], but this was not confirmed elsewhere [103].

Pre-eclampsia may be the result of an immunogenetic incompatibility between mother and foetus [136], and it has been suggested that this early immunological disturbance may be related to diabetes in later life [14]. Genetic pre-disposition to diabetes, however, may be a confounding variable. There is evidence that HLA-DR4, which is strongly associated with IDDM, is also associated with pre-eclampsia [137]. If it were possible to stratify on HLA status of the child the raised risk with pre-eclampsia may disappear. The observation that pre-eclampsia was associated with HLA-DR4, however, was not confirmed in subsequent studies [138], and more generally, no evidence was found for linkage to the HLA region [139]. Thus it is not clear if HLA-DR4 status can account for the association between pre-eclampsia and diabetes in offspring. Further studies would be needed to clarify the association between HLA status and pre-eclampsia before confounding can be ruled out.

The relation between diabetes in offspring and maximum blood pressure was unusual. Raised blood pressure is one of the defining characteristics of pre-eclampsia and might be expected to reflect the results seen for pre-eclampsia. There was a strong trend with both systolic and diastolic blood pressure among the older cases, but little evidence for such a trend among younger cases. The relative risks were too large to be explained away by the migration bias which calculations show would only account for 10% of the raised risk in the high blood pressure groups. The greater trend among older cases would suggest that pre-eclampsia itself might be a stronger risk factors among the older cases, although there was no strong evidence for this. Thus the results relating maximum blood pressure and IDDM are difficult to interpret and should be checked in other studies.

5.4.5 Susceptible controls

One weakness of this study, and common to most epidemiological studies of IDDM, is that a proportion of the control group do not have the right genetic profile that predisposes one to IDDM. About half the control group will not have HLA-DR3 or HLA-DR4. Presumably, these controls, even if exposed to the environmental causes of IDDM will not be able to

develop IDDM. Within this study it was not feasible to HLA type the controls, but future studies of IDDM might consider this.

5.4.6 Conclusions

At first sight there was a disappointing lack of association between IDDM and previously reported epidemiological risk factors, although closer examination of the literature revealed that conflicting results are common. IDDM is often considered synonymous with type I diabetes, where the mechanism of pathogenesis is thought to be an autoimmune destruction of pancreatic β-cells in genetically susceptible individuals. It is, however, not known what triggers or controls this process, and there may be different pathways that eventually lead to IDDM. It is possible that under different conditions different risk factors are important in the aetiology of IDDM. It remains to be seen what these modifying conditions are. It may be that only on an international scale will there be enough heterogeneity in the modifying factors to allow them to be detected in epidemiological studies.

The association between pre-eclampsia and IDDM has been reported before [14], and suggests that an immunological disturbance in foetal life may be important. The result, however, may be due to confounding by HLA status, and this issue needs to be clarified first. If, however, pre-eclampsia is related to subsequent IDDM then, because it is a weak risk factor, it may help explain only a small proportion of cases.

Part III

Cryptorchidism

Chapter 6

Brief Review of the Cryptorchidism Literature

6.1 Normal descent of the testes

The gonads begin to form near the primitive kidneys around the fifth week of embryonic development, and under the influence of genetic and hormonal factors sex-differentiation begins by the seventh to eighth week [140, 141]. Transabdominal migration of the testes occurs around 10–15 weeks of gestation, possibly stimulated by Müllerian inhibiting substance [142]. During the 25–30th week the gubernaculum, a fibrous cord that connects the testis to the developing genital swelling in the groin, expands and dilates the inguinal canal to a size which will allow the testis and epididymis to pass through. During the next five weeks the gubernaculum shrinks and disappears as a sheath of peritoneum, the processus vaginalis, extends into the scrotum [141]. By the seventh or eighth month of gestation the normal testis begins its descent down the inguinal canal to the scrotum [143]. This inguino-scrotal stage may be stimulated by androgens [142]. Descent at first is rapid and then slower as the testis enters the upper part of the scrotum. The final descent into the scrotum may take place after delivery but is usually complete by three to four months after birth [144]. After one year of age descent without medical intervention is rare [145].

6.2 Undescended testis

Cryptorchidism is a failure of one or both of the testes to descend fully into the scrotum. Throughout this text the term cryptorchidism and undescended testis (or testes) will be used inter-changeably. In Britain, Scorer [146] reported that 41%, 49% and 10% of cryptorchid

testes were left, right and bi-lateral, which was similar to the distribution seen three decades later by the John Radcliffe Hospital Cryptorchidism Study Group: 42%, 41% and 17% respectively [147]. About 10% of undescended testes remain in the abdomen or are absent, 20% within the inguinal canal, 44% high in the scrotum, and 26% are blocked from entering the scrotum by a fascial obstruction [146]; the lower end of the superficial inguinal pouch is closed and the testis remains in the groin [148].

In childhood the testis may retract up into the upper part of the scrotum, or even the superficial inguinal pouch, by a reflex action of the cremasteric muscle. The testis then appears to be undescended and may be retracted for days or years but will drop before puberty [149]. The retractile testis may be misdiagnosed as an undescended testis. There are carefully documented reports that the descended testis may ascend during later childhood [150–152]. Ascent may occur if the testis does not maintain its position relative to the scrotum as a boy grows [148].

6.2.1 Incidence and prevalence

An early report based upon three large series of records from army recruiting files and one from 15 years of surgical admissions to the Manchester Royal Infirmary suggested that the prevalence of cryptorchidism in adult males was about 0.5% during the early decades of this century [153]. Studies carried out in Britain [154] and Denmark [155] during the 1950s–60s indicated that 2%–3% of full-term boys and 17%–21% of premature boys had an undescended testis at birth. After 7–11 years of follow-up 0.8% of boys in the British study still had an undescended testis. In the Danish study follow-up was at 12 months of age, when the prevalence of undescended testis was 0.8%–0.9%. A study from Western Australia [156] reported that, in 1962, 2.6% of boys had an undescended testis at birth, and that this fell to 1% at 12 months of age. In Scotland the prevalence of a neonatal diagnosis of cryptorchidism on discharge from hospital was 1.4% during 1976–85 [157].

More recently, in a hospital based cohort study of births from New York City, carried out during 1987–90, 3.7% of boys had an undescended testis at birth, 1.0% were undescended at three months and 1.1% were undescended at one year of age [158]. During 1984–88, a study in Oxford estimated that 5.0% of boys were cryptorchid at birth and by three months of age 1.8% still had an undescended testicle [147]. Comparison with the British rates of the 1950's suggested that, after adjusting for differences in birth weight, the prevalence at three months of age had increased by 93% [147].

6.2.2 Familial associations

The majority of cases of cryptorchidism occur sporadically but there are reports of clusters within families. Cryptorchidism, often unilateral, in father and sons [159], twins [159, 160], brothers [159, 161], half-brothers [162] and even in four generations of the same family [163] suggest that at least some cases are familial. The pattern of inheritance is unclear, with suggestions of a dominant autosomal character [159, 162], although in addition to this X-linked [162] and Y-linked [159] inheritance has also been postulated. Reports of familial cryptorchidism, however, are difficult to interpret because they are usually opportunistic publications each based upon a small number of pedigrees.

Estimates of risk in relatives of affected boys have been calculated using data from the population-based Hungarian Congenital Abnormality Registry [164]. This study found that 6.2% of brothers of cryptorchid boys were themselves cryptorchid. Among fathers of cases 1.5% were currently cryptorchid, but this rose to 4.0% if previous, but usually unconfirmed, cryptorchidism was also counted [165].

There is also reported an association between cryptorchidism and familial cases of testicular cancer. For example, in one report all three male members of two twin pairs of dizygotic twins in a sibship were cryptorchid and two of the brothers developed testicular cancer [160]. Prevalence of cryptorchidism, inguinal hernia and hydrocele was also found to be high among three familial clusters of testicular cancer [166]. It was suggested that an underlying alteration in urogenital embryogenesis may be associated with the familial predisposition to testicular neoplasia [166].

6.2.3 Orchidopexy

Orchidopexy is the surgical procedure used to correct an undescended testis. In Scotland, 1961–85, hospital in-patient records showed a 26-fold increase in the orchidopexy rate for 0–4 year olds; a 16-fold increase for 5–9 year olds and a three-fold increase in 10–14 year olds [157]. Between 1962 and 1981 there was an apparent doubling in the orchidopexy rate in England and Wales [167] and throughout this period the proportion of boys undergoing orchidopexy by age 15 years remained roughly twice the proportion of boys with an undescended testis at 3 months of age [168]. Similarly, in Western Australia the orchidopexy rate increased by 86% between 1971–1980, and was twice the expected rate based on the prevalence of undescended testis at 12 months of age [156]. The difficulty in accurately distinguishing an undescended testis from a retractile testis may have led to orchidopexy on a considerable number of retractile testes [167]. Some, however, regard the retractile

Table 6.1: Age at operation for orchidopexy during the 1980s

Location	Period	Age (years) at orchidopexy	Reference
12 British Hospitals	1981–83	68% after age 5	[176]
Denmark	1982–85	median age 11–12	[177]
A British military hospital in Germany	1984–88	average age 5	[178]
Western Australia	1980	average age 6.9	[156]
An Australian children's hospital	1985	average age 5.6	[179]

testis as part of the spectrum of pathological maldescended testes [169] which may require surgery in its own right [170].

The recommended age for orchidopexy has been dropping, recently from six years of age [171, 172] to between six months and two years of age [173], in the hope of preserving some spermatic function [174]. Table 6.1 shows that in the 1980s many orchidopexies were carried out after five or six years of age. In north-east Essex, 1983–86, a study of the referral pattern for orchidopexy showed that 43% of cases were first referred to a GP by parents and that 26% were referred by clinical medical officers, usually at ages five to six years [175]. Not only can diagnosis at a young age be difficult but there may be other reasons why surgery is delayed until a later age; for example, if the testes ascend or retract in late childhood.

6.2.4 Impaired fertility

Cryptorchidism is associated with severely impaired spermatogenic function. It is reported [180] that no untreated bilateral cryptorchid men have a normal sperm count (20×10^6 per ml or more), and of those treated only about a quarter have normal counts. Orchidopexy or hormonal treatment of unilateral cryptorchidism results in sperm counts which are similar to each another, with 15% of men azoospermic (0 count) and 30% oligospermic ($0–20\times10^6$ per ml) [180]. It has been proposed that the impaired spermatogenesis in unilateral cryptorchids may be due to an underlying bilateral testicular abnormality [181].

Based upon knowledge about the natural development of the testis the recommended time for therapy to start is one to two years of age [182]. Until recently most orchidopexies, however, were carried out at a later age, and in the age range 4–14 years there is no evidence that early operation has a beneficial effect on sperm count or future fertility [180].

6.2.5 Testicular cancer

Undescended testes are strongly associated with testicular cancer [183]. In three different studies 1.7%, 3.2%, and 8.0% of men with a history of cryptorchidism were found to have carcinoma *in situ*, usually in the testis that was undescended [184–186]. This is considerably higher than would be expected in men with normal descent, which is less than 0.8%, as measured in an autopsy series among men who had died suddenly and unexpectedly [187]. Estimates from case-control studies suggest that cryptorchidism increases the risk of testicular cancer by a factor of 3–8, not 20–46 as previously suggested [188]. Cohort studies, although based on smaller numbers of cases, are in broad agreement with the case-control studies. Table 6.2 provides a summary of the relative risks from these recent studies. A recent review of the epidemiology of testicular cancer combined the relative risks from nine case-control studies to give an odds ratios of 5.3 (4.1–6.9) for the association between undescended testis and testicular cancer [183].

The association between an undescended testis and testicular cancer may be causal. Certain reports have indicated that orchidopexy before age ten or eight years may reduce risk of testicular cancer [193, 198, 201]. More specifically orchidopexy, or other treatment that causes descent, may reduce the risk of presenting with seminoma [200, 207–209]. Others suggest that age of treatment of an undescended testis has no effect on risk of testicular cancer [210]. The evidence to support these claims is weak and with few orchidopexies carried out before four years of age there are currently insufficient data to assess the benefits associated with orchidopexy around two years of age.

Alternatively, undescended testis and testicular cancer may be manifestations of a common underlying condition. In cases of unilateral maldescent the contralateral testis, which descended normally, is also at increased risk of neoplasia by a factor of about two [183, 200, 211]. One theory suggests that an excess of oestrogen early in pregnancy, perhaps at the time of differentiation of the testes, is linked to both undescended testis and testicular cancer [10, 190].

6.3 Risk factors for undescended testis

Prematurity is a strong risk factor for undescended testes at birth, but this is to be expected because the testes do not normally enter the scrotum until seven or eight months of gestation. In over 75% of cases where an affected baby is premature the testes descend spontaneously in the first few months after birth [147]. For this reason studies of cryptor-

Table 6.2: Association between undescended testis and testicular cancer

Relative risk	95% confidence interval	Author and year of publication	Reference
Case control studies			
8.8	2.3–56.3	Morrison, 1976	[189]
5.0	p=0.02*	Henderson, 1979	[190]
2.5	†	Schottenfeld, 1980	[191]
3.5	†		
∞	5.7–∞	Coldman, 1982	[192]
17.1	2.3–365.8		
9.0	1.5–54.9	Depue, 1983	[10]
3.7	1.6–8.6	Pottern, 1985	[193]
4.5	1.7–13.7	Moss, 1986	[194]
8.3	2.8–32.9		
3.4	1.3–8.8	Brown, 1986	[195]
6.3	2.9–13.9	Swerdlow, 1987	[196]
2.5	0.3–20.1	Gershman, 1988	[197]
6.0	0.5–69.3		
5.9	3.4–10.2	Strader, 1988	[198]
5.2	2.4–32.5	Haughey, 1989	[199]
18.0	12–26	Stone, 1991	[200]
3.8	2.2–6.5	Forman, 1994	[201]
5.2	21.–13.0	Prener, 1996	[202]
3.6	1.8–6.9	Møller, 1996	[203]
1.6	1.2–2.3		
Cohort studies			
4.7	1.7–10.2	Giwercman, 1987	[204]
7.4	2.0–19.0	Pinczowski, 1991	[205]
11.4	†	Benson, 1991	[206]

* one-sided p-value
† no confidence interval or p-value reported

chidism often determine the status of the testes at three months or one year of age, or use a record of an orchidopexy to define cases, because this operation is uncommon before the age of one year and is unlikely to be performed if natural descent is probable.

Cryptorchidism is frequently associated with, or a feature of, major congenital disorders like anencephaly, chromosome 13 and 18 trisomy, Noonan's, Kallmann's, Down's and the Prader-Willi syndrome [212–214]. The causes of cryptorchidism among these cases are most likely secondary to the aetiology of the major malformation itself. These cases of cryptorchidism, however, are uncommon when compared to the number of cases that are not complicated by a major congenital anomaly. Cryptorchidism is also strongly associated with inguinal hernia [24, 215–218]. Inguinal hernia is discussed in more detail in chapter 9. In addition to an association with congenital malformations another risk factor for crypt-

orchidism is a twin or higher order delivery, although in one study this was shown to be secondary to low birth weight [217].

Table 6.3 summarises the main findings from selected epidemiological studies of cryptorchidism. These studies were selected because they examined a range of perinatal risk factors for cryptorchidism. Not included are studies that reported risk only in relation to birth weight or gestation. Some exposures that were similar, but not strictly comparable, have been condensed to simplify the presentation. For example, 'breech' includes breech presentation and breech delivery whilst 'hypertension' covers chronic and pregnancy induced hypertension.

With few exceptions [216, 220] low birth weight and short gestation were found to be associated with cryptorchidism [217, 218, 221, 222], even in studies which excluded twins [24, 215, 219]. Being small for gestational age was also a risk factor for cryptorchidism [219, 222] but it is not clear from existing studies if this is independent of low birth weight.

Breech presentation, labour or delivery was another risk factor for cryptorchidism that was present in most studies [24, 215, 217–219, 222], as was caesarean delivery [215, 219–221]. Breech presentation is an indication for caesarean delivery and these two risk factors may not be independent of one another.

The association with maternal age was less clear, with one study showing increased risk with older maternal age [219] while others show the opposite [24, 215, 216]. Similarly, being first born is mostly associated with an increased risk [24, 215, 221], but the opposite has also been reported [219].

Not breast-feeding and maternal smoking have not been examined in many studies but both appear to be associated with increased risk of cryptorchidism [215, 216]. There is also evidence for a raised risk with pre-eclampsia [218, 221] and its components, albuminuria (proteinuria) [217] and hypertension [216, 219], although the opposite has also been seen for albuminuria [215, 216]. Similarly a high maternal body mass index may increase the risk of cryptorchidism [219].

The evidence for increased risk with high maternal oestrogen levels or oestrogen use during pregnancy is circumstantial. Diethylstilbestrol (DES) has been shown to induce undescended testes in mice if given at days 17 and 19 of gestation; which in humans corresponds to weeks 11 to 16 of gestation [223]. In utero exposure to ethinyl oestradiol increases risk of cryptorchidism, and perhaps testicular teratoma, in mice [224]. In pregnant women treatment with DES starting at the seventh week of gestation was strongly associated with cryptorchidism in male offspring [225]. The use of hormonal pregnancy tests has shown

some increase in risk [226] and there was a raised prevalence of undescended testis seen for oral contraceptive use within one month of conception [227]. Both these studies, however, were primarily interested in the overall malformation rate and the results for cryptorchidism were based upon small numbers of cases and were not statistically significant. All the studies in table 6.3 have looked at markers for possible raised levels of endogenous oestrogen or oestrogen treatment, like high body mass index, vomiting and nausea, threatened abortion, previous miscarriage or stillbirth, and on balance these show an association with cryptorchidism. There are studies that have actually measured oestrogen levels during pregnancy, but their results are inconclusive [228, 229].

Other associations with uncertain significance have been identified, for example, maternal blood group B [24], maternal diabetes [24, 221], shorter duration of menses and later age at menarche in mothers of boys with undescended testis [165], season of birth [219, 221, 230, 231] and asthma [216].

6.4 Summary

The mechanisms that control the descent of the normal testis are not understood well, but hormonal influences [232] are thought to be important. Even less is known about the aetiology of the testis that does not spontaneously descend. During pregnancy there are three critical stages in the development of the testes: during the fifth to seventh week of embryonic development the testes begin to form; around 10–15 weeks of gestation transabdominal migration occurs; and final descent begins to take place at the end of the seventh month of gestation. It is plausible that the agent, or agents, responsible for the recent increases in the prevalence of cryptorchidism acts at one or more of these points in time. Other factors that predispose to an undescended testis may also act at these times and it might be expected that the earlier an agent acts the greater the severity of the mal-descent.

Table 6.3: Summary of epidemiological studies of prenatal risk factors for cryptorchidism

First author	Berkowitz	Mori	McBride	Hjertkvist	Depue	Davies	Depue	Beard	Swerdlow
Reference	[219]	[215]	[220]	[221]	[222]	[216]	[217]	[218]	[24]
Study period	1987–90	1978–1986	1982–1984	1973–82	1958–65	1978–	1958–65	1943–72	1976–78
Selection	diagnosis	orchidopexy	diagnosis or orchidopexy	diagnosis or orchidopexy	diagnosis	diagnosis	diagnosis	diagnosis	orchidopexy
Age at diagnosis	1 year	at operation	1 year	after 1 year	1 year	not stated	1 year	not stated	at operation
Number of cases	63	104	244	2424	300	106	385	113	146
Region	New York	Sapporo	British Columbia		Perinatal Project	Cambridge	Perinatal Project	Rochester	Oxford
Country	USA	Japan	Canada	70% of Sweden	USA	UK	USA	USA	UK
Exclusions	twins	twins	twins, malformations		non-white	twins		younger siblings	twins
Prevalence	1.08%			about 0.5%	2.62%		2.62%		3.38%
Risk factors									
Twin	...	...	...	...	YES, sig	...	YES, n/sig	...	...
Congenital malformations	YES, sig	...	...	yes	...	yes, n/sig	...	...	...
Inguinal hernia	...	YES, sig	...	...	...	yes, n/sig	yes	YES?, sig?	YES, sig
Low birth weight	YES, sig	yes, n/sig	no, n/sig	yes, sig	...	no, n/sig	YES, sig	YES, sig	yes, n/sig
Short gestation	YES, sig	n/sig	n/sig	yes, n/sig	YES, sig	yes, n/sig?	YES, sig	yes, sig	YES, sig
Small for gestational age	yes, n/sig	...	...	...	YES, sig	...	...	...	...
Older mother	yes, sig	no, n/sig	n/sig	n/sig?	no diff	no, n/sig	n/sig	n/sig	NO, n/sig
First born	no, sig	yes, n/sig	n/sig	yes, sig	no diff	...	n/sig	n/sig	yes, n/sig
Lower social class/education	no, n/sig	...	...	...	no diff	not sig	n/sig	...	YES, n/sig
Smoking	...	n/sig	yes, sig	...	...	yes, n/sig	...	n/sig	...
Not breast feeding	...	YES, sig	...	...	...	n/sig	...	...	...
Breech	YES, sig	YES, n/sig	n/sig	...	YES, sig	no, n/sig	yes, n/sig	YES, n/sig	YES, sig
Caesarean section	YES, sig	yes, n/sig	yes, sig	yes, sig	...	...	n/sig	n/sig	...
Pre-eclampsia/eclampsia	...	...	...	YES, sig	...	...	...	yes, n/sig	n/sig
Albuminuria/proteinuria	...	no, n/sig	...	...	...	no, n/sig	YES, sig	...	n/sig
Hypertension	yes, n/sig	no, n/sig	...	...	no diff	yes, n/sig	n/sig	...	...
High BMI, weight, height	YES, sig	n/sig	no, n/sig	...	yes, sig	...	yes, sig	...	yes, n/sig?
Maternal diabetes	yes, n/sig	...	...	yes, sig	no diff	no, n/sig	no diff	...	yes, n/sig
Nausea, vomiting	...	no, sig	n/sig	yes, n/sig	...	yes, n/sig	...	...	n/sig
Oestrogens	...	yes, n/sig	yes, n/sig	...	YES, sig	...	YES, sig	yes, n/sig	...
Threatened abortion,	...	n/sig	n/sig	...	...	YES, sig	...	YES, sig	...
spotting or bleeding	...	...	...	...	...	...	...	...	...
Previous spontaneous	yes, n/sig	n/sig	yes, n/sig	...	no diff	yes, n/sig	n/sig	yes, n/sig	n/sig
abortion or miscarriage	...	...	...	...	...	...	...	...	...
History of infertility	yes, n/sig	...	yes, n/sig	...	no diff	yes, sig	n/sig	yes, n/sig	...

Where the direction of an effect is given it is indicated by a 'yes' or 'no' as to whether it increases or decreases risk, irrespective of statistical significance. Large effects, where relative risks are greater than two or less than one-half, are shown in uppercase. If a result was statistically significant, usually at $p < 0.05$, then this is shown by 'sig' or if not significant then 'n/sig'. For some risk factors there was only a mention in the text of the paper that the exposure was unrelated to cryptorchidism. In this case the result is reported as 'n/sig' but no direction of effect is given.

Chapter 7

Undescended Testis Diagnosed at Birth

7.1 Introduction

Undescended testis is a difficult condition to diagnose at birth. Routine examination, often by junior hospital staff, may be unreliable or postponed if more serious conditions, like prematurity or major anomalies, are present. Partly for these reasons the risk factors for cryptorchidism diagnosed at birth, other than birth weight and gestation, have not previously been studied in detail. A large proportion of testes undescended at birth will descend spontaneously within the first year of life [147] and it is not known if this abnormality at birth is associated with infertility or other later pathological events. It is of interest, therefore, to compare and contrast the risk factors of cryptorchidism at birth with those for cryptorchidism that is diagnosed in later life. This chapter presents results for undescended testes diagnosed at birth.

7.2 Boys with a diagnosis of 'undescended testicle' at birth

The Oxford Record Linkage Study (ORLS) identified 1070 boys from delivery records who were born during 1970-86 and had undescended testes recorded at birth. Boys with major congenital anomalies or boys who were part of twin or higher order deliveries were subsequently excluded from the case-control analyses. Each case was individually matched with up to eight controls on sex, year and hospital of delivery. There were, in total, 947 cases and 7036 controls remaining after exclusions. Over 99% of cases had four or more matched controls. A description of the case series given in detail in appendix H.

7.3 Identifying risk factors

7.3.1 Birth weight and gestational age

Table 7.1 shows prevalence ratios for cryptorchidism, as defined by a diagnosis of undescended testis made at birth, in relation to birth weight, gestation, birth weight for gestational age, size of baby's head and retention in a special care baby unit.

Prevalence of cryptorchidism increased significantly as birth weight decreased, with the trend apparent across all birth weight groups. A different pattern was seen for gestation where prevalence of cryptorchidism was raised significantly at shorter gestational ages ($\leq$ 38 weeks) but was similar among boys who had reached 39 or more weeks of gestation. The raised prevalence with short gestation generated a significant test for trend but this was a reflection of the high prevalence ratios at short gestational ages.

Section 5.3.1 described the reference distribution used to derive birth weight for gestational age. Prevalence of cryptorchidism was raised significantly amongst boys who were small for their gestational age. There was also a significant trend, which was mostly a reflection of the raised prevalence among small for gestational age babies.

Table 7.1 also shows that there was a significant association between cryptorchidism and size of baby's head. Size of baby's head is strongly related to birth weight and other measures of intra-uterine development and after adjusting for birth weight there was no longer evidence for an overall association or trend with size of baby's head (heterogeneity: p=0.209; trend: p=0.743).

There was a significant association between a diagnosis of undescended testis at birth and being retained in a special care baby unit. After adjusting for birth weight, however, this association vanished (adjusted prevalence ratio: 0.84; 95% confidence interval (95% CI): 0.60–1.18).

Further analysis of birth weight and gestational age

Table 7.2 gives further details about the prevalence of cryptorchidism and its relation to birth weight and gestation. To avoid over-stratification of the data the highest two birth weight groups were joined. The category with the highest birth weights and lowest gestational ages only contained three cases but all other cells contained five or more cases. Birth weight remained significantly associated with cryptorchidism after adjustment for gestation (heterogeneity: p<0.001; trend: p<0.001). Gestational age was also significantly associated with cryptorchidism after adjustment for birth weight (heterogeneity: p=0.001; trend:

Table 7.1: Prevalence ratios for boys with undescended testes diagnosed at birth: birth weight, gestational age, birth weight for gestational age, size of baby's head and retention in special care baby unit

Risk factor	Cases (total=947) number	percent	Controls (total=7036) number	percent	Prevalence ratio	95% confidence interval	p-value
Birth weight (kg)							
≤2.4	78	8.2	279	4.0	2.04	1.55 – 2.70	<0.001
2.5–2.9	183	19.3	886	12.6	1.50	1.24 – 1.83	<0.001
3.0–3.4	361	38.1	2653	37.8	1.00	baseline	
3.5–3.9	253	26.7	2354	33.5	0.79	0.66 – 0.93	0.006
4.0 or more	72	7.6	851	12.1	0.62	0.48 – 0.81	<0.001
Not known	0		13				
* LRS[4]= 81.20, p <0.001; Trend LRS[1]= 79.28, p <0.001							
Gestation (completed weeks from date of last menstrual period)							
≤36	83	10.7	308	5.3	2.37	1.80 – 3.11	<0.001
37–38	186	23.9	1036	17.7	1.57	1.29 – 1.90	<0.001
39–40	329	42.3	2886	49.3	1.00	baseline	
41–42	148	19.0	1394	23.8	0.93	0.75 – 1.14	0.466
43 or more	31	4.0	229	3.9	1.15	0.78 – 1.72	0.479
Not known	170		1183				
LRS[4]= 54.30, p <0.001; Trend LRS[1]= 39.04, p <0.001							
†Birth weight for gestational age							
LGA	68	8.8	569	9.7	0.94	0.72 – 1.23	0.655
AGA	596	76.8	4742	81.2	1.00	baseline	
SGA	112	14.4	532	9.1	1.63	1.31 – 2.04	<0.001
Not known	171		1193				
LRS[2]= 18.15, p <0.001; Trend LRS[1]= 13.18, p <0.001							
Size of head (cm)							
20.0–34.0	186	26.9	859	16.8	2.06	1.63 – 2.61	<0.001
34.1–35.0	155	22.4	1279	25.1	1.15	0.91 – 1.46	0.244
35.1–36.0	195	28.2	1521	29.8	1.21	0.96 – 1.51	0.102
36.1 or more	155	22.4	1443	28.3	1.00	baseline	
Not known	63		434				
Not collected	193		1500				
LRS[3]= 41.70, p <0.001; Trend LRS[1]= 30.73, p <0.001							
Retention in special care baby unit							
No	883	93.2	6697	95.2	1.00	baseline	
Yes	64	6.8	339	4.8	1.43	1.09 – 1.89	0.011
LRS[1]= 5.99, p= 0.014							

* LRS[n]: Log-likelihood Ratio Statistic with n degrees of freedom
† LGA: Large for Gestational Age (above 90th percentile for birth weight)
† AGA: Appropriate for Gestational Age (between 10th and 90th percentile for birth weight)
† SGA: Small for Gestational Age (below 10th percentile for birth weight)
Cases individually matched with up to 8 controls on year of birth, sex and hospital of delivery

Table 7.2: Prevalence ratios for gestation and birth weight for gestational age by birth weight for boys with undescended testis diagnosed at birth

	Prevalence ratios (95% confidence intervals)					
	Birth weight (kg)				Adjusted for	
	≤2.4	2.5–2.9	3.0–3.4	3.5 or more	birth weight	
Gestation (weeks)						
≤36	2.53 (1.68–3.81)	1.89 (1.13–3.17)	2.97 (1.71–5.17)	0.80 (0.24–2.69)	1.64 (1.18–2.26)	Trend p<0.001
37–38	1.74 (0.85–3.56)	1.90 (1.36–2.66)	1.39 (1.03–1.88)	1.19 (0.82–1.74)	1.39 (1.14–1.70)	
39–40	3.13 (1.51–6.51)	1.26 (0.87–1.83)	1.00 baseline	0.79 (0.61–1.01)	1.00 baseline	
41 or more	2.65 (1.02–6.90)	1.80 (1.12–2.89)	0.90 (0.65–1.25)	0.76 (0.58–1.01)	0.99 (0.81–1.20)	
Adjusted for gestation	1.69 (1.18–2.41)	1.35 (1.08–1.68)	1.00 baseline	0.78 (0.65–0.93)		
			Trend: p<0.001			
*** Birth weight for gestational age**						
LGA	3.49 (1.16–10.51)		3.00 (1.40–6.40)	0.76 (0.56–1.04)	1.18 (0.89–1.57)	Trend p=0.247
AGA	1.98 (1.25–3.16)	1.61 (1.22–2.12)	1.00 baseline	0.76 (0.63–0.92)	1.00 baseline	
SGA	2.47 (1.66–3.67)	1.40 (1.05–1.88)	0.90 (0.40–1.98)	†	0.93 (0.70–1.24)	
Adjusted for birth weight for gestational age	2.32 (1.66–3.26)	1.53 (1.19–1.97)	1.00 baseline	0.72 (0.60–0.87)		
			Trend: p<0.001			

* LGA: Large for Gestational Age (above 90th percentile for birth weight)
* AGA: Appropriate for Gestational Age (between 10th and 90th percentile for birth weight)
* SGA: Small for Gestational Age (below 10th percentile for birth weight)
† too few or no cases in this category for appropriate analysis
Cases individually matched with up to 8 controls on year of birth, sex and hospital of delivery

p<0.001).

Closer examination of table 7.2 suggested there was an interaction between birth weight and gestation in relation to their association with cryptorchidism. There was a strong negative association between birth weight and cryptorchidism within each of the gestational age groups. The negative association between gestation and cryptorchidism, however, was apparent for birth weights of 3.0 kg or more but was not so clear at lower birth weights, suggesting the presence of a statistical interaction. The overall test for statistical interac-

tion between birth weight and gestation was not significant (p=0.181), but the individual prevalence ratio associated with the combination of low birth weight (<2.5 kg) *and* short gestation (≤36 weeks) was smaller than that expected (p=0.008) based on the assumption that birth weight and gestation were independent risk factors for cryptorchidism (i.e. the joint effects of birth weight and gestation were multiplicative). One interpretation of this observation is that small premature babies might be less likely to be routinely examined for undescended testes and, therefore, less likely to be selected into this study. The result would be a deficit of cases, and lower than expected prevalence, in the low birth weight and short gestation category, as seen in table 7.2.

Birth weight remained significantly associated with cryptorchidism after adjustment for birth weight for gestational age (heterogeneity: p<0.001; trend: p<0.001). Birth weight for gestational age, however, was no longer significantly associated with cryptorchidism after adjustment for birth weight (heterogeneity: p=0.459; trend: p=0.247). Controlling for birth weight reversed the unadjusted trend of birth weight for gestational age, such that being large for gestational age was associated with a raised prevalence of cryptorchidism. In fact, for a fixed birth weight, it was babies of short gestation who were classified as large for their gestational age. The increased prevalence associated with large for gestational age, therefore, can be interpreted as a reflection of the raised prevalence of cryptorchidism associated with short gestation.

Table 7.3: Prevalence ratios for boys with undescended testes diagnosed at birth: maternal age and parity

Risk factor	Cases (total=947) number	percent	Controls (total=7036) number	percent	Prevalence ratio	95% confidence interval	p-value
Maternal age (years)							
≤19	80	8.4	505	7.2	1.08	0.83 – 1.39	0.581
20–24	253	26.7	1895	27.0	0.91	0.77 – 1.08	0.266
25–29	381	40.2	2590	36.9	1.00	baseline	
30–34	174	18.4	1534	21.9	0.77	0.64 – 0.93	0.007
35 or over	59	6.2	496	7.1	0.80	0.60 – 1.07	0.134
Not known	0		16				
* LRS[4]= 10.07, p= 0.039; Trend LRS[1]= 4.42, p= 0.035							
Parity (before this pregnancy)							
0	418	44.2	3035	43.2	1.00	baseline	
1	321	34.0	2465	35.1	0.95	0.81 – 1.11	0.498
2	134	14.2	1041	14.8	0.94	0.76 – 1.15	0.537
3 or more	72	7.6	485	6.9	1.08	0.83 – 1.42	0.563
Not known	8		2				
Not collected	2		8				
LRS[3]= 1.31, p= 0.726; Trend LRS[1]= 0.00, p= 0.971							

* LRS[n]: Log-likelihood Ratio Statistic with n degrees of freedom
Cases individually matched with up to 8 controls on year of birth, sex and hospital of delivery

7.3.2 Maternal age and parity

Table 7.3 shows that there was significant trend (p-0.035) with maternal age, such that older maternal ages were associated with a lower prevalence of cryptorchidism than younger maternal ages. Maternal age is usually associated with birth weight [233] and adjusting for birth weight reduced the prevalence associated with teenage motherhood (adjusted prevalence ratio: 1.01; 95% CI: 0.78–1.31). The adjustment made little change to the remaining prevalence ratios at the other ages although the trend was now no longer statistically significant (p=0.205).

Table 7.3 also shows that there was no significant association between parity and cryptorchidism. Adjusting for birth weight resulted in a small increase in the prevalence ratio for parity three or more (adjusted prevalence ratio: 1.16; 95% CI: 0.88–1.52) but overall there was no significant association (p=0.769) or trend (p=0.434) with cryptorchidism.

Table 7.4: Prevalence ratios for boys with undescended testes diagnosed at birth: social class and feeding at discharge

Risk factor	Cases (total=947) number	Cases (total=947) percent	Controls (total=7036) number	Controls (total=7036) percent	Prevalence ratio	95% confidence interval	p-value
Social class							
I	67	8.0	699	11.2	0.63	0.48 – 0.82	0.001
II	139	16.6	1344	21.6	0.69	0.56 – 0.85	<0.001
III	375	44.8	2481	39.8	1.00	baseline	
IV	128	15.3	791	12.7	1.06	0.85 – 1.31	0.628
V	50	6.0	285	4.6	1.18	0.86 – 1.63	0.304
Other occupations	78	9.3	629	10.1	0.80	0.62 – 1.05	0.103
Not known	71		517				
Not collected	39		290				
* LRS[5]= 28.11, p <0.001							
Feeding at discharge							
Breast	507	65.9	4062	69.5	1.00	baseline	
Artificial	249	32.4	1697	29.0	1.18	1.01 – 1.40	0.043
Complement	13	1.7	83	1.4	1.21	0.67 – 2.21	0.529
Not known	38		123				
Not collected	140		1071				
LRS[2]= 4.23, p= 0.121							

* LRS[n]: Log-likelihood Ratio Statistic with n degrees of freedom
Cases individually matched with up to 8 controls on year of birth, sex and hospital of delivery

7.3.3 Social class and feeding at discharge

There was a significant association between social class and cryptorchidism, as shown in table 7.4. Prevalence was lowest among those born into social class groups I and II and increased up to group V (trend: p<0.001). Prevalence among boys born to parents in the group 'other occupations' was lower than that in the baseline group, but this was not statistically significant.

Table 7.4 also shows that artificial feeding compared to breast feeding was significantly associated with cryptorchidism but that there was no overall statistically significant association with method of feeding. Breast-feeding rates are often associated with social class [233] so that one of these two risk factors may only be associated with cryptorchidism through its association with the other risk factor. To explore this, prevalence ratios for cryptorchidism were tabulated for breast-feeding status by social class (table not shown here). Adjusting for social class reduced the strength of the association between artificial feeding and cryptorchidism (adjusted prevalence ratio: 1.07; 95% CI: 0.89–1.29), suggesting that breast feeding

Table 7.5: Prevalence ratios for boys with undescended testes diagnosed at birth: presentation at birth

Risk factor	Cases (total=947) number	percent	Controls (total=7036) number	percent	Prevalence ratio	95% confidence interval	p-value
Presentation							
Breech	37	4.6	157	2.6	1.78	1.23 – 2.57	0.002
Vertex (anterior)	707	88.3	5282	88.9	1.00	baseline	
Vertex (posterior)	34	4.2	261	4.4	0.99	0.69 – 1.43	0.963
Others	23	2.9	239	4.0	0.72	0.46 – 1.11	0.133
Not known	7		48				
Not collected	139		1049				
* LRS[3]= 11.25, p= 0.010							

* LRS[n]: Log-likelihood Ratio Statistic with n degrees of freedom
Cases individually matched with up to 8 controls on year of birth, sex and hospital of delivery

was associated with cryptorchidism through social class. Social class remained significantly associated with cryptorchidism (p=0.002) after adjusting for feeding at discharge.

7.3.4 Presentation

Breech presentation once labour has been established was associated with a significantly increased prevalence of cryptorchidism, as shown in table 7.5. Breech presentation is known to be related to impaired foetal growth [234] and adjusting for birth weight reduced, but did not eliminate, the association (adjusted prevalence ratio: 1.54; 95% CI: 1.06–2.24). Prevalence of cryptorchidism was also raised for breech delivery relative to vaginal delivery (not shown in the table, prevalence ratio: 1.49; 95% CI: 0.96–2.33).

7.3.5 Pre-eclampsia

As shown in table 7.6 any mention of pre-eclampsia or eclampsia was associated with a significantly increased prevalence of cryptorchidism. Albuminuria (proteinuria) and raised maximum systolic and maximum diastolic blood pressure were also associated with cryptorchidism. The maximum blood pressure measurements must be interpreted with caution, as mentioned in section 5.3.4. Briefly, the definition of maximum blood pressure may have changed in 1975 but the distribution of blood pressure readings before and after 1975 were similar and, therefore, it was assumed that the readings were comparable.

Diagnosis of pre-eclampsia is based upon measurement of albuminuria and blood pressure [235] and so these two risk factors may either be markers for pre-eclampsia or risk

Table 7.6: Prevalence ratios for boys with undescended testes diagnosed at birth: pre-eclampsia and eclampsia, albuminuria, and maximum blood pressure

Risk factor	Cases (total=947) number	percent	Controls (total=7036) number	percent	Prevalence ratio	95% confidence interval	p-value
Pre-eclampsia and eclampsia							
No mention	752	79.4	5971	84.9	1.00	baseline	
Yes	195	20.6	1065	15.1	1.46	1.23 – 1.74	<0.001
* LRS[1]= 17.67, p <0.001							
Albuminuria							
No trace	492	56.2	3752	57.7	1.00	baseline	
Trace only	327	37.3	2454	37.7	1.12	0.82 – 1.53	0.478
More than trace once only	38	4.3	218	3.4	1.36	0.94 – 1.96	0.107
More than trace more than once	19	2.2	77	1.2	1.95	1.13 – 3.36	0.016
Not known	32		245				
Not collected	39		290				
LRS[3]= 7.17, p= 0.067; Trend LRS[1]= 6.57, p= 0.010							
Maximum systolic blood pressure (mmHg)							
≤119	122	14.3	872	13.8	1.14	0.92 – 1.42	0.230
120–139	468	55.0	3753	59.6	1.00	baseline	
140–159	210	24.7	1390	22.1	1.21	1.01 – 1.44	0.036
160 or more	51	6.0	287	4.6	1.42	1.03 – 1.95	0.030
Not known	57		444				
Not collected	39		290				
LRS[3]= 7.92, p= 0.048; Trend LRS[1]= 3.08, p= 0.079							
Maximum diastolic blood pressure (mmHg)							
≤69	49	5.8	380	6.0	1.10	0.79 – 1.52	0.577
70–79	253	29.7	1894	30.1	1.10	0.93 – 1.32	0.274
80–89	326	38.3	2665	42.3	1.00	baseline	
90–99	121	14.2	890	14.1	1.11	0.89 – 1.39	0.366
100 or more	102	12.0	473	7.5	1.81	1.41 – 2.31	<0.001
Not known	57		444				
Not collected	39		290				
LRS[4]= 20.63, p <0.001; Trend LRS[1]= 6.91, p= 0.009							

* LRS[n]: Log-likelihood Ratio Statistic with n degrees of freedom
Cases individually matched with up to 8 controls on year of birth, sex and hospital of delivery

factors for cryptorchidism in their own right. Among those mothers with no mention of pre-eclampsia or eclampsia the prevalence of cryptorchidism in their sons was not associated with albuminuria (heterogeneity: p=0.394; trend p=0.741), maximum systolic (heterogeneity: p=0.533; trend: p=0.651) or maximum diastolic (heterogeneity: p=0.222; trend: p=0.927) blood pressure. This suggested that albuminuria and maximum blood pressure

Table 7.7: Prevalence odds ratios for boys with undescended testes diagnosed at birth: selected complications of pregnancy

Risk factor	Cases (total=947) number	percent	Controls (total=7036) number	percent	Prevalence ratio	95% confidence interval	p-value
Vomiting during pregnancy							
No mention	778	82.2	5714	81.2	1.00	baseline	
Yes	169	17.8	1322	18.8	0.91	0.74 – 1.12	0.384
* LRS[1]= 0.76, p= 0.383							
Diagnosis of hypertension							
No mention	927	97.9	6953	98.8	1.00	baseline	
Yes	20	2.1	83	1.2	1.78	1.08 – 2.93	0.024
LRS[1]= 4.57, p= 0.033							
Blood transfusion (mother)							
No	863	95.3	6531	97.0	1.00	baseline	
Yes	43	4.7	204	3.0	1.61	1.15 – 2.26	0.006
Not known	1		4				
Not collected	40		297				
LRS[1]= 6.92, p= 0.009							

* LRS[n]: Log-likelihood Ratio Statistic with n degrees of freedom
Cases individually matched with up to 8 controls on year of birth, sex and hospital of delivery

were secondary to pre-eclampsia in relation to cryptorchidism.

7.3.6 Other complications of pregnancy

Table 7.7 shows prevalence ratios for some other complications during pregnancy. Vomiting during pregnancy was not significantly associated with cryptorchidism. A diagnosis of hypertension was significantly associated with cryptorchidism, but like maximum blood pressure, it was not associated with cryptorchidism among those boys whose mothers had no mention of pre-eclampsia during pregnancy (prevalence ratio: 0.89; 95% CI: 0.31–2.55). Maternal blood transfusion was associated with a raised prevalence of cryptorchidism but rhesus incompatibility between mother and child (prevalence ratio: 0.99; 95% CI: 0.80–1.23) and any mention of haemorrhage, abruptio placentae or placenta praevia (prevalence ratio: 1.02; 95% CI: 0.83–1.25) were not.

7.3.7 Other risk factors

Maternal body mass index or a clinical diagnosis of obesity during pregnancy, as shown in table 7.8, were not significantly associated with cryptorchidism. Maternal weight and

Table 7.8: Prevalence ratios for boys with undescended testes diagnosed at birth: **other** risk factors

Risk factor	Cases (total=947) number	percent	Controls (total=7036) number	percent	Prevalence ratio	95% confidence interval	p-value
Body Mass Index (kg/m^2)							
≤19.9	60	8.8	467	9.2	0.94	0.70 – 1.26	0.695
20.0–24.9	381	55.9	2911	57.6	1.00	baseline	
25.0–29.9	199	29.2	1330	26.3	1.13	0.94 – 1.36	0.196
30.0–34.5	35	5.1	272	5.4	0.99	0.68 – 1.44	0.972
35.0 or more	6	0.9	70	1.4	0.69	0.29 – 1.61	0.385
Not known	70		478				
Not collected	196		1508				
* LRS[4]= 3.14, p= 0.535; Trend LRS[1]= 0.35, p= 0.552							
Diagnosis of obesity							
No mention	939	99.2	6984	99.3	1.00	baseline	
Yes	8	0.8	52	0.7	1.13	0.54 – 2.40	0.742
LRS[1]= 0.11, p= 0.745							
Smoking during pregnancy							
No	494	71.2	3871	75.2	1.00	baseline	
Yes	200	28.8	1279	24.8	1.22	1.02 – 1.45	0.030
Not known	75		545				
Not collected	178		1341				
LRS[1]= 4.63, p= 0.031							
Systolic blood pressure at 1st ante-natal visit (mmHg)							
≤119	295	41.4	2284	43.6	0.98	0.83 – 1.16	0.848
120–139	334	46.9	2551	48.7	1.00	baseline	
140–159	75	10.5	370	7.1	1.55	1.18 – 2.04	0.002
160–179	8	1.1	28	0.5	2.06	0.93 – 4.58	0.075
Not known	38		320				
Not collected	197		1483				
LRS[3]= 12.64, p= 0.005; Trend LRS[1]= 6.83, p= 0.009							
Diastolic blood pressure at 1st ante-natal visit (mmHg)							
≤69	247	34.7	1826	35.0	1.00	0.79 – 1.26	0.987
70–79	308	43.3	2283	43.8	1.00	0.80 – 1.24	0.992
80–89	130	18.3	951	18.2	1.00	baseline	
90–99	23	3.2	134	2.6	1.22	0.76 – 1.98	0.410
100–109	3	0.4	19	0.4	1.15	0.33 – 3.97	0.822
Not known	38		320				
Not collected	198		1503				
LRS[4]= 0.79, p= 0.940; Trend LRS[1]= 0.20, p= 0.657							

* LRS[n]: Log-likelihood Ratio Statistic with n degrees of freedom
Cases individually matched with up to 8 controls on year of birth, sex and hospital of delivery

height (not shown here) were not associated with cryptorchidism (trend: p=0.402, p=0.647 respectively). Smoking during pregnancy, also shown in table 7.8, was associated with cryptorchidism, but after adjusting for birth weight this association was weaker and not statistically significant (adjusted prevalence ratio: 1.09; 95% CI: 0.91–1.31).

Raised maternal systolic blood pressure at the first ante-natal visit was significantly associated with cryptorchidism, but raised diastolic blood pressure was not, although the numbers of mothers with raised blood pressure were small. Raised maternal blood pressure at the first ante-natal visit might be a marker for a subsequent diagnosis pre-eclampsia. A raised maternal systolic blood pressure, however, was significantly associated with undescended testis (prevalence ratio for 140 or more mmHg: 1.51; 95% CI: 1.05–2.17) among sons of women who did not have a mention of pre-eclampsia. Among the small number of sons of women with a subsequent mention of pre-eclampsia the association was less clear (prevalence ratio for 140 or more mmHg: 1.08; 95% CI: 0.56–2.07), but there was no statistical evidence for an interaction (p=0.699) between pre-eclampsia and systolic blood pressure in relation to undescended testis at birth in offspring.

Other risk factors were also examined but are not shown here because the results were not statistically significant or notable. The risk factors included Apgar score, duration of labour, maternal blood group, episiotomy, co-habitation, contraceptive failure, and resuscitation with oxygen.

There was no evidence for seasonal variation in the births of cases with undescended testis, as estimated by testing for departure from a uniform distribution of prevalence by month of birth (p=0.447) or by fitting a sinusoidal seasonal trend (p=0.138). There was a strong association of cryptorchidism with a diagnosis at birth of inguinal hernia (prevalence ratio: 5.33; 95% CI: 1.69–16.82) and an operation for inguinal hernia (prevalence ratio: 5.26; 95% CI: 4.00–6.91). These last two results must be treated with caution because an examination and positive diagnosis for one condition may lead to other related conditions being uncovered. Inguinal hernia and undescended testis may be the result of the same underlying pathological process and have risk factors in common, so it was considered inappropriate to treat inguinal hernia as an aetiological risk factor for cryptorchidism.

7.4 Multivariate analysis

7.4.1 Selection of risk factors

The previous sections identified low birth weight, short gestation, and a possible interaction between these two variables, young maternal age, low social class, not breast feeding, breech presentation, maternal eclampsia or pre-eclampsia, mother receiving a blood transfusion, maternal smoking during pregnancy and raised systolic blood pressure at the first ante-natal visit, as risk factors for cryptorchidism at birth. To try and gain further insights into the aetiology of cryptorchidism these variables were studied in more detail using a multivariate analysis.

Other risk factors were also statistically significant, but there were reasons to suppose that they were either measuring an exposure that was better represented by another variable, or that they were secondary to another risk factor. For example, birth weight, gestational age, birth weight for gestational age, size of baby's head and retention in a special care baby unit were strongly associated with cryptorchidism, but were not necessarily independent risk factors. There was a significant independent association between cryptorchidism and gestational age after adjusting for birth weight, suggesting that both these variables should be carried over into a multivariate analysis. After adjusting for birth weight, size of baby's head and retention in a special care baby unit were no longer independently associated with cryptorchidism, and birth weight for gestational age only reflected the initial association seen with gestational age. In the context of this study these variables provided no further information about cryptorchidism beyond that already provided by birth weight and gestational age. Similarly, the association with albuminuria, maximum blood pressure and a diagnosis of hypertension during pregnancy were all considered to be a consequence of pre-eclampsia. This idea was reinforced by the observation that these risk factors were not related to cryptorchidism among women without a diagnosis of pre-eclampsia. Parity was also included in the analysis because there were *a-priori* reasons to stratify by parity: first and subsequent pregnancies may be hormonally [236] and immunologically [237] different.

7.4.2 Multivariate model

Table 7.9 presents results of a multivariate analysis. Each perinatal exposure in table 7.9 has been adjusted for all the other exposures in the table. The statistical significance of each term in the model, and tests for trend, were assessed by adding the term to a multivariate model containing all the other variables shown in table 7.9 and comparing the change in

$-2\times$ log-likelihood to the chi-squared distribution [238].

Any 'missing data' or 'not collected' data items were included as a separate exposure level, except for birth weight and maternal age where there were too few missing values to make a useful category. Where the prevalence ratios across levels of an exposure were similar in size in the univariate analysis the exposure levels were collapsed to avoid over-stratifying the data. Unadjusted prevalence ratios were first estimated using the new categories and these were compared to the adjusted prevalence ratios. A comment was included if the adjusted prevalence ratios changed by more than $\pm 10\%$ from their unadjusted values.

7.4.3 Multivariate results

Table 7.9 presents results from the multivariate analysis. It was earlier concluded that birth weight and gestation were not independent of each other in relation to risk of undescended testis. A new variable was created by cross-tabulating birth weight and gestation, although some cells had to be combined to ensure that there were at least five cases in each category. The combined birth weight by gestation term was significant ($p<0.001$) when added to the model containing all the other variables in table 7.9. The prevalence ratios for low birth weight (≤ 2.4 kg), in all three categories of gestational age, were reduced by 11–17% from their unadjusted values, which suggested confounding with one or more of the other variables in the model.

The prevalence ratios in the youngest maternal age group was smaller by 10% when the adjusted values were compared to the unadjusted values, again an indication of confounding. Overall maternal age was no longer a statistically significant variable in the multivariate model (heterogeneity: $p=0.085$; trend: $p=0.472$) even though the prevalence ratios for ages 20–24 and 30–34 years were just statistically significant.

There was no evidence that the prevalence ratios for social class were confounded by other variables in the model because none of the prevalence ratios changed by more than 7% from their unadjusted value. Overall social class was significantly associated with prevalence of cryptorchidism (heterogeneity: $p=0.005$) and the trend across groups I–V was significant ($p<0.001$).

The highest category and missing value level of systolic blood pressure at the first antenatal visit decreased by 10% from the unadjusted value. Overall systolic blood pressure was significant ($p=0.041$) but the trend across the three groups where blood pressure was not missing was not ($p=0.069$).

Type of presentation was not significantly associated with cryptorchidism (heterogene-

Table 7.9: Multivariate analysis: prevalence ratios for boys with cryptorchidism diagnosed at birth

	Prevalence ratios (95% confidence intervals)			
Gestation (weeks)	**Birth weight (kg)**			
	≤2.4	2.5–2.9	3.0–3.4	3.5 or more
≤36	2.08 (1.34–3.24)	1.89 (1.29–2.77)		
37–38		1.79 (1.28–2.51)	1.31 (0.97–1.77)	1.18 (0.80–1.72)
39–40	2.30 (1.43–3.71)	1.20 (0.83–1.75)	1.00 baseline	0.79 (0.61–1.02)
41 or more		1.65 (1.02–2.65)	0.90 (0.65–1.24)	0.77 (0.58–1.03)
* Missing	1.31 (0.66–2.58)	2.11 (1.37–3.25)	1.19 (0.83–1.69)	0.94 (0.65–1.36)

† LRS[15]= 77.94, p<0.001

Maternal age (years)		
≤ 19	0.97	(0.73–1.29)
20–24	0.82	(0.69–0.99)
25–29	1.00	baseline
30–34	0.80	(0.66–0.97)
35 or over	0.80	(0.60–1.09)
	LRS[4]= 8.19, p=0.085; Trend LRS[1]= 0.52, p=0.472	
Social class		
I	0.68	(0.51–0.90)
II	0.72	(0.58–0.90)
III	1.00	baseline
IV	1.05	(0.85–1.32)
V	1.15	(0.83–1.59)
Other occupations	0.81	(0.61–1.06)
* Missing	0.88	(0.65–1.19)
	LRS[6]= 18.39, p=0.005	
Systolic blood pressure at 1st ante-natal visit (mmHg)		
≤ 119	1.01	(0.85–1.20)
120–139	1.00	baseline
140–179	1.45	(1.10–1.91)
* Missing	0.86	(0.61–1.21)
	LRS[3]= 8.24, p=0.041	

Presentation		
Breech	1.45	(0.99–2.12)
Other	1.00	baseline
* Missing	0.99	(0.44–2.22)
	LRS[2]= 3.41, p=0.182	
Pre-eclampsia		
No mention	1.00	baseline
Yes	1.33	(1.10–1.60)
	LRS[1]= 8.79, p=0.003	
Blood transfusion (mother)		
No	1.00	baseline
Yes	1.51	(1.07–2.14)
* Missing	1.69	(0.37–7.84)
	LRS[2]= 5.37, p=0.068	
Smoking during pregnancy		
No	1.00	baseline
Yes	1.07	(0.89–1.30)
* Missing	1.18	(0.80–1.76)
	LRS[2]= 1.06, p=0.589	
Feeding at discharge		
Breast and complement	1.00	baseline
Artificial	0.99	(0.83–1.18)
* Missing	1.39	(0.91–2.14)
	LRS[2]= 2.34, p=0.310	
Parity		
Nulliparous	1.00	baseline
Parous	1.05	(0.90–1.22)
	LRS[1]= 0.41, p=0.524	

* Missing level includes missing and not collected data items
† LRS[n]: Log-likelihood ratio statistic with n degrees of freedom
All variables adjusted for all other variables in the table
Cases individually matched with up to 8 controls on year of birth, sex and hospital of delivery

ity: p=0.182) even though the prevalence ratio for breech presentation was raised. There was a decrease of 18% in the prevalence ratio for breech presentation from the unadjusted value suggesting that it was confounded with another variable, or variables, in the model. Breech presentation was most likely to have been confounded with prematurity and low birth weight because breech presentation is associated with these two variables [234] and all three are associated with a raised prevalence of cryptorchidism. The adjusted value for the missing value level also became smaller by 15% from the unadjusted value.

Pre-eclampsia or eclampsia was significantly associated with cryptorchidism in the multivariate model (heterogeneity: p=0.003) even though the adjusted value was smaller by 9% from the unadjusted value.

The only change of more than ±10% between unadjusted and adjusted prevalence ratios for blood transfusion was in the missing value group. Overall maternal blood transfusion was not statistically significant (p=0.068) but the prevalence of cryptorchidism was significantly raised for the sons of mothers who had received a blood transfusion.

The adjusted prevalence ratio for maternal smoking during pregnancy was 12% lower than the unadjusted value. This suggested that maternal smoking was confounded with another variable, or variables, already in the model. The univariate analysis showed that part of the association between maternal smoking and cryptorchidism was removed by adjusting for birth weight. Overall maternal smoking was not significant (p=0.589).

The adjusted prevalence ratio for artificial feeding relative to breast feeding decreased by 15% in the multivariate analysis such that artificial feeding was no longer associated with a raised prevalence of cryptorchidism. In section 7.3.3, which covered the univariate analyses of social class and type of feeding, social class was able to account for much of the association between type of feeding and cryptorchidism.

There was a small change between the adjusted and unadjusted values for parity but overall parity was not significant (p=0.524).

Most of the major changes between unadjusted to adjusted prevalence ratios were downward, weakening the unadjusted associations, suggesting that some of the variables in the multivariate model were correlated and were markers for the same underlying risk factor or factors.

7.4.4 Boys with a subsequent orchidopexy

Twenty-one percent (n=196) of cases went on to have a subsequent orchidopexy. These boys also appear in the study of undescended testes defined by orchidopexy as reported

in chapter 8. When these boys were removed from the analysis the multivariate results remained essentially unchanged. The only notable difference was that the raised prevalence ratio for the combination of low birth weight and prematurity was larger than before (prevalence ratio: 2.72; 95% CI: 1.65–4.48).

7.4.5 Stratification by parity

Tables 7.10 and 7.11 present multivariate results for nulliparous and parous mothers respectively. Stratification by parity modified the prevalence ratios by differing amounts, but much of this was in the range that could be attributed to chance variation. The difference in a risk factor's prevalence ratios between the 'nulliparous' and 'parous' analysis was assessed by testing the statistical interaction between the risk factor and parity in the multivariate model. At $p<0.15$, a level sometimes used to identify potential interactions [239], there was a suggestion of an interaction only with presentation at delivery ($p=0.131$). Breech presentation was a stronger risk factor for cryptorchidism among nulliparous mothers than parous mothers, although this difference was not statistically significant ($p=0.212$).

Apart from the observation that breech presentation may be more important among nulliparous mothers there were no compelling reasons to prefer the stratified analysis over the unstratified analysis presented in table 7.9.

Table 7.10: Multivariate analysis: prevalence ratios for boys with cryptorchidism diagnosed at birth—nulliparous mothers only

	Prevalence ratios (95% confidence intervals)			
Gestation (weeks)	**Birth weight (kg)**			
	≤2.4	2.5–2.9	3.0–3.4	3.5 or more
≤36	1.43 (0.67–3.06)	1.65 (0.86–3.14)		
37–38		1.43 (0.81–2.56)	1.56 (0.95–2.55)	1.57 (0.80–3.07)
39–40	3.38 (1.57–7.31)	1.25 (0.70–2.24)	1.00 baseline	0.75 (0.48–1.17)
41 or more		1.48 (0.72–3.04)	0.67 (0.39–1.14)	0.89 (0.56–1.41)
* Missing	0.55 (0.17–1.72)	2.90 (1.29–6.49)	1.10 (0.58–2.10)	1.19 (0.62–2.25)

† LRS[15]= 39.19, p=0.001

Maternal age (years)		
≤ 19	0.90	(0.59–1.36)
20–24	0.87	(0.65–1.18)
25–29	1.00	baseline
30–34	0.94	(0.63–1.40)
35 or over	0.92	(0.43–1.96)
	LRS[4]= 0.81, p=0.937; Trend LRS[1]= 0.21, p=0.650	
Social class		
I	0.79	(0.50–1.24)
II	0.78	(0.53–1.15)
III	1.00	baseline
IV	1.10	(0.74–1.63)
V	1.07	(0.56–2.03)
Other occupations	0.72	(0.45–1.18)
* Missing	0.96	(0.58–1.61)
	LRS[6]= 4.36, p=0.628	
Systolic blood pressure at 1st ante-natal visit (mmHg)		
≤ 119	0.90	(0.66–1.21)
120–139	1.00	baseline
140–179	1.68	(1.06–2.65)
* Missing	0.78	(0.43–1.42)
	LRS[3]= 7.11, p=0.068	

Presentation		
Breech	2.09	(1.13–3.87)
Other	1.00	baseline
* Missing	1.23	(0.24–6.44)
	LRS[2]= 5.27, p=0.072	
Pre-eclampsia		
No mention	1.00	baseline
Yes	1.32	(0.99–1.75)
	LRS[1]= 3.55, p=0.060	
Blood transfusion (mother)		
No	1.00	baseline
Yes	1.30	(0.69–2.44)
* Missing	1.06	(0.11–9.83)
	LRS[2]= 0.65, p=0.723	
Smoking during pregnancy		
No	1.00	baseline
Yes	1.21	(0.87–1.67)
* Missing	1.54	(0.80–2.95)
	LRS[2]= 2.63, p=0.269	
Feeding at discharge		
Breast and complement	1.00	baseline
Artificial	0.95	(0.69–1.31)
* Missing	2.43	(1.12–5.28)
	LRS[2]= 5.32, p=0.070	

* Missing level includes missing and not collected data items
† LRS[n]: Log-likelihood ratio statistic with n degrees of freedom
All variables adjusted for all other variables in the table
Cases individually matched with up to 8 controls on year of birth, sex and hospital of delivery

Table 7.11: Multivariate analysis: prevalence ratios for boys with cryptorchidism diagnosed at birth—parous mothers only

Prevalence ratios (95% confidence intervals)

Gestation (weeks)	Birth weight (kg) ≤2.4	2.5–2.9	3.0–3.4	3.5 or more
≤36	2.86 (1.44–5.68)		1.64 (0.92–2.91)	
37–38		2.79 (1.66–4.67)	1.22 (0.77–1.91)	0.98 (0.57–1.69)
39–40	1.60 (0.68–3.74)	1.31 (0.73–2.36)	1.00 baseline	0.76 (0.54–1.08)
41 or more		1.35 (0.61–2.97)	0.99 (0.61–1.59)	0.71 (0.47–1.05)
* Missing	1.65 (0.63–4.34)	2.58 (1.38–4.83)	1.33 (0.81–2.19)	0.78 (0.46–1.31)

† LRS[15]= 56.03, p<0.001

Maternal age (years)		
≤ 19	1.72	(0.97–3.04)
20–24	0.78	(0.60–1.03)
25–29	1.00	baseline
30–34	0.86	(0.66–1.11)
35 or over	0.95	(0.66–1.37)
LRS[4]= 8.47, p=0.076; Trend LRS[1]= 0.07, p=0.794		
Social class		
I	0.56	(0.37–0.86)
II	0.62	(0.45–0.84)
III	1.00	baseline
IV	0.91	(0.67–1.24)
V	1.17	(0.75–1.84)
Other occupations	0.94	(0.63–1.39)
* Missing	0.93	(0.59–1.49)
LRS[6]= 15.62, p=0.016		
Systolic blood pressure at 1st ante-natal visit (mmHg)		
≤ 119	1.13	(0.89–1.44)
120–139	1.00	baseline
140–179	1.50	(0.97–2.31)
* Missing	0.90	(0.56–1.44)
LRS[3]= 4.19, p=0.241		
Presentation		
Breech	1.37	(0.71–2.63)
Other	1.00	baseline
* Missing	1.74	(0.55–5.56)
LRS[2]= 1.65, p=0.438		
Pre-eclampsia		
No mention	1.00	baseline
Yes	1.34	(1.00–1.81)
LRS[1]= 3.72, p=0.054		
Blood transfusion (mother)		
No	1.00	baseline
Yes	2.14	(1.24–3.68)
* Missing	1.18	(0.12–11.98)
LRS[2]= 6.91, p=0.032		
Smoking during pregnancy		
No	1.00	baseline
Yes	0.96	(0.73–1.26)
* Missing	1.14	(0.63–2.07)
LRS[2]= 0.34, p=0.842		
Feeding at discharge		
Breast and complement	1.00	baseline
Artificial	1.07	(0.85–1.37)
* Missing	0.85	(0.43–1.67)
LRS[2]= 0.69, p=0.709		

* Missing level includes missing and not collected data items
† LRS[n]: Log-likelihood ratio statistic with n degrees of freedom
All variables adjusted for all other variables in the table
Cases individually matched with up to 8 controls on year of birth, sex and hospital of delivery

7.5 Discussion of results from the case-control study

Low birth weight, short gestation, low social class, breech presentation, pre-eclampsia, raised systolic blood pressure at the first ante-natal visit and maternal blood transfusion were identified as the main risk factors for cryptorchidism after univariate and multivariate analyses. Maternal age, not breast feeding and smoking during pregnancy had also been identified as risk factors, but they showed little association with risk of cryptorchidism after adjusting for the above variables. There was an indication that breech presentation was a stronger risk factor for cryptorchidism among first born children than among later born children, but the statistical evidence for this was weak.

Cryptorchidism at birth may be a transient abnormality because a large proportion of these testes will descend spontaneously within the first few months after birth [147]. The long term implication of cryptorchidism at birth is not known because there appear to be no studies of subsequent fertility or malignancy. There are also no large studies of risk factors for undescended testes diagnosed at birth other than for birth weight and gestation. In this study, however, it was possible to look at the role of risk factors that have only been examined in studies of boys who remain undescended some months after birth, and to examine the interaction between related variables, like birth weight and gestation in more detail than previously done.

7.5.1 Diagnosis of cryptorchidism at birth using routine data

As will be shown in the study of cryptorchidism defined by orchidopexy, in chapter 8, only 13.5% of boys undergoing orchidopexy had undescended testes diagnosed and recorded at birth. A registry based study from Sweden also reported that only 30% of boys with orchidopexy had a diagnosis of cryptorchidism in the newborn period. Boys with ascending [150] and retractile [152] testes undergoing orchidopexy may partly account for the missing diagnoses at birth. It appears likely, however, that a proportion of boys with undescended testes at birth were not routinely recorded as such. The interpretation of these results, therefore, needs care.

Routine examination for, or recording of, undescended testis may be postponed or not take place if a baby required intensive care for a serious illness. Assuming ill babies were more likely to be of lower birth weight or shorter gestation, this would result in a deficit of cases with low birth weight, short gestation, or both. If serious illness at birth was associated with pregnancy or delivery complications then the prevalence ratios for these complications would also be biased. This bias might be described as a 'healthy baby' selection bias,

operating in favour of the cases (i.e. making the case group relatively more healthy, or less prone to complications during delivery, than the control group). Boys with major congenital malformations were excluded from the case *and* control group, and this would have reduced the effect of this selection bias. There are, however, other major conditions at birth that may be recorded in preference to, or delay a routine examination for, undescended testes. As discussed later, there was evidence for a deficit of cases among small and premature babies.

In addition to serious illness causing cryptorchidism to be not recorded, the format of the ORLS delivery abstract form and computer database influenced the way in which data were recorded. During 1970–72 there was only room for one malformation code on the delivery record and it was possible that this affected selection of cases born during that period to a greater degree than those born in later years. For cases born after 1972 there was room for up to ten diagnoses and hence more chance of undescended testes being recorded along with other diseases or illnesses. When the multivariate analysis was restricted to those cases and controls born 1973–86 there was little change to the final results. Selection bias due to changes in the number of diagnoses routinely recorded by ORLS, therefore, had little effect on the results of this study.

It is possible that a baby from a delivery with complications would be examined in more detail than a baby from an uneventful delivery. In such situations undescended testes may be more likely to be diagnosed and recorded. There were, however, several complications of pregnancy and delivery like maternal diabetes, rhesus incompatibility or caesarean section, that did not show significantly increased risks for undescended testis at birth; neither was a poor Apgar score associated with an increased prevalence of cryptorchidism. It appears unlikely, therefore, that the increased prevalence that was seen with some complications of pregnancy, like breech presentation and maternal blood transfusion, were due to a more detailed examination of the baby because of the presence of those complications.

7.5.2 Advantages and disadvantages of routine exposure data

The advantages and disadvantages of routine data were discussed in section 5.4.3 and apply equally to this study.

7.5.3 Heterogeneity of disease

Another point important for the interpretation of these results is the possible heterogeneous nature of undescended testes. The aetiology of cryptorchidism may be different for different

types of maldescent. Bilateral cryptorchidism may be aetiologically distinct from unilateral cryptorchidism and the testis that remains in the abdomen may do so for different reasons than one that stops in the inguinal canal, or one that remains high in the scrotum or is stopped because of an obstruction at the end of the inguinal canal [146]. The testis that is undescended at birth but descends naturally shortly after birth may also be aetiologically different to one that does not descend without medical intervention. Cryptorchidism at birth, therefore, may cover a heterogeneous group of conditions, each with a differing aetiology.

Twenty-one percent of the cases in this study were also included in the study of cryptorchidism as defined by orchidopexy, but the majority of cases in this study did not have an orchidopexy within the study period. It has been reported that 75% of boys with cryptorchidism at birth will be descended within the first few months after birth [147], which is consistent with the case series here. The multivariate results were essentially unchanged when the cases who went on to have an orchidopexy were removed from the analysis. The only notable difference was the raised prevalence with the combination of low birth weight and prematurity was greater when boys who had an orchidopexy were removed from the analysis. This suggests that boys who were undescended at birth and subsequently had an orchidopexy were less likely to be premature and low birth weight than boys whose condition, presumable, resolved itself naturally.

7.5.4 Risk factors

Birth weight and gestation

Short gestation was related to an increased prevalence of undescended testis at birth, but this was expected because the testes do not normally begin to enter the scrotum until seven or eight months of gestation [143]. There was an apparent relative deficit of cryptorchid boys with short gestation and low birth weight, but it was probable that this was due to under recording of cryptorchidism among premature babies because the treatment of other more serious conditions would take precedence over an examination for or recording of undescended testes. Low birth weight was also associated with an increased prevalence or cryptorchidism, among preterm and term boys, and it accounted for the increased prevalence seen with small head size. Low birth weight and prematurity have previously been identified as risk factors for cryptorchidism diagnosed at birth [154, 155], but it is not known if one is independent of the other. The findings here indicate that prematurity and being a small baby, regardless of gestational age, were both important in relation to undescended testis

at birth.

Parity and social class

There was no strong evidence that the risk factors for undescended testes diagnosed at birth were different among sons born to nulliparous and parous mothers. Neither was prevalence raised among first born children, which has previously been reported as a risk factor for undescended testes that have not spontaneously descended some months after birth [24, 215, 221].

Prevalence was lowest among the high social class groups which is opposite to the association seen between social class and testicular cancer [240]. This difference is of interest because testicular cancer is strongly associated with cryptorchidism [240] (although the association is with cryptorchidism that is usually diagnosed some months after birth, or at orchidopexy). It was unlikely that the routine diagnosis of undescended testes could be biased by the social class of the parents to the degree seen in this study, especially since there was no other obvious diagnostic label that might have been used, and the alternative was to not record cryptorchidism. Indeed, there were no compelling reasons to believe that any bias due to social class would be in the right direction to produce such an association seen here. The lower prevalence with higher social class, therefore, is likely to be real. It remains to be seen which correlates of social class are associated with cryptorchidism, and if the association holds in other populations where measures of social class may reflect different underlying risk factors.

Presentation

Breech presentation was a risk factor for undescended testes, perhaps more so among first births than later ones. It had been suggested that breech delivery, or attempted breech delivery, may result in testicular damage [24, 217]. If so, damage may prevent the testes from descending fully after birth, but this would not account for undescended testes 'at birth.' If such a mechanism were at work it might be expected to occur more frequently among attempted breech deliveries that were in some way more traumatic than usual. This may be true of first births but further work would be needed to establish this. Breech presentation, however, might be a marker for other complications of pregnancy like intra-uterine growth retardation [234]. Possible causes of intra-uterine growth retardation will be discussed later in the study of cryptorchidism defined by orchidopexy (see section 8.5.5).

Pre-eclampsia

Studies of cryptorchidism, usually diagnosed after three months of age, have also identified pre-eclampsia as a risk factor [218, 221]. Pre-eclampsia may lead to an early delivery [241] and hence prematurity and low birth weight, which are themselves strong risk factors for undescended testes. In the multivariate analysis, however, pre-eclampsia was still associated with undescended testes after adjusting for birth weight, gestation and the remaining selected risk factors. Pre-eclampsia may act as a marker for complications of pregnancy, like vascular abnormalities [242] and reduced uterine circulation [243]. Foetal distress and abnormally low urinary oestriol excretion may also occur in pregnancies complicated by pre-eclampsia [244]. Pre-eclampsia in relation to cryptorchidism and intra-uterine growth retardation will be discussed in more detail in the study of cryptorchidism defined by orchidopexy (see section 8.5.5).

Systolic blood pressure at first ante-natal visit

Systolic blood pressure at the first ante-natal visit was significantly associated with cryptorchidism among women who did not develop eclampsia or pre-eclampsia, implying that this measure of blood pressure was not simply a marker for subsequent pre-eclampsia. Raised blood pressure in early pregnancy, however, may have a similar consequence to the raised blood pressure associated with pre-eclampsia: reduced uterine circulation and possible intra-uterine growth retardation, which is discussed in more detail in section 8.5.5. Raised blood pressure at the first ante-natal visit has not previously been associated with cryptorchidism, so this finding needs confirmation.

Maternal blood transfusion

Maternal blood transfusion was also identified as a risk factor for undescended testes at birth. There was no association with any mention of haemorrhage, abruptio placenta, or placenta praevia, but there are other reasons why blood transfusion would be necessary. Maternal blood transfusion, however, has not previously been linked with cryptorchidism either diagnosed at birth or in later childhood, and the association needs confirmation.

7.5.5 Summary of results from the case-control study

Low birth weight and prematurity were both found to be important in relation to undescended testis diagnosed at birth; these associations may reflect immaturity at birth,

perhaps because of early delivery, slow intra-uterine growth, or both. Artefactual explanations did not appear to be able to account for the associations. Two other risk factors, breech presentation and pre-eclampsia, may also be associated with intra-uterine growth retardation. Risk of cryptorchidism was relatively low in the highest social class group, in contrast to the association between testicular cancer and high social class [240]. Biases were unlikely to account for this association and, therefore, this finding deserves to be examined in more detail in other studies. The significance of the associations between undescended testis and systolic blood pressure and maternal blood transfusion was uncertain, and as these risk factors have not previously been identified they need confirmation.

Table 7.12: Number of sibships with r boys with undescended testis diagnosed at birth in sibship of boys of size s

Sibship size (s)	Number of sibships: Number of affected boys in sibship (r) 0	1	2	3	4	5	6	Total	Risk (%)
Male sibships with at least one case									
1	—	584						584	—
2	—	280	3					283	2.10
3	—	59	2	0				61	3.21
4	—	9	0	0	0			9	0.00
5	—	5	0	0	0	0		5	0.00
6	—	0	0	0	0	0	0	0	—
Total	—	937	5	0	0	0	0	942	2.18
					95% confidence interval				(0.79–4.60)
Male sibships with at least one control									
1	4083	58						4141	1.40
2	1872	61	1					1934	1.63
3	360	12	1	0				373	1.25
4	68	3	0	0	0			71	1.06
5	9	2	0	0	0	0		11	3.64
6	4	0	0	0	0	0	0	4	0.00
Total	6396	136	2	0	0	0	0	6534	1.48
							95% confidence interval		(1.25–1.73)

7.6 Risk of undescended testis in siblings

The 947 cases were part of 942 sibships containing in total 1905 children; an average of 2.02 children per sibship. It was possible to estimate the prevalence of undescended testes in sibships which contained at least one affected boy by using the affected-sib method [245]. Maximum likelihood methods [246] were used to estimate the probability (with confidence intervals) of an individual being affected conditional on there already being one affected boy in that sibship. Only sibships of size two or more contributed information about prevalence in affected sibships. It was appropriate only to use sibships which were made up of children eligible to become cases (i.e. only singleton boys without a major congenital anomaly diagnosed at birth). There were 1394 boys left after removing girls, and boys who had a diagnosis of a major congenital malformation at birth or were part of a twin or higher order delivery. Sibship sizes were re-calculated counting only eligible boys. There were now 1394 eligible boys in 942 sibships for an average of 1.48 boys per affected sibship.

The number of affected boys (i.e. cases) in a sibship of given size made up only of eligible boys is shown in table 7.12. By definition each case sibship had to contain at least

one affected boy. Five sibships had two affected boys. Overall the risk of undescended testis diagnosed at birth in siblings of affected boys was 2.18% (0.79%—4.60%).

Table 7.12 also shows the number of affected boys among sibships containing at least one control boy. Again, only eligible boys were included. There were 9491 eligible boys in 6534 sibships for an average of 1.45 boys per control sibship. Overall the risk of undescended testis among boys in control sibships was 1.48% (1.25%—1.73%). This was similar to the prevalence in Scotland, 1976–85 [157], of 1.4% as derived from routine hospital neonatal discharge diagnoses, but less than the estimated 5.0% seen in a hospital based study from Oxford, 1984–88, where a large number of boys were specifically examined for undescended testis at birth [147].

7.7 Discussion of disease risk among siblings

The risk of being diagnosed with undescended testis at birth was higher in case sibships than control sibships but this difference was not large enough to be statistically significant. There were, however, only five case sibships where two or more boys were affected so the power to detect any clustering within sibships was low. Even in the absence of true clustering within sibships it might be expected that younger male siblings of an already affected boy might be more likely to have undescended testis recorded at birth. For example, the mother of an affected son might be more aware about, and demand careful examination for, cryptorchidism in her subsequent male children. Nonetheless the absence of a clear clustering with undescended testis diagnosed at birth is contrary to the reported familial association from one population based study [165], and to the striking examples in the literature of case-reports describing cryptorchidism occurring within families [159, 163]. These reports, however, generally refer to undescended testes that require medical intervention. Many of the boys in this study, perhaps 75% [147], would be expected to have testes that would descend naturally in the first few months after birth [144], and only 20.7% were recorded as having had an orchidopexy by the end of the study period. The familial association previously reported in the literature may, therefore, not apply as strongly to cases of undescended testis at birth.

7.8 Risk factors in siblings

The risk factors for undescended testis so far examined relate to delivery and maternity variables associated with the birth of the cases and controls. This section looks at risk factors for undescended testis at birth in relation to selected exposures associated with the delivery of a sibling of a case or control.

7.8.1 Methods

The list of cases and controls was reduced to a person-based file where boys appeared only once and were either affected (i.e. had a diagnosis of cryptorchidism at birth) or not-affected (i.e. no mention of cryptorchidism at birth). The deliveries for these boys will sometimes be called the *index* deliveries. The matching within the original study was broken so as to make best use of the available data. If the matching had been retained, for example, all the siblings of a controls who were matched to a case with no siblings would themselves have been lost to the analysis.

The immediately previous born and immediately subsequent born sibling of the affected and not-affected boys were identified. Selected exposures were extracted from the maternity and delivery record associated with the birth of these siblings.

In the original matched analyses there was no evidence of strong confounding between the matching variables and the risk factors presented here (i.e. by looking for changes in the matched and crude odds ratios in tables 7.1, 7.4, and 7.5), however, the matching variables, year and hospital of delivery, were grouped and entered into the analysis as strata. In addition, the sex of the sibling was also entered into the analysis because some perinatal variables, like birth weight, are influenced by the sex of the child. Odds ratios are presented for selected risk factors present at the delivery of the siblings in relation to risk of undescended testis at the index delivery. Odds ratios adjusted for the same risk factor at the index delivery are also presented.

A technically more complex sibling analysis would have been too time-consuming to attempt and was beyond the intended scope of this thesis. The results presented here, however, extend the findings from the matched case-control study in a way that may give useful insights into the aetiology of cryptorchidism.

Duplicates and exclusions

There were two sibling delivery records with the same date of birth as their index case or control, and after closer inspection against the index record these appeared to be 'near

Table 7.13: Odds ratios for undescended testis diagnosed at birth for risk factors present in sibling born immediately before cases and controls: index matching variables and sex of sibling

Risk factor	Cases (total=362) number	Controls (total=2517) number	Odds ratio*	95% confidence interval
Year of birth of index case or control				
1970–74	27	183	1.04	0.66–1.65
1975–79	94	666	1.00	baseline
1980–86	241	1668	1.02	0.79–1.32
			† LRS[2]= 0.05, p =0.978; Trend LRS[1]= 0.00, p =0.978	
Hospital district of birth of index case or control				
Oxfordshire	233	1616	1.00	baseline
West Berkshire	129	901	0.99	0.79–1.25
			LRS[1]= 0.00, p =0.956	
Sex of sibling				
Boy	189	1337	1.00	baseline
Girl	173	1180	1.04	0.83–1.29
			LRS[1]= 0.10, p =0.750	

* all variables adjusted for other variables in the table

† LRS[n]: Log-likelihood ratio statistic with n degrees of freedom

duplicate' records. Each pair of records had a different delivery form number and system number, but the pairs contained almost identical information on the rest of the record. These records were dropped from the analyses.

Twelve siblings were born within 200 days of the index delivery, at impossible or highly improbable values for the inter-pregnancy interval [247]. Closer examination of these records suggested that they were not duplicates but distinct delivery events. It was possible that these deliveries were wrongly linked records and in any case they were removed from this analysis. Siblings who were part of twin or higher order deliveries, and siblings who had a major congenital malformation diagnosed at birth were also excluded from the analysis. Where a sibling record was excluded from the analysis the index case or control was also excluded.

7.8.2 Results

Immediately prior deliveries

Table 7.13 shows odds ratios for the matching variables and the sex of the sibling born immediately prior to the index case or control. To enter this analysis the cases and controls had to have had a sibling born before themselves, during 1970–86. As a consequence of this the index cases and controls in this analysis were more likely to be born towards the end of the study period. There was little difference between cases and controls in the sex of their previous sibling.

Table 7.14 shows unmatched odds ratios for risk of undescended testis based upon birth weight, gestational age and birth weight for gestational age of the previously born siblings. Risk of undescended testis was significantly associated with the birth weight of the sibling, with a significant trend towards greater risk at lower birth weights. After adjusting for birth weight at the index delivery the association between undescended testes and birth weight at the sibling's delivery disappeared. A similar pattern was seen with gestational age. The risk of undescended testis was increased if the sibling was of short gestation, but this was not statistically significant. Adjusting for gestational age of the index case or control reduced the strength of this association. There was no statistically significant associations with birth weight for gestational age of the sibling.

Table 7.15 shows unmatched odds ratios for social class, pre-eclampsia, presentation at delivery and caesarean section during the sibling's delivery. There was a strong association with undescended testis among cases and controls and the social class of their siblings, with a significant trend across groups social class groups I to V (trend: p=0.001). The association was no longer significant (trend: p=0.606) after adjusting for social class at the index delivery.

The risk of undescended testis was raised if there was mention of pre-eclampsia during the pregnancy associated with the prior sibling, but this was not statistically significant, either before or after adjusting for pre-eclampsia during the index delivery. There was no strong evidence for an association with pre-eclampsia during the subsequent delivery. Boys with undescended testis were more likely to have a sibling present in the breech position than were controls. Even after adjusting for breech presentation at the index delivery this remained significant and was apparent for previous and subsequent deliveries. There was no significant association between risk of undescended testis and having the previous sibling delivered by caesarean section.

Table 7.14: Odds ratios for undescended testis diagnosed at birth for risk factors present in sibling born immediately before cases and controls: birthweight and gestational age

Risk factor in sibling	Cases (total=362) number	Controls (total=2517) number	Odds ratio*	95% confidence interval	Odds ratio*†	95% confidence interval
Birth weight (kg) of sibling						
≤2.4	24	128	1.38	0.86–2.20	0.92	0.55–1.52
2.5–2.9	86	425	1.50	1.12–2.01	1.24	0.92–1.68
3.0–3.4	137	1005	1.00	baseline	1.00	baseline
3.5–3.9	87	734	0.87	0.65–1.16	1.06	0.79–1.42
4.0 or more	25	215	0.85	0.54–1.34	1.28	0.79–2.07
Missing	3	10				
			‡ LRS[4]= 13.81, p =0.008; Trend LRS[1]= 10.91, p =0.001		LRS[4]= 3.15, p =0.533; Trend LRS[1]= 0.02, p =0.880	
Gestational age (weeks) of sibling						
≤36	27	124	1.50	0.91–2.50	1.18	0.69–2.00
37–38	60	370	1.23	0.86–1.75	1.12	0.78–1.60
39–40	153	1071	1.00	baseline	1.00	baseline
41–42	72	589	1.02	0.74–1.41	1.09	0.78–1.52
43 or more	16	113	0.76	0.37–1.54	0.80	0.39–1.63
Missing	34	250				
			LRS[4]= 4.35, p =0.361; Trend LRS[1]= 3.33, p =0.068		LRS[4]= 1.33, p =0.856; Trend LRS[1]= 0.43, p =0.511	
§ Birth weight for gestational age of sibling						
LGA	29	197	1.26	0.81–1.96	1.42	0.90–2.25
AGA	247	1826	1.00	baseline	1.00	baseline
SGA	51	240	1.37	0.94–2.00	1.26	0.85–1.86
Missing	35	254				
			LRS[2]= 3.18, p =0.204; Trend LRS[1]= 0.30, p =0.585		LRS[2]= 3.15, p =0.207; Trend LRS[1]= 0.01, p =0.926	

* adjusted for period and hospital of index birth, and sex of sibling
† also adjusted for same risk factor in index child
‡ LRS[n]: Log-likelihood ratio statistic with n degrees of freedom
§ LGA: Large for gestational age
§ AGA: Appropriate for gestational age
§ SGA: Small for gestational age

Table 7.15: Odds ratios for undescended testis diagnosed at birth for risk factors present in sibling born immediately before cases and controls: other risk factors

Risk factor in sibling	Cases (total=362) number	Controls (total=2517) number	Odds ratio*	95% confidence interval	Odds ratio*†	95% confidence interval
Social class at birth of sibling						
I	18	208	0.48	0.28–0.84	0.79	0.36–1.73
II	36	399	0.54	0.36–0.80	0.65	0.38–1.10
III	151	935	1.00	baseline	1.00	baseline
IV	49	305	1.01	0.70–1.45	0.90	0.59–1.38
V	22	125	1.18	0.71–1.95	0.99	0.56–1.75
Other	21	111	1.18	0.71–1.98	1.10	0.59–2.08
Missing	42	241				
Not collected	23	193				
			‡ LRS[5]= 19.63, p =0.002		LRS[5]= 3.14, p =0.678	
Pre-eclampsia at birth of sibling						
No mention	305	2234	1.00	baseline	1.00	baseline
Yes	57	283	1.25	0.94–1.67	1.14	0.85–1.55
			LRS[1]= 2.34, p =0.126		LRS[1]= 0.75, p =0.387	
Presentation of sibling						
Not breech	247	1751	1.00	baseline	1.00	baseline
Breech	19	60	2.25	1.32–3.83	2.27	1.33–3.87
Missing	4	22				
Not collected	92	684				
			LRS[1]= 7.76, p =0.005		LRS[1]= 7.87, p =0.005	
Caesarean section for sibling						
No	332	2325	1.00	baseline	1.00	baseline
Yes	30	192	1.10	0.73–1.64	1.02	0.62–1.68
			LRS[1]= 0.19, p =0.662		LRS[1]= 0.01, p =0.942	

* adjusted for period and hospital of index birth, and sex of sibling
† also adjusted for same risk factor in index child
‡ LRS[n]: Log-likelihood ratio statistic with n degrees of freedom

Table 7.16: Odds ratios for undescended testis diagnosed at birth for risk factors present in sibling born immediately after cases and controls: index matching variables and sex of sibling

Risk factor	Cases (total=302) number	Controls (total=1979) number	Odds ratio*	95% confidence interval
Year of birth of index case or control				
1970–74	54	343	1.09	0.77–1.55
1975–79	106	737	1.00	baseline
1980–86	142	899	1.10	0.84–1.44
			† LRS[2]= 0.50, p =0.781	
			Trend LRS[1]= 0.05, p =0.819;	
Hospital district				
Oxfordshire	177	1191	1.00	baseline
West Berkshire	125	788	1.06	0.83–1.36
			LRS[1]= 0.23, p =0.631	
Sex of sibling				
Boy	146	1037	1.00	baseline
Girl	156	942	1.18	0.92–1.50
			LRS[1]= 1.73, p =0.189	

* all variables adjusted for other variables in the table
† LRS[n]: Log-likelihood ratio statistic with n degrees of freedom

Immediately subsequent deliveries

Table 7.16 shows odds ratios for the matching variables and the sex of the sibling born immediately after the birth of the index case or control. There was a small excess of female siblings, but this was not statistically significant.

Risk of undescended testis was significantly increased if the subsequent sibling was low birth weight, as shown in table 7.17. This trend was no longer significant after adjusting for birth weight at the index delivery, although there was still a raised risk at lower birth weights. Risk was also increased if the sibling was premature, but this was not statistically significant. There was little change after adjustment for gestational age of the index case or control. There was a strong trend with the siblings' birth weight for gestational age and risk of undescended testis in the index cases and controls. Even after adjusting for birth weight for gestational age at the index delivery this association and trend remained significant.

Table 7.18 shows unmatched odds ratios for social class, pre-eclampsia, presentation at delivery and caesarean section during the sibling's delivery. There was no significant association between social class at the delivery of the sibling and risk of undescended testis. The

Table 7.17: Odds ratios for undescended testis diagnosed at birth for risk factors present in sibling born immediately after cases and controls: birth weight and gestational age

Risk factor in sibling	Cases (total=302) number	Controls (total=1979) number	Odds ratio*	95% confidence interval	Odds ratio*†	95% confidence interval
Birth weight (kg) of sibling						
≤2.4	17	66	1.89	1.07–3.35	1.46	0.80–2.65
2.5–2.9	59	258	1.65	1.16–2.34	1.44	1.00–2.06
3.0–3.4	105	763	1.00	baseline	1.00	baseline
3.5–3.9	88	645	1.00	0.74–1.35	1.09	0.80–1.49
4.0 or more	33	241	1.02	0.67–1.54	1.33	0.84–2.08
Missing	0	6				
			‡ LRS[4]= 12.41, p =0.015; Trend LRS[1]= 7.34, p =0.007		LRS[4]= 5.23, p =0.265; Trend LRS[1]= 0.41, p =0.520	
Gestational age (weeks) of sibling						
≤36	14	67	1.60	0.87–2.97	1.40	0.74–2.63
37–38	50	296	1.09	0.75–1.59	0.95	0.65–1.40
39–40	121	805	1.00	baseline	1.00	baseline
41–42	53	408	0.87	0.61–1.24	0.93	0.65–1.34
43 or more	12	53	0.89	0.37–2.15	0.91	0.37–2.19
Missing	52	350				
			LRS[4]= 3.53, p =0.473; Trend LRS[1]= 2.90, p =0.088		LRS[4]= 1.47, p =0.832; Trend LRS[1]= 0.56, p =0.454	
§ Birth weight for gestational age sibling						
LGA	23	225	0.64	0.39–1.03	0.59	0.35–0.97
AGA	194	1286	1.00	baseline	1.00	baseline
SGA	33	115	1.78	1.13–2.80	1.65	1.04–2.64
Missing	52	353				
			LRS[2]= 10.49, p =0.005; Trend LRS[1]= 10.38, p =0.001		LRS[2]= 9.86, p =0.007; Trend LRS[1]= 9.86, p =0.002	

* adjusted for period and hospital of index birth, and sex of sibling
† also adjusted for same risk factor in index child
‡ LRS[n]: Log-likelihood ratio statistic with n degrees of freedom
§ LGA: Large for gestational age
§ AGA: Appropriate for gestational age
§ SGA: Small for gestational age

trend across groups I–V was not significant before (p=0.226) or after (p=0.264) adjusting for social class at the index delivery. There were no significant associations between risk of undescended testis and pre-eclampsia or caesarean section. There was a raised risk with breech presentation of the subsequently born sibling but the numbers of such infants was small and the association was not statistically significant.

Table 7.18: Odds ratios for undescended testis diagnosed at birth for risk factors present in sibling born immediately after cases and controls: other risk factors

Risk factor in sibling	Cases (total=302) number	Controls (total=1979) number	Odds ratio*	95% confidence interval	Odds ratio*†	95% confidence interval
Social class at birth of sibling						
I	19	165	0.73	0.43–1.24	1.34	0.62–2.90
II	48	375	0.73	0.50–1.06	1.30	0.80–2.11
III	124	787	1.00	baseline	1.00	baseline
IV	36	221	0.98	0.64–1.49	1.10	0.66–1.83
V	17	108	1.01	0.55–1.84	0.95	0.48–1.89
Other	16	77	1.34	0.74–2.46	1.72	0.86–3.43
Missing	31	154				
Not collected	11	92				
			‡ LRS[5]= 5.49, p =0.360		LRS[5]= 3.17, p =0.673	
Pre-eclampsia at birth of sibling						
No	266	1786	1.00	baseline	1.00	baseline
Yes	36	193	1.28	0.87–1.87	0.96	0.64–1.46
			LRS[1]= 1.51, p =0.219		LRS[1]= 0.03, p =0.862	
Presentation of sibling						
Not breech	265	1762	1.00	baseline	1.00	baseline
Breech	7	37	1.41	0.62–3.23	1.35	0.59–3.12
Missing	2	17				
Not collected	28	163				
			LRS[1]= 0.62, p =0.432		LRS[1]= 0.48, p =0.489	
Caesarean section for sibling						
No	284	1814	1.00	baseline	1.00	baseline
Yes	18	165	0.70	0.43–1.17	0.62	0.34–1.16
			LRS[1]= 2.02, p =0.155		LRS[1]= 2.34, p =0.126	

* adjusted for period and hospital of index birth, and sex of sibling
† also adjusted for same risk factor in index child
‡ LRS[n]: Log-likelihood ratio statistic with n degrees of freedom

7.8.3 Discussion of risk factors in siblings

The results presented for immediately previous and subsequently born siblings of cases and controls need to be interpreted with care. Cases and controls who had no eligible siblings did not enter into the analysis, and the consequences of this need to be considered because women who have two or more children may differ from women who only have one child. For example, it is plausible that a woman who experiences a difficult pregnancy, perhaps with lasting complications, may not wish or may not be able to have more children. Alternatively, it has been shown that women with good reproductive histories tend to stop having pregnancies sooner than those with poor histories [248]. This self-selection, however, applies equally to mothers of cases and controls and would, therefore, be unlikely to greatly bias the results.

The comparison between immediately previous and subsequent deliveries also needs care because, on average, the mothers of the cases and controls will be younger and of lower parity during the previous deliveries. In addition, cases and controls that have a previously born sibling may not necessarily have a subsequently born sibling. That is, the prior and subsequent siblings analysis do not refer to the same set of cases and controls and, therefore, any comparison between them must be made with this in mind.

The sibling analysis is also subject to the same problems of case diagnosis and control selection, and determination of exposure status, as in the original matched case-control study. These issues have already been discussed in relation to that analysis in sections 5.4.3, 7.5.1 and 7.5.3. Despite all these caveats the results give some useful insights into the aetiology of undescended testis diagnosed at birth.

Birth weight and gestation

A low birth weight sibling was associated with an increased risk of undescended testis at the index delivery, but not when account was taken of the birth weight of the index case or control. A similar pattern was seen for gestational age.

There is an established tendency for mothers to repeat deliveries of low birth weight or short gestation [249]. Women may repeat low birth weight deliveries because of genetic and environmental factors [250] (e.g. uterine and placental size and shape, poverty, smoking). It is difficult, however, to determine if the factors underlying a tendency to repeat low birth weight also directly influence risk of undescended testis, or influence it indirectly through low birth weight which confers an increased risk of undescended testis on the child.

The results for being small for gestational age were different. There was a strong trend

towards greater risk if the sibling was small for gestational age, but only in relation to the next born sibling; this was present even after adjusting for birth weight for gestational age of the case or control infant. The results here suggest that deliveries after the birth of the child with cryptorchidism were somehow different from deliveries before the affected child was born. A permanent change to the mother may have occurred at or before the pregnancy resulting in the cryptorchid boys, leading to the next sibling being small for gestational age. Clearly the next born siblings were more likely to be higher order deliveries and to have occurred at older maternal ages than the previous siblings' deliveries but these issues apply equally to cases and controls, so the results are unlikely to be biased by these differences. Cases or controls, however, who have a subsequent sibling may not have a prior sibling and, therefore, the same cases and controls do not necessarily appear in both analyses. Caution, therefore, is needed when interpreting the difference between prior and subsequent deliveries. If, however, results like these are confirmed in other studies then changes to the mother, during or after the pregnancy and delivery of an affected boy, should be investigated.

Social class

The association with social class at the delivery of the previous sibling was similar to that seen in the original matched case-control analysis. This was not surprising because siblings of cases and controls were likely to be born into a similar social class group as their index siblings. The association was weaker for subsequent deliveries but social class, as used here, was based upon occupation and this may change between deliveries.

Breech presentation

A sibling presenting in the breech position was associated with increased risk of undescended testis, even allowing for presentation at the index delivery. This association was strongest for the prior siblings. Breech presentation is more common in first ever pregnancies [234] and a large proportion of previous deliveries would be first ever pregnancies, but this should apply equally to case and control sibling deliveries. Breech presentation is more common if previous deliveries were also breech [234] and it is possible that mothers of cases have a pre-disposition towards breech presentation, perhaps due to associated underlying uterine abnormalities [234]. Complications during pregnancy, however, may alter subsequent plans for child-bearing such that women who experience complications, like breech delivery or caesarean section, may decide not to have more children. This possible self-selection makes comparison between previous and subsequent siblings difficult.

Caesarean section

Caesarean section was not identified as a risk factor in the original matched case-control study but because it may be associated with breech presentation it was examined here. Caesarean section might be expected to show a similar pattern of risk as breech presentation but there was no strong evidence that caesarean section was more common among siblings of cases than siblings of controls.

7.9 Conclusions to study of undescended testis diagnosed at birth

Little is known about risk factors for undescended testis at birth, other than the major associations with prematurity and low birth weight [147]. In this study it was confirmed that the prevalence of undescended testis was strongly influenced by the degree of foetal development reached at delivery, as measured by birth weight and gestational age, probably because the testes do not usually begin their final descent until seven or eight months of gestation [143]. Possible artefacts in the data were considered, but these were unlikely to account for all the results.

There was no strong evidence for an increased risk of undescended testis at birth in siblings of cases. This is in contrast to the reported familial clustering of cryptorchidism [159–162, 164], although these reports probably only apply to cases that remain undescended some years after birth.

Some of the risk factors examined here, like birth weight, gestational age and social class, would be expected to track or repeat across deliveries. These variables, when measured at the siblings' delivery, would be expected to be markers for the same variables at the index delivery, and this was seen for these variables. Adjusting for the variable at the index delivery would reduce or eliminate the association between the same variable at the siblings' delivery and the risk of undescended testis in the index delivery if simple tracking were the explanation. Birth weight, gestational age and social class fitted in with this pattern.

The more interesting results were for those variables that remained important after adjusting for the exposure during the index event. These variables were probably not simple markers for the same type of exposure at the index delivery. There also was an interesting difference between prior and later siblings in relation to birth weight for gestational age. Although the interpretation of these results are difficult they suggest that changes lasting beyond the immdeiate pregnancy may occur in the mother that predispose to, or less plausibly are a consequence of, having a son born with undescended testes. These results, however, need to be confirmed in other studies.

These findings will be discussed in more detail in relation to the results from the orchidopexy study (section 8.8.2).

Chapter 8

Undescended Testis Diagnosed at Orchidopexy

8.1 Introduction

Cryptorchidism is a difficult condition to diagnose in the new-born boy, such that routinely recorded diagnoses at birth, often based on examinations performed by junior staff, are likely to be unreliable. The testes may also descend spontaneously a few months after delivery making the diagnosis at birth of uncertain long-term meaning. If, however, the testes have not descended by about 3–12 months of age they are unlikely ever to descend naturally [145].

Surgery is usually undertaken to correct the undescended testis that does not respond to hormonal treatment, so that most boys with permanently cryptorchid testes will be captured by routine data systems at the time of operation. The examination and diagnosis that leads to a surgical decision to operate is likely to have been made more carefully than a decision simply to record a diagnostic label in case-notes. Orchidopexy, therefore, may provide the best routinely available diagnosis of cryptorchidism, and was used to define cryptorchidism in this case-control study.

8.2 Boys with a record of an orchidopexy

The Oxford Record Linkage Study (ORLS) identified 1570 boys, from general hospital files, who had a record of an orchidopexy during 1970-87 and had been born during 1970–86. Boys with major congenital anomalies or who were part of twin or higher order deliveries were excluded from the analyses. Each case was individually matched with up to eight controls

on sex, year and hospital of delivery. There were, in total, 1449 cases and 10811 controls after exclusions. Over 99% of cases had four or more matched controls. A description of the case series given in detail in appendix I.

8.3 Identifying risk factors

The following univariate analyses presents prevalence ratios for cryptorchidism as defined by orchidopexy in relation to perinatal exposures. A potential bias caused by migration may affect these results. Migration bias was discussed in detail in chapter 3, where a theoretical development led to a way to compensate for the bias. In the following sections migration bias is discussed when relevant.

8.3.1 Birth weight and gestation

Table 8.1 shows the prevalence ratios for cryptorchidism, in relation to birth weight, gestation, birth weight for gestational age, size of baby's head and retention in a special care baby unit.

Prevalence of cryptorchidism increased significantly as birth weight decreased, but for birth weights larger than the reference level of 3.0–3.4 kg there was little change in the prevalence ratio. A similar pattern was seen for gestation and cryptorchidism; there was little change in prevalence among boys who had reached 39 or more weeks of gestation, but at less than 39 weeks prevalence increased significantly with shorter gestation. The raised prevalence of cryptorchidism with low birth weight and short gestation each generated a statistically significant test for trend. It is clear, however, that the trends do not extend to the larger birth weights or longer periods of gestation but are a reflection of the high prevalence ratios at low birth weight and short gestation.

Section 5.3.1 described the reference distribution used to derive birth weight for gestational age. Prevalence of cryptorchidism was raised significantly amongst boys who were small for their gestational age. There was also a trend with birth weight for gestational age such that prevalence was lowest among boys who were large for their gestational age. There was no significant association or trend between size of baby's head and cryptorchidism.

Prevalence of cryptorchidism was raised among boys who had been retained in a special care baby unit, and adjusting for birth weight reduced the strength of this association (adjusted prevalence ratio: 1.34; 95% Confidence Interval (95% CI): 0.98–1.83).

Table 8.1: Prevalence ratios for boys with undescended testis diagnosed at orchidopexy: birth weight, gestational age, size of baby's head and retention in a special care baby unit

Risk factor	Cases (total=1449) number	percent	Controls (total=10811) number	percent	Prevalence ratio	95% confidence interval	p-value
Birth weight (kg)							
≤2.4	92	6.4	357	3.3	2.06	1.60 – 2.64	<0.001
2.5–2.9	208	14.4	1340	12.4	1.25	1.05 – 1.49	0.012
3.0–3.4	497	34.4	3988	37.0	1.00	baseline	
3.5–3.9	470	32.6	3647	33.8	1.03	0.90 – 1.18	0.634
4.0 or more	176	12.2	1450	13.4	0.98	0.81 – 1.17	0.801
Not known	6		29				
* LRS[4]= 34.87, p <0.001; Trend LRS[1]= 17.71, p <0.001							
Gestation (completed weeks from date of last menstrual period)							
≤36	84	6.4	410	4.2	1.58	1.23 – 2.04	<0.001
37–38	248	18.9	1632	16.9	1.20	1.03 – 1.41	0.022
39–40	611	46.5	4801	49.8	1.00	baseline	
41–42	328	25.0	2475	25.7	1.03	0.90 – 1.20	0.641
43 or more	43	3.3	331	3.4	0.98	0.71 – 1.37	0.926
Not known	135		1162				
LRS[4]= 15.44, p= 0.004; Trend LRS[1]= 8.75, p= 0.003							
† Birth weight for gestational age							
LGA	120	9.1	1009	10.5	0.88	0.72 – 1.07	0.203
AGA	1038	79.1	7752	80.4	1.00	baseline	
SGA	155	11.8	884	9.2	1.34	1.11 – 1.61	0.002
Not known	136		1166				
LRS[2]= 11.84, p= 0.003; Trend LRS[1]= 10.67, p= 0.001							
Size of head (cm)							
20.0–34.0	91	16.2	644	14.5	1.11	0.85 – 1.46	0.444
34.1–35.0	124	22.1	1109	24.9	0.90	0.71 – 1.16	0.419
35.1–36.0	167	29.7	1275	28.7	1.03	0.82 – 1.29	0.828
36.1 or more	180	32.0	1420	31.9	1.00	baseline	
Not known	101		545				
Not collected	786		5818				
LRS[3]= 2.12, p= 0.549; Trend LRS[1]= 0.04, p= 0.840							
Retention in special care baby unit							
No	1358	93.7	10441	96.6	1.00	baseline	
Yes	91	6.3	370	3.4	1.89	1.49 – 2.40	<0.001
LRS[1]= 24.25, p <0.001							

* LRS[n]: Log-likelihood Ratio Statistic with n degrees of freedom
† LGA: Large for Gestational Age (above 90th percentile for birth weight)
† AGA: Appropriate for Gestational Age (between 10th and 90th percentile for birth weight)
† SGA: Small for Gestational Age (below 10th percentile for birth weight)
Cases individually matched with up to 8 controls on year of birth, sex and hospital of delivery

Table 8.2: Prevalence ratios for gestation and birth weight for gestational age by birth weight for boys with undescended testis diagnosed at orchidopexy

	Prevalence ratios (95% confidence intervals)					
	Birth weight (kg)				Adjusted for birth weight	
	≤2.4	2.5–2.9	3.0–3.4	3.5 or more		
Gestation (weeks)						
≤36	1.86 (1.25–2.76)	1.75 (1.11–2.76)	1.25 (0.70–2.24)	0.84 (0.36–1.98)	1.20 (0.90–1.60)	Trend p=0.235
37–38	2.32 (1.40–3.83)	1.49 (1.12–1.99)	1.09 (0.84–1.40)	0.98 (0.71–1.33)	1.15 (0.97–1.35)	
39–40	2.01 (1.09–3.69)	1.13 (0.85–1.51)	1.00 baseline	0.95 (0.79–1.15)	1.00 baseline	
41 or more	1.48 (0.50–4.36)	0.78 (0.48–1.25)	0.95 (0.75–1.21)	1.10 (0.90–1.33)	1.04 (0.90–1.19)	
Adjusted for gestation	1.79 (1.32–2.44)	1.20 (0.99–1.44)	1.00 baseline	1.01 (0.88–1.15)		
			Trend: p=0.004			
*** Birth weight for gestational age**						
LGA	†	†	1.00 (0.39–2.57)	0.93 (0.74–1.16)	0.91 (0.74–1.13	Trend p=0.52
AGA	1.73 (1.10–2.71)	1.33 (1.05–1.69)	1.00 baseline	1.02 (0.89–1.17)	1.00 baseline	
SGA	2.22 (1.59–3.10)	1.17 (0.91–1.49)	1.20 (0.66–2.17)	†	1.00 (0.78–1.28)	
Adjusted for birth weight for gestational age	2.02 (1.47–2.77)	1.24 (1.00–1.54)	1.00 baseline	1.01 (0.88–1.16)		
			Trend: p=0.004			

* LGA: Large for Gestational Age (above 90th percentile for birth weight)
* AGA: Appropriate for Gestational Age (between 10th and 90th percentile for birth weight)
* SGA: Small for Gestational Age (below 10th percentile for birth weight)
†: too few or no cases in this category for appropriate analysis
Cases individually matched with up to 8 controls on year of birth, sex and hospital of delivery

Further analysis of birth weight and gestational age

Low birth weight was more strongly associated with prevalence of cryptorchidism than gestational age or birth weight for gestational age, although all three of these measures of intra-uterine development are correlated amongst themselves. It is worthwhile considering, therefore, if short gestation or being small for gestational age were associated with cryptorchidism independently of low birth weight. Table 8.2 gives further details about

the relation of cryptorchidism to birth weight and gestation, and birth weight and being small for a given gestational age. To avoid over-stratification of the data the highest two birth weight groups were joined. Three cells were excluded from the analysis because they contained too few or no cases for an appropriate analysis. The category with lowest birth weight and highest gestational age only contained four cases but all other cells contained five or more cases.

Low birth weight remained significantly associated with cryptorchidism even after adjustment for gestation (heterogeneity: p=0.002; trend: p=0.004). The increased prevalence of cryptorchidism at low birth weight was apparent for all categories of gestational age. Gestation was no longer statistically significantly associated with cryptorchidism (heterogeneity: p=0.329) after adjustment for birth weight. There was a small overall increase in prevalence with shorter gestation but this trend was not significant (trend: p=0.249) and was not apparent among low birth weight ($\leq$2.4 kg) or large (3.5 kg or more) babies.

After adjustment for birth weight, birth weight for gestational age was no longer significantly associated with cryptorchidism (heterogeneity: p=0.706; trend: p=0.526). Low birth weight was still associated with an increased prevalence of cryptorchidism (heterogeneity: p<0.001; trend: p=0.004) even after adjustment for birth weight for gestational age. Birth weight for gestational age had little or no independent association with cryptorchidism after birth weight had been taken into account (heterogeneity: p=0.706).

Table 8.3: Prevalence ratios for boys with undescended testis diagnosed at orchidopexy by maternal age

Risk factor	Cases (total=1449) number	percent	Controls (total=10811) number	percent	Prevalence ratio	95% confidence interval	p-value
Maternal age (years)							
≤19	97	6.7	900	8.3	0.77	0.61 – 0.96	0.023
20–24	423	29.3	3147	29.2	0.96	0.84 – 1.10	0.591
25–29	564	39.1	4043	37.5	1.00	baseline	
30–34	265	18.4	2035	18.9	0.93	0.80 – 1.09	0.382
35 or over	94	6.5	660	6.1	1.01	0.80 – 1.28	0.942
Not known	6		25				
Not collected	0		1				
* LRS[4]= 5.83, p= 0.212; Trend LRS[1]= 1.35, p= 0.246							

* LRS[n]: Log-likelihood Ratio Statistic with n degrees of freedom
Cases individually matched with up to 8 controls on year of birth, sex and hospital of delivery

8.3.2 Maternal age

Table 8.3 shows that boys born to teenage mothers had a significantly lower prevalence of cryptorchidism than boys born to older mothers and prevalence was similar across each of these older age groups. Adjusting for birth weight made little change to this association (adjusted prevalence ratio for maternal age ≤19 years: 0.74; 95% CI: 0.59–0.93).

The results in table 8.3 may be biased because any child who migrates and later has an orchidopexy in a hospital outside the ORLS region will not be ascertained into the case group. It is known from work presented in chapter 3 that children of young mothers (or rather, their families) are more likely to migrate than those of older mothers, and subsequently there may be a proportionately greater deficit of boys with young mothers among the case group; the control group will be unaffected because controls were selected at birth, before any opportunity for migration. In the absence of any association between maternal age and cryptorchidism the bias due to migration would act to produce prevalence ratios similar to those seen in table 8.3. Based on earlier calculations, using the methods developed in chapter 3, migration bias would act to reduce the true prevalence ratio for the sons of the teenage mothers by about 3–6%. After allowing for this bias (i.e. by adjusting the observed prevalence ratio upwards by 3–6%) teenage motherhood was less strongly but still negatively associated with cryptorchidism in male offspring.

Table 8.4: Prevalence ratios for boys with undescended testis diagnosed at orchidopexy by parity

Risk factor	Cases (total=1449) number	percent	Controls (total=10811) number	percent	Prevalence ratio	95% confidence interval	p-value
Parity (before this pregnancy)							
0	636	44.0	4489	41.6	1.00	baseline	
1	527	36.4	3924	36.4	0.95	0.84 – 1.08	0.426
2	188	13.0	1579	14.6	0.84	0.70 – 1.00	0.047
3 or more	96	6.6	796	7.4	0.85	0.68 – 1.07	0.171
Not known	1		15				
Not collected	1		8				
* LRS[3]= 5.10, p= 0.164; Trend LRS[1]= 4.54, p= 0.033							

* LRS[n]: Log-likelihood Ratio Statistic with n degrees of freedom
Cases individually matched with up to 8 controls on year of birth, sex and hospital of delivery

8.3.3 Parity

Table 8.4 shows that boys born to nulliparous mothers had a raised prevalence of cryptorchidism and this decreased as parity increased from one to two, but not thereafter (trend: p=0.033). After adjustment for birth weight this association weakened (trend: p=0.063).

Differential migration may have biased the strength of the association between maternal parity and cryptorchidism in a similar way to that for maternal age and described in more detail in chapter 3. Migration rates are higher than average among mothers of low parity; and subsequently there may be a proportionately greater deficit of first born children among the case group. The effect of correcting for migration bias would be to *increase* the difference between nulliparity and high parity by around 8%. The correction acts in a direction to strengthen the observation that nulliparity was associated with a higher prevalence of cryptorchidism in male offspring.

8.3.4 Social class

Table 8.5 shows a trend with social class of the head of household and cryptorchidism across groups I–V (p=0.001), with the lowest prevalence among those in group I. Even lower than this prevalence, however, was the prevalence in the group classified to 'other occupations'. This group was made up of students, armed forces personnel, and after 1972, housewives. Adjusting for birth weight made little difference to the prevalence ratios.

High social class families have been shown to be more mobile than families from others

Table 8.5: Prevalence ratios for boys with undescended testis diagnosed at orchidopexy by social class

Risk factor	Cases (total=1449) number	percent	Controls (total=10811) number	percent	Prevalence ratio	95% confidence interval	p-value
Social class							
I	111	8.7	992	10.9	0.70	0.57 – 0.87	0.002
II	249	19.6	1913	20.9	0.84	0.72 – 0.99	0.037
III	625	49.2	4006	43.9	1.00	baseline	
IV	174	13.7	1193	13.1	0.94	0.78 – 1.12	0.473
V	82	6.5	475	5.2	1.11	0.87 – 1.43	0.404
Other	29	2.3	555	6.1	0.33	0.23 – 0.49	<0.001
Not known	128		1307				
Not collected	51		370				
* LRS[5]= 51.87, p <0.001							

* LRS[n]: Log-likelihood Ratio Statistic with n degrees of freedom
Cases individually matched with up to 8 controls on year of birth, sex and hospital of delivery

social class groups, as described in chapter 3, such that there may be a deficit of orchidopexy cases from the high social class group relative to the other groups. Migration bias would be expected to produce a pattern similar to that seen in table 8.5 in the absence of any real association between social class and cryptorchidism.

Calculations show that correcting for migration bias would reduce the trend with social class such that prevalence in groups I and II would be lower than in group III, but to a lesser degree than shown in table 8.5 (about 0.90, 0.94 respectively), and the raised prevalence in group V would disappear. The prevalence ratio in the group 'other occupations' would be less extreme but still low, around 0.50 instead of 0.33. After correcting for the bias the relation between social class and cryptorchidism was not as strong as it first appeared to be, but it probably cannot be attributed completely to migration bias.

The association between social class and cryptorchidism may be affected by another bias because social class is related to access and use of medical services. It is conceivable that children operated on for undescended testis at a relatively young age may belong to higher social class groups than those operated on at older ages or those with cryptorchidism who were never operated upon. In addition, to qualify for inclusion into this study children born towards the end of the study period must have had an orchidopexy at an early age. Selection of cases, therefore, may be biased towards boys from the higher social class groups, especially towards the end of the study period.

Cross-tabulation of age at orchidopexy (0–4; 5–9; 10 and over) by social class groups I–V

Table 8.6: Prevalence ratios for boys with undescended testis diagnosed at orchidopexy by feeding at discharge

Risk factor	Cases (total=1449) number	percent	Controls (total=10811) number	percent	Prevalence ratio	95% confidence interval	p-value
Feeding at discharge							
Breast	505	65.4	3992	69.0	1.00	baseline	
Artificial	255	33.0	1683	29.1	1.21	1.03 – 1.42	0.022
Complement	12	1.6	114	2.0	0.82	0.44 – 1.50	0.515
Not known	24		101				
Not collected	653		4921				
* LRS[2]= 5.96, p= 0.051							

* LRS[n]: Log-likelihood Ratio Statistic with n degrees of freedom
Cases individually matched to 8 controls on year of birth, sex and hospital of delivery

(not shown here) showed that there was a relative excess of the youngest cases (8.6%) compared with the oldest cases (4.1%) in social class I. As a consequence of this the prevalence ratio, for high social class, compared to the baseline or low social class groups, would be expected to be biased upwards especially among the children born near the end of the study period. Since social class I was already associated with a low prevalence of cryptorchidism the true unbiased association with cryptorchidism would be expected to be even lower. This bias, therefore, cannot account for the low prevalence in the high social class group.

8.3.5 Feeding at discharge

There was a significantly increased prevalence of cryptorchidism among boys who were artificially fed at discharge compared with those who were breast-fed as shown in table 8.6. Breast-feeding rates are related to social class [233], which is itself strongly associated to cryptorchidism, and it may be that one of these risk factors was associated with cryptorchidism only because of its association with the other risk factor. Adjusting for social class reduced the strength of the association with artificial feeding (adjusted prevalence ratio: 1.14; 95% CI 0.95–1.38); social class remained significantly associated with cryptorchidism ($p<0.001$) after adjusting for type of feeding.

8.3.6 Presentation

Breech presentation once labour had been established (table 8.7) was associated with an increased prevalence of cryptorchidism whereas vertex and the other remaining positions

Table 8.7: Prevalence ratios for boys with undescended testis diagnosed at orchidopexy by presentation at birth

Risk factor	Cases (total=1449) number	percent	Controls (total=10811) number	percent	Prevalence ratio	95% confidence interval	p-value
Presentation							
Breech	40	5.1	170	2.9	1.79	1.25 – 2.57	0.001
Vertex (anterior)	678	86.5	5157	88.6	1.00	baseline	
Vertex (posterior)	39	5.0	295	5.1	1.01	0.71 – 1.43	0.959
Others	27	3.4	201	3.5	1.06	0.70 – 1.60	0.787
Not known	14		77				
Not collected	651		4911				
* LRS[3]= 9.22, p= 0.027							

* LRS[n]: Log-likelihood Ratio Statistic with n degrees of freedom
Cases individually matched to 8 controls on year of birth, sex and hospital of delivery

of presentation were not. Breech presentation is known to be associated with impaired foetal growth [234] and its association with cryptorchidism may be as a consequence of low birth weight. After adjusting for birth weight, however, the prevalence of cryptorchidism, although somewhat reduced (adjusted prevalence ratio: 1.65; 95% CI: 1.15–2.39), was still significantly raised for boys presenting in the breech position. Prevalence was also raised for breech delivery relative to vaginal delivery (not shown in the table, prevalence ratio: 1.38; 95% CI: 0.97–1.98) although the association was not as strong as that for breech presentation.

8.3.7 Pre-eclampsia

As shown in table 8.8 any mention of pre-eclampsia or eclampsia during the mother's pregnancy was associated with a significantly raised prevalence of cryptorchidism, even after adjusting for birth weight (adjusted prevalence ratio: 1.20; 95% CI: 1.02–1.40).

Table 8.8 also shows that prevalence of cryptorchidism increased with albuminuria (proteinuria), but not significantly so. There was a raised prevalence of cryptorchidism with high maximum systolic blood pressure and high maximum diastolic blood pressure. See section 5.3.4 for details and limitations about the maximum blood pressure measurements. When pre-eclampsia was adjusted for maximum blood pressure the original association with cryptorchidism was weakened (prevalence ratio adjusted for maximum systolic blood pressure: 1.13 (0.94–1.35); prevalence ratio adjusted for maximum diastolic blood pressure: 1.14 (0.93–1.40)). When maximum systolic or diastolic blood pressure was adjusted for

Table 8.8: Prevalence ratios for boys with undescended testis diagnosed at orchidopexy: maternal pre-eclampsia and eclampsia during pregnancy and related factors

Risk factor	Cases (total=1449) number	percent	Controls (total=10811) number	percent	Prevalence ratio	95% confidence interval	p-value
Pre-eclampsia and eclampsia							
No mention	1225	84.5	9419	87.1	1.00	baseline	
Yes	224	15.5	1392	12.9	1.24	1.06 – 1.45	0.007
* LRS[1]= 7.07, p= 0.008							
Albuminuria							
No trace	1063	85.2	8077	86.4	1.00	baseline	
Trace only	116	9.3	869	9.3	1.00	0.76 – 1.33	0.975
More than trace once only	58	4.6	332	3.6	1.29	0.96 – 1.72	0.087
More than trace more than once	11	0.9	71	0.8	1.14	0.60 – 2.19	0.692
Not known	150		1092				
Not collected	51		370				
LRS[3]= 2.90, p= 0.407; Trend LRS[1]= 2.11, p= 0.146							
Maximum systolic blood pressure (mmHg)							
≤119	169	14.1	1373	15.4	0.99	0.82 – 1.18	0.884
120–139	646	54.0	5164	57.9	1.00	baseline	
140–159	317	26.5	2006	22.5	1.26	1.09 – 1.46	0.002
160 or more	65	5.4	376	4.2	1.32	0.99 – 1.75	0.057
Not known	201		1522				
Not collected	51		370				
LRS[3]= 12.39, p= 0.006; Trend LRS[1]= 9.60, p= 0.002							
Maximum diastolic blood pressure (mmHg)							
≤69	59	4.9	592	6.6	0.77	0.58 – 1.03	0.075
70–79	363	30.3	2771	31.1	1.00	0.86 – 1.16	0.997
80–89	497	41.5	3790	42.5	1.00	baseline	
90–99	179	15.0	1202	13.5	1.13	0.94 – 1.36	0.190
100 or more	99	8.3	562	6.3	1.33	1.05 – 1.69	0.018
Not known	201		1522				
Not collected	51		372				
LRS[4]= 11.45, p= 0.022; Trend LRS[1]= 8.87, p= 0.003							

* LRS[n]: Log-likelihood Ratio Statistic with n degrees of freedom
Cases individually matched with up to 8 controls on year of birth, sex and hospital of delivery

pre-eclampsia they were no longer significantly associated with cryptorchidism (systolic: p=0.203; diastolic: p=0.213). Maximum blood pressure and pre-eclampsia probably represent the same underlying risk factor, partly because a raised blood pressure is one of the defining characteristics of pre-eclampsia. In future multivariate analyses only one of these risk factors, pre-eclampsia, will be used.

Table 8.9: Prevalence ratios for boys with undescended testis diagnosed at orchidopexy: selected complications of pregnancy

Risk factor	Cases (total=1449) number	percent	Controls (total=10811) number	percent	Prevalence ratio	95% confidence interval	p-value
Vomiting during pregnancy							
No mention	1385	95.6	10323	95.5	1.00	baseline	
Yes	64	4.4	488	4.5	0.94	0.70 – 1.28	0.714
* LRS[1]= 0.14, p= 0.713							
Haemorrhage, abruptio placentae, placenta praevia							
No mention	1331	91.9	10033	92.8	1.00	baseline	
Yes	118	8.1	778	7.2	1.13	0.92 – 1.39	0.237
LRS[1]= 1.36, p= 0.243							
Diabetes							
No mention	1445	99.7	10801	99.9	1.00	baseline	
Yes	4	0.3	10	0.1	2.96	0.93 – 9.43	0.067
LRS[1]= 2.80, p= 0.094							

* LRS[n]: Log-likelihood Ratio Statistic with n degrees of freedom
Cases individually matched with up to 8 controls on year of birth, sex and hospital of delivery

8.3.8 Other complications of pregnancy

Table 8.9 shows that vomiting during pregnancy was not associated with a raised prevalence of cryptorchidism. This complication of pregnancy has previously been postulated as a marker for high maternal levels of oestrogen during pregnancy [190, 217] and as a possible risk factor for testicular cancer [240], hence the interest in it here. Also not significantly associated with cryptorchidism was any mention of haemorrhage, abruptio placentae or placenta praevia. The prevalence of cryptorchidism was high among boys whose mothers had diabetes mentioned during the pregnancy, but with the small number of mothers with diabetes this did not reach statistical significance.

8.3.9 Other risk factors

Table 8.10 presents results for selected other perinatal risk factors. Boys whose mothers had an episiotomy during delivery had a significantly increased prevalence of cryptorchidism. The prevalence of cryptorchidism was raised among boys delivered by caesarean section, but this was not statistically significant. Breech presentation is an indication for caesarean section and after stratifying by presentation (breech or not breech) the positive association between caesarean section and cryptorchidism vanished (adjusted prevalence ratio:

Table 8.10: Prevalence ratios for boys with undescended testis diagnosed at orchidopexy: other risk factors

Risk factor	Cases (total=1449) number	percent	Controls (total=10811) number	percent	Prevalence ratio	95% confidence interval	p-value
Episiotomy							
No	697	48.1	5540	51.3	1.00	baseline	
Yes	751	51.9	5259	48.7	1.14	1.02 – 1.28	0.025
Not collected	1		12				
* LRS[1]= 5.06, p= 0.024							
Caesarean section							
No mention	1329	91.7	10062	93.1	1.00	baseline	
Yes	120	8.3	749	6.9	1.21	0.98 – 1.48	0.072
LRS[1]= 3.11, p= 0.078							
Body Mass Index (kg/m^2)							
≤19.9	61	9.9	379	8.6	1.14	0.85 – 1.54	0.368
20.0–24.9	351	57.0	2466	56.1	1.00	baseline	
25.0–29.9	168	27.3	1251	28.5	0.96	0.79 – 1.17	0.707
30.0–34.5	28	4.5	242	5.5	0.85	0.56 – 1.28	0.439
35.0 or more	8	1.3	55	1.3	0.98	0.46 – 2.10	0.958
Not known	103		839				
Not collected	730		5579				
LRS[4]= 1.80, p= 0.773; Trend LRS[1]= 1.33, p= 0.249							
Diagnosis of obesity							
No mention	1431	98.8	10676	98.8	1.00	baseline	
Yes	18	1.2	135	1.2	0.99	0.60 – 1.63	0.973
LRS[1]= 0.00, p= 0.973							
Smoking during pregnancy							
No	455	75.0	3414	75.7	1.00	baseline	
Yes	152	25.0	1093	24.3	1.04	0.86 – 1.27	0.667
Not known	140		1020				
Not collected	702		5284				
LRS[1]= 0.18, p= 0.667							

* LRS[n]: Log-likelihood Ratio Statistic with n degrees of freedom
Cases individually matched to 8 controls on year of birth, sex and hospital of delivery

0.89; 95% CI: 0.66–1.19). There was no significant association between cryptorchidism and mother's body mass index nor was there one with a clinical diagnosis of obesity during pregnancy. Obesity, like vomiting during pregnancy, has been postulated as a marker for raised maternal oestrogen levels during pregnancy [190, 217]. The prevalence of cryptorchidism among boys whose mothers smoked during pregnancy was similar to that among boys whose mothers did not.

Other risk factors were also examined but were not shown because none of the results

Table 8.11: Prevalence ratios for boys with undescended testis diagnosed at orchidopexy by month of birth

Risk factor	Cases (total=1449) number	percent	Controls (total=10811) number	percent	Relative risk	95% confidence interval	p-value
Month of birth							
January	121	8.4	873	8.1	1.00	baseline	
February	117	8.1	832	7.7	1.01	0.77 – 1.33	0.937
March	147	10.1	966	8.9	1.10	0.85 – 1.42	0.473
April	137	9.5	937	8.7	1.05	0.81 – 1.37	0.706
May	130	9.0	901	8.3	1.03	0.79 – 1.35	0.807
June	114	7.9	934	8.6	0.88	0.67 – 1.16	0.357
July	131	9.0	992	9.2	0.95	0.73 – 1.24	0.712
August	124	8.6	919	8.5	0.98	0.75 – 1.28	0.858
September	104	7.2	829	7.7	0.90	0.68 – 1.19	0.457
October	113	7.8	919	8.5	0.89	0.67 – 1.16	0.385
November	101	7.0	889	8.2	0.81	0.61 – 1.07	0.139
December	110	7.6	820	7.6	0.96	0.73 – 1.27	0.788

* Heterogeneity LRS[11]= 8.91, p= 0.630
Sinusoidal seasonality LRS[2]= 5.36, p= 0.068

LRS[n]: Log-likelihood Ratio Statistic with n degrees of freedom
Cases individually matched with up to 8 controls on year of birth, sex and hospital of delivery

were statistically significant or notable. For example, there was no association between cryptorchidism and maternal height, weight, systolic or diastolic blood pressure at the first ante-natal visit. Nor were there associations with duration of labour, mother's blood group, rhesus incompatibility, mother requiring blood transfusion, failure of contraceptive, Apgar score or resuscitation of baby with oxygen.

As shown in table 8.11 there was some indication of a sinusoidal seasonal pattern (p=0.068) in prevalence of cryptorchidism by month of birth, with a peak around March. There was a strong association with either a diagnosis at birth of inguinal hernia (prevalence ratio: 6.97; 95% CI: 1.73–28.12) or an operation for inguinal hernia (prevalence ratio: 9.66; 95% CI: 8.01–11.66). These last two results must be treated with caution because a diagnosis or operation for one condition may lead to other conditions being uncovered. Inguinal hernia and undescended testis may be the result of the same underlying pathological process and have risk factors in common, so it would be inappropriate to treat inguinal hernia as a risk factor for cryptorchidism.

8.4 Multivariate analysis

8.4.1 Selection of risk factors

The previous sections identified low birth weight, young maternal age, low social class, pre-eclampsia, breech presentation, not breast-feeding, episiotomy and low parity as risk factors for cryptorchidism, as defined by orchidopexy. Caesarean section, short gestation and small for gestational age appeared to be secondary to the other stronger factors like breech presentation and low birth weight. Diabetes during pregnancy was strongly related to cryptorchidism in male offspring but the small number of diabetic mothers made it difficult to explore this finding further. Maximum blood pressure and pre-eclampsia were both related to risk of cryptorchidism in offspring, but as they were probably both representing the same underlying risk factor only pre-eclampsia was carried into the multivariate analysis. There was no compelling evidence that the other remaining perinatal risk factors were associated with cryptorchidism. To try and gain further insights into the aetiology of cryptorchidism the previously identified risk factors were examined in more detail. Parity was also included because there were *a-priori* reasons to suspect that a woman's first pregnancy may be hormonally [236] and immunologically [237] different to subsequent ones.

8.4.2 Multivariate model

Table 8.12 presents results of a multivariate analysis with stratification by parity. The methods used were similar to those described in section 7.4.2. Any 'missing data' or 'not collected' data items were included as a separate exposure level, except for birth weight, maternal age and episiotomy where there were too few missing values to make a useful category: any subjects missing data for these variables were dropped from the analyses.

Each perinatal exposure in table 8.12 was adjusted for all the other exposures in the table. Only three prevalence ratios changed by more than ±10% from their unadjusted values, in the category 'presentation (missing)' for the 'all parities' and 'nulliparous' analysis, and in the social class missing group for the 'nulliparous' analysis. Other smaller changes occurred but they did not indicate strong confounding effects between the selected variables.

Stratification by parity modified the prevalence ratios by differing amounts, but much of this was within the range that might be attributed to chance variation. Differences approaching $p<0.15$ are commented upon because this has been suggested as a level to use when assessing interactions [239].

8.4.3 Multivariate results

The interaction between birth weight and parity (p=0.075) was suggestive of a difference by parity. In particular, the prevalence ratios associated with birth weights of ≤2.4 kg and 4.0 kg or more were significantly different between the 'nulliparous' and 'parous' groups (p=0.037 and p=0.027 respectively). The prevalence of cryptorchidism was high among low birth weight sons of nulliparous women but the trend was not as pronounced as it was in the parous group.

The interaction between maternal age and parity was not significant (p=0.346) but there was a statistically significant trend among nulliparous women (p=0.017) which was not apparent among the parous women (p=0.892). The raised prevalence of cryptorchidism among sons of 'elderly primiparae', although not statistically significant, is worth highlighting because of a similarity between risk of testicular cancer and maternal age found in one study [251].

There were significant trends with social class in the analyses based on nulliparous (p=0.037) and parous (p=0.018) women and all parities combined (p=0.001). The trends and prevalence ratios were similar to those in the univariate analysis and so similar corrections for migration bias and conclusions would apply: the relation between social class and cryptorchidism would not be as strong as it first appeared to be but it probably could not be attributed completely to migration bias. There was no evidence for an interaction between social class and parity (p=0.667).

The raised prevalence associated with breech presentation in the univariate analysis remained after adjusting for the other variables in table 8.12. The prevalence associated with breech presentation was more pronounced among boys born to nulliparous women than those born to parous women, but the difference was not statistically significant (p=0.221), nor was the overall interaction with parity significant (p=0.452).

The prevalence ratios for pre-eclampsia, feeding at discharge and episiotomy were similar to their unadjusted values from the univariate analysis. The interactions with parity were not significant (p=0.934, 0.831 and 0.727 respectively).

8.4.4 Boys with undescended testes diagnosed at birth

Fourteen percent of cases (n=196) in this study had undescended testes diagnosed at birth, as recorded in the ORLS files. These boys were part of the study of undescended testes diagnosed at birth described in chapter 7. When these boys were removed from the analysis the multivariate results remained essentially unchanged.

Table 8.12: Multivariate analysis: prevalence ratios for boys with undescended testis diagnosed at orchidopexy—stratification by maternal parity

Risk factor	Nulliparous		Parous		All parities	
	Prevalence ratio	95% confidence interval	Prevalence ratio	95% confidence interval	Prevalence ratio	95% confidence interval
Parity						
Nulliparous					1.00	baseline
Parous					0.89	0.78–1.01
					* LRS[1]= 3.19, p=0.074	
Birth weight (kg)						
≤2.4	2.84	1.90–4.26	1.37	0.89–2.10	1.87	1.45–2.42
2.5–2.9	1.33	1.00–1.77	1.17	0.91–1.51	1.23	1.04–1.47
3.0–3.4	1.00	baseline	1.00	baseline	1.00	baseline
3.5–3.9	1.29	1.02–1.63	0.92	0.77–1.11	1.04	0.90–1.19
4.0 or more	1.25	0.89–1.74	0.86	0.67–1.10	0.99	0.83–1.20
	LRS[4]= 26.16, p<0.001 Trend LRS[1]= 3.59, p=0.058		LRS[4]= 7.36, p=0.118 Trend LRS[1]= 6.93, p=0.009		LRS[4]= 25.46, p<0.001 Trend LRS[1]= 12.34, p<0.001	
Maternal age (years)						
≤19	0.70	0.50–0.99	0.98	0.60–1.61	0.74	0.58–0.94
20–24	0.98	0.78–1.23	0.89	0.72–1.10	0.93	0.81–1.07
25–29	1.00	baseline	1.00	baseline	1.00	baseline
30–34	1.11	0.80–1.52	0.91	0.75–1.12	0.98	0.84–1.15
35 or over	1.55	0.85–2.82	0.96	0.71–1.30	1.03	0.80–1.31
	LRS[4]= 7.93, p=0.094 Trend LRS[1]= 5.66 , p=0.017		LRS[4]= 1.49, p=0.828 Trend LRS[1]= 0.02, p=0.892		LRS[4]= 6.67, p=0.155 Trend LRS[1]= 3.36, p=0.067	
Social class						
I	0.73	0.51–1.04	0.68	0.49–0.94	0.71	0.57–0.89
II	0.92	0.70–1.20	0.80	0.64–1.01	0.85	0.72–1.00
III	1.00	baseline	1.00	baseline	1.00	baseline
IV	0.88	0.63–1.23	1.00	0.78–1.28	0.94	0.79–1.13
V	1.47	0.92–2.35	0.99	0.69–1.41	1.15	0.89–1.48
Other	0.31	0.18–0.54	0.34	0.19–0.61	0.34	0.23–0.50
† Missing	0.61	0.43–0.86	0.64	0.46–0.88	0.60	0.48–0.75
	LRS[6]= 34.46, p<0.001		LRS[6]= 28.11, p<0.001		LRS[6]=65.30, p<0.001	
Presentation						
Breech	2.20	1.23–3.93	1.38	0.77–2.49	1.67	1.16–2.41
Not breech	1.00	baseline	1.00	baseline	1.00	baseline
† Missing	0.81	0.28–2.36	1.66	0.75–3.65	1.29	0.72–2.31
	LRS[2]= 6.83, p=0.033		LRS[2]= 2.50, p=0.287		LRS[2]= 7.48, p=0.024	
Pre-eclampsia						
No mention	1.00	baseline	1.00	baseline	1.00	baseline
Yes	1.15	0.90–1.47	1.17	0.91–1.50	1.17	1.00–1.37
	LRS[1]= 1.18, p=0.277		LRS[1]= 1.55, p=0.214		LRS[1]= 3.69, p=0.055	
Feeding at discharge						
Breast and complement	1.00	baseline	1.00	baseline	1.00	baseline
Artificial	1.12	0.83–1.52	1.19	0.95–1.50	1.22	1.04–1.45
† Missing	1.18	0.52–2.69	1.88	0.90–3.90	2.20	1.34–3.61
	LRS[2]= 0.65, p=0.722		LRS[2]= 4.46, p=0.107		LRS[2]= 12.87, p=0.002	
Episiotomy						
No	1.00	baseline	1.00	baseline	1.00	baseline
Yes	1.13	0.91–1.40	1.12	0.95–1.33	1.13	1.00–1.27
	LRS[1]= 1.26, p=0.261		LRS[1]= 1.85, p=0.174		LRS[1]= 3.76, p=0.053	

* LRS[n]: Log-likelihood Ratio Statistics with n degrees of freedom
† All variables adjusted for the other variables in the table
Cases individually matched with up to 8 controls on year of birth, sex and hospital of delivery
All variables adjusted for other variables in the table

8.5 Discussion of results from case-control study

Low birth weight, older maternal age, low social class, breech presentation, pre-eclampsia, artificial feeding and episiotomy were identified as risk factors for cryptorchidism. Low birth weight, and perhaps breech presentation and older maternal age, were stronger risk factors among first born than later born boys. Hormonal abnormalities are thought to play an important part in the aetiology of cryptorchidism [142] and there are reasons to suspect that first pregnancies may be hormonally [236] and immunologically [237] different to subsequent ones.

With the exception of one study from Sweden [221] the results presented here were based on a far larger number of cases than previous epidemiological studies of cryptorchidism. The large sample size made it possible to examine the interaction between related variables, like birth weight and gestation, with more detail than in past studies. In addition it was possible to compare and contrast the results with those from the study of undescended testis diagnosed at birth. Before considering the aetiological interpretation of the findings, however, some of the limitations of this study need to be considered.

8.5.1 Orchidopexy as a marker for cryptorchidism

The results from this study were dependent on the validity of orchidopexy as a marker for undescended testes. Before a boy undergoes orchidopexy he will have been examined carefully to confirm the initial diagnosis of cryptorchidism. Orchidopexy is not a trivial procedure and before operating a surgeon will want to confirm that the testis is truly undescended. Some boys with an undescended testis will be initially treated with hormones [252], and if this is successful orchidopexy will not be necessary. Hormonal treatment, however, has been reported to be almost ineffective in causing descent among truly undescended testes, but to be very effective in producing descent of retractile testes [253]. In routine medical records a mention of orchidopexy is likely to be a better indicator of true cryptorchidism than a diagnostic label recorded at a time other than at operation. Orchidopexies are also uncommon before three months of age, a period when spontaneous descent of the testis is still a possibility. Using an orchidopexy as a marker for undescended testis, therefore, selected into this study those boys who were likely to remain truly cryptorchid without medical intervention.

The operation code orchidopexy, however, does not always imply cryptorchidism. A small proportion of boys undergoing orchidopexy may have had an absent testis, but the numbers of such cases is likely to be small. Testicular torsion, which is most common in

the perinatal period and between 10–25 years of age, is also a condition that may lead to an orchidopexy [254]. In this study 69 boys had a concurrent diagnosis of testicular torsion during the hospital visit where they had their first orchidopexy. Excluding these 69 boys from the study made little difference to the final results.

A proportion of boys whose testes may have ascended after birth [150–152], but who were not cryptorchid at birth, would have been selected into this study. For the purpose of this study these boys with ascending testes were considered to have had an underlying abnormality that was present from birth, and so were counted as cases from birth even though they were ascertained at a later date. Boys with retractile testes may have been erroneously operated upon [167] and so would also have been selected into the study. These cases would add to the heterogeneity of the condition studied and might dilute the association between the risk factors and true cryptorchidism. Previous studies (see table 6.3), whether they selected cases based only on diagnosis or on a combination of diagnosis and orchidopexy would also have suffered from this problem. Nevertheless further studies are needed on boys with retractile testes to determine where they fit in the aetiology of cryptorchidism.

8.5.2 Migration bias

The method of selecting cases at orchidopexy and controls at birth leads to a potential bias. Biased estimates of the prevalence ratio may arise because cases had to be present in the study area up to the date when they had their orchidopexy, whereas there was no comparable constraint on the controls. As discussed in chapter 3, this bias was potentially serious for social class, maternal age and parity, but it was possible to determine the extent of the bias and to estimate a correction it. Other perinatal exposures were only weakly, or not at all, associated with differential migration and so were not affected by the migration bias.

8.5.3 Advantages and disadvantages of routine data

The advantages and disadvantages of routine data were discussed in section 5.4.3 and apply equally to this study.

8.5.4 Heterogeneity of disease

The heterogeneity of the conditions underlying a diagnosis of cryptorchidism were discussed in section 7.5.3. There may well be less heterogeneity of disease in this study because it was limited to those testes that required orchidopexy. A possibly aetiologically different

group, undescended testes that descend spontaneously, were not included here. Some testes, however, may be operated upon because they are retractile [167], and they were included in this study. Cryptorchidism defined by orchidopexy, therefore, may be made up of conditions with differing aetiology, and this must be considered when interpreting the results.

8.5.5 Risk factors

Maternal oestrogen levels

It has been hypothesised that raised levels of maternal oestrogens may cause intra-abdominal arrest of testicular descent by inhibiting Müllerian inhibiting substance [229]. Müllerian inhibiting substance is thought to be important early in foetal development at the trans-abdominal phase of testicular descent [142]. In support of this theory animal studies [223, 224] show that exogenous oestrogens early in pregnancy can increase the risk of undescended testis in mice. In humans exogenous oestrogens [225–227] may be associated with an increased risk of cryptorchidism.

It has been suggested that *in utero* exposure to high levels of oestrogens, from either endogenous or exogenous sources, may have a direct effect on the risk of testicular cancer [10, 190]. Maternal oestrogens may interrupt the progression of primitive germ cells to mature germ cells early in foetal development [11] and that during puberty and in young adulthood these primitive germ cells may multiply under stimulation by gonadotropins and give rise to germ cell tumours [224, 229]. It is, therefore, useful to consider markers for raised maternal oestrogen levels as possible risk factors for undescended testis because cryptorchidism is a strong risk factor for testicular cancer.

Indirect markers of raised maternal oestrogen levels, like nausea and vomiting during pregnancy [255], nulliparity [255, 256], and high maternal body mass index [255] are considered possible aetiological risk factors for testicular cancer [240]. High body mass index or weight [24, 217, 219], nausea or vomiting during pregnancy [216, 221] and being first born [24, 215, 221] have also been associated with cryptorchidism, but the evidence was not always statistically significant. In addition there are other studies that show the opposite or no association, for example for: body mass index [215, 220]; nausea and vomiting [24, 215, 220]; or being first born [218–220, 222]. There was no strong evidence for a raised risk with nulliparity, vomiting during pregnancy, or a high body mass index in the studies presented here, of undescended testis diagnosed at birth or at orchidopexy. No direct information was available on endogenous or exogenous oestrogen levels during pregnancy and other studies which have measured this are inconclusive [228, 229].

In common with most previous studies (e.g. those in table 6.3) it was not possible to distinguish abdominal testes from other forms of maldescent. It is early in the process of testicular descent that oestrogens are thought to be important, and so oestrogen levels may be more closely associated with abdominal testes than with testes that come to rest in the inguinal canal or high in the scrotum. Abdominal testes may only make up about 10% of undescended testes [146] and risk factors for this type of maldescent would be difficult to detect when all forms of maldescent were grouped together. Thus while there is no evidence that the indirect markers of maternal oestrogen levels were related to cryptorchidism this study would not be expected to detect such an association if raised levels of oestrogens acted to cause testes to remain in the abdomen. It is also possible, however, that hormonal imbalances early in foetal life might lead to problems at a later date, perhaps due to the incorrect setting of hormonal receptors, as has been suggested in relation to the foetal origins of some adult diseases [257].

Clearly further work is needed in this area, preferably with more direct measures of bio-available endogenous and exogenous oestrogen exposures in relation to degree or position of maldescent.

Maternal diabetes

There was a large increase in risk with maternal diabetes during pregnancy but the number of affected mothers was small and the result was not statistically significant. An earlier study [24] based upon the ORLS population also found a raised risk with maternal diabetes, but the cases in that study were essentially a sub-group of those presented here. There are, however, two other independent reports of raised risk with maternal diabetes, one of which was statistically significant [221] while the second was not [219].

The connection between diabetes during pregnancy and broad classes of major birth defects is well known [258], but the relation with cryptorchidism has received little attention. Diabetes is associated with metabolic and hormonal anomalies and it would be interesting to study the association between maternal diabetes and cryptorchidism by discriminating between pre-existing diabetes, gestational diabetes and the type of diabetes: type I (insulin dependent) or type II (non insulin dependent). This was not possible here, or in previous studies [24, 219, 221], because of the small number of mothers with diabetes.

Birth weight and gestation

Low birth weight was strongly related to cryptorchidism, as found in other studies (see table 6.3). A similar association also exists between low birth weight and testicular cancer [183, 240]. In this study it was possible to show that the association between low birth weight and cryptorchidism was not because of shortened gestation. The same conclusion was reached in a large population-based study from Sweden [221], where it was reported that cryptorchidism was associated with low birth weight when the child was "small for date", but not when he was born prematurely. The Swedish study and this study both showed that there was little change in risk for birth weights of 3.0 kg or more. In contrast to this, the study of cryptorchidism diagnosed at birth (see table 7.1) showed that the protective influence of larger birth weight continued beyond 3.0 kg to 4.0 kg or more.

There was no strong independent association with gestational age, unlike that found in the study of undescended testis diagnosed at birth. It was possible, however, that there remained a small association between cryptorchidism diagnosed at orchidopexy and gestation, independent of birth weight. Gestational age is a less accurate measure of foetal maturity than is birth weight because the former must be estimated by recalling the date of the last menstrual period, which itself is an imprecise proxy for date of conception. Length of gestation is more likely to be misclassified than birth weight and this misclassification may have reduced the strength of its association with cryptorchidism and its usefulness as an independent measure of intra-uterine development.

Cryptorchid cases diagnosed at orchidopexy had a similar distribution of head size at birth as the controls, yet on average the cases had lower birth weights. This suggested that cases were disproportionately or 'asymmetrically' growth retarded, i.e. 'thin' at birth. This was not so in the study of cryptorchidism diagnosed at birth where a small head size was directly related to low birth weight (i.e. babies were proportionately or 'symmetrically' small).

The type of disproportionate growth retardation that causes below average birth weight but normal head circumference usually occurs after 28 weeks gestation and may be due to utero-placental insufficiency [259]. The foetus compensates for decreased placental blood-flow by reallocating its limited resources to the brain, heart and adrenals at the expense of glycogen storage and liver mass [259]. It is during the last trimester, around the seventh or eighth month of gestation, that the majority of undescended testes come to a halt, in the inguinal canal or high in the scrotum [146]. It is plausible that the factors that cause 'thinness at birth' are also those that cause permanent failure of testicular descent in the

third trimester.

Maternal age

Prevalence of cryptorchidism was low among first born sons of teenage mothers and there was a suggestion of an increased risk with older maternal age, also among first born boys; a pattern similar to that seen in one study of testicular cancer [251]. This increase in risk with maternal age cannot be attributed to more multiple deliveries or major congenital malformations at older ages because such deliveries were removed from the analyses. Women who delay childbearing to a late age (i.e. 35 years or older) are more prone to low birth weight infants than younger mothers [260, 261], but birth weight had been adjusted for in the multivariate analysis.

The number of 'elderly primiparae' was small so it was not possible to explore risk in sons of these mothers in more detail. Elderly primaparae, however, may be subject to placental and other child-bearing problems and, because of the possible similarity with testicular cancer [251] and the observation that oestrogen levels may be higher in first than subsequent pregnancies [236], more attention should be focused on this group in the future.

Social class

Few studies have reported risk with social class, but one found an increased risk with a higher level of maternal education [219] while a second found the opposite [231]; only the result from the latter study was statistically significant. In this study the observed association between low social class and a higher prevalence of cryptorchidism cannot be explained appreciably by migration bias or age at orchidopexy, although these do somewhat bias the association. A similar trend with low social class being associated with a higher prevalence of cryptorchidism was seen in the study of undescended testes diagnosed at birth, where these two biases do not act. It seems likely, therefore, that the association in this study between undescended testes and social class is real. The raised risk with low social class is opposite to the trend seen for testicular cancer, where high social class is associated with increased risk [240]. This suggests that there may be some differences between the aetiology of cryptorchidism and testicular cancer.

Social class itself does not cause undescended testis, but acts as a marker for other exposures. Future studies are needed to confirm this result and to establish if the association is present in other populations, where local indicators of social class may represent a different set of exposures.

Breech presentation

Breech presentation or breech delivery has previously been found as a risk factor for cryptorchidism, as has caesarean section (see table 6.3). In this study caesarean section was only related to cryptorchidism through its association with breech presentation but there are reports where caesarean was, and breech was not, a risk factor for cryptorchidism [220, 221]. The indications for caesarean may, however, be different in different regions or countries and it is possible that this could influence the relative importance of breech presentation and caesarean section as risk factors for cryptorchidism. There was an indication that breech presentation was more important among first pregnancies than subsequent ones, an association also suggested in the study of cryptorchidism diagnosed at birth.

It has been suggested that breech delivery, or attempted breech delivery, may cause trauma to the testes [24] although breech is also associated with uterine abnormalities, placenta praevia, curtailed gestation and impaired foetal growth [234]. When discussing birth weight and gestational age it was suggested that cryptorchidism might be associated with asymmetrical growth retardation in the third trimester. This is consistent with one theory for the mechanism of breech presentation which suggests that the foetal head moves naturally to the pelvis late in pregnancy when the body catches up in size relative to the head. If the body does not increase in size adequately the foetus may not rotate and might present in the breech position [262]. Breech presentation, therefore, may be acting as a marker for impaired foetal growth.

Pre-eclampsia

Pre-eclampsia or eclampsia has previously been identified as a risk factor for cryptorchidism [221], where it was suggested that pre-eclampsia might be related to high levels of unbound oestrogen during pregnancy; a suspected risk factor for cryptorchidism [225, 226] and testicular cancer [10, 190]. This study confirms the association between undescended testis and pre-eclampsia, and the previous study showed that this is apparent among cases diagnosed at birth. It is questionable, however, that pre-eclampsia is associated with high oestrogen levels during pregnancy. In one epidemiological study of prenatal influences on breast cancer risk presence of pre-eclampsia or eclampsia was used as a marker for *low* oestrogen levels [263]. Additionally, pre-eclampsia is a condition of late pregnancy whereas high levels of oestrogen during pregnancy might act during the early stages of pregnancy to cause cryptorchidism.

In keeping with a theme developed earlier, an alternative hypothesis is that pre-eclampsia

may be a marker for, or cause of, intra-uterine growth retardation during the later stages of pregnancy. Pre-eclampsia is associated with vascular abnormalities [242] and reduced uterine blood flow to the placenta [243], and it has been proposed that pre-eclampsia and intra-uterine growth retardation share a common aetiology of poor placental perfusion [264]. In future studies it would be interesting to measure placental function, shape and size in relation to cryptorchidism.

There appear to be no reports of pre-eclampsia as a risk factor for testicular cancer in male offspring. Pre-eclampsia is more common among first pregnancies than subsequent ones [265–267] and it might be worth looking at pre-eclampsia as a risk factor for testicular cancer, which is also reported to be more common in first born than later born boys [183].

Pre-eclampsia may be caused by an immunological response in the mother to the foetus [136, 237, 268] but it was not possible to explore this further with the available data. The mechanism that prevents the mother from rejecting the foreign tissue that is the foetus is not well understood and small disturbances in this may have serious implications for the development of the foetus.

Breast feeding and episiotomy

Not breast-feeding at discharge was associated with increased risk of cryptorchidism, as has been reported once before [215]. After adjusting for social class there was a small increased prevalence with not breast-feeding, but the association was weak and may not be independent of social class. Breast-feeding was not important as a risk factor in the study of undescended testis diagnosed at birth and its significance here is uncertain.

Episiotomy does not appear to have previously been associated with cryptorchidism, possibly because the strength of the association appears to be small. If, during labour, the mother or foetus become distressed episiotomy may be performed to hasten delivery. This operation, however, is used so liberally that it is likely to be a poor marker of foetal distress: among women giving birth for the first time between 50%–90% may have an episiotomy [269]. The association needs confirmation, especially in different regions and countries where the indications for episiotomy may be different to those in Oxfordshire and West Berkshire; however, other more sensitive markers of foetal distress might also be examined.

8.6 Summary of results from case-control study

The testes do not begin their final descent until the seventh or eighth month of gestation [143], and descent is usually complete in most boys by three to four months of age [144]. Thus maturity at birth, as measured by gestational age, birth weight and head size, may be important in determining if the testes have descended *at birth*. The full process of testicular descent may be slower among babies who develop slowly while *in utero*, or descent may be interrupted by an early delivery. If the baby is otherwise normal then descent may still occur naturally in the first few months after birth. If, however, the child has suffered from some form of growth retardation, as suggested by Hjertkvist [221], then descent may never occur naturally. It was postulated that in cases of permanent cryptorchidism this growth retardation may be asymmetric and be due to poor placental perfusion during the third trimester of pregnancy. The nutrients and oxygen a baby receives *in-utero* from the mother depend not only on maternal nutrition during pregnancy, but on the mothers previous nutritional experience and on factors during her own foetal life [270]. In future studies it would be of interest to look in detail at growth retardation and placental function, not only in relation to cryptorchidism but also in relation to testicular cancer.

One test of the above hypothesis would be to look at risk factors for cryptorchidism that were proxy measures or signs of intra-uterine growth retardation by the degree of maldescent. Testes that come to rest in the abdomen early in foetal development would not be expected to show an association with growth retardation in the third trimester, whereas the association should be strongest for testes that remain in the inguinal canal or high in the scrotum. The data available from the ORLS did not allow this type of analysis. Direct, rather than proxy, measures of placental function might also give insights into the aetiology of cryptorchidism. There was no evidence that maternal oestrogen levels were associated with cryptorchidism, but this theory might also benefit from analyses by degree of maldescent and by more direct measures of oestrogen levels.

The low risk of cryptorchidism with high social class, opposite to that seen for testicular cancer [240], suggests that there are differences in the aetiology of these two diseases. It would be useful to determine which correlates of social class are important in relation to testicular cancer and cryptorchidism.

Table 8.13: Number of sibships with r boys with undescended testis diagnosed at orchidopexy in sibship of boys of size s

	Number of sibships									
Sibship size (s)	Number of affected boys in sibship (r) 0	1	2	3	4	5	6	7	Total	Risk (%)
Male sibships with at least one case										
1	—	829							829	—
2	—	463	18						481	7.21
3	—	88	7	0					95	7.03
4	—	13	2	0	0				15	8.29
5	—	1	0	0	0	0			1	0.00
6	—	1	0	0	0	0	0		1	0.00
7	—	0	0	0	0	0	0	0	0	—
Total	—	1395	27	0	0	0	0	0	1422	7.15
							95% confidence interval			(4.87–9.95)
Male sibships with at least one control										
1	6229	100							6329	1.58
2	2794	95	6						2895	1.85
3	513	31	3	0					547	2.25
4	75	6	1	0	0				82	2.44
5	14	0	0	0	0	0			14	0.00
6	3	0	0	0	0	0	0		3	0.00
7	1	0	0	0	0	0	0	0	1	0.00
Total	9629	232	10	0	0	0	0	0	9871	1.78
							95% confidence interval			(1.57–2.00)

8.7 Risk of cryptorchidism in siblings

The 1449 cases were part of 1422 sibships containing in total 2935 children; an average of 2.06 children per sibship. The affected-sib method [245] was used to estimate the prevalence of undescended testis within sibships, as described in section 7.6. There were 2147 boys left after excluding all girls, and boys who had a diagnosis of a major congenital malformation at birth or were part of a twin or higher order delivery. The distribution of affected boys by sibship size is shown in table 8.13 where the average number of eligible boys per sibship was 1.51. The risk of cryptorchidism among boys with at least one affected brother was 7.15% (4.87%—9.95%). Table 8.13 also shows the number of affected boys among sibships containing at least one control boy. There were 14183 eligible boys in 9871 sibships for an average of 1.44 boys per sibship. The risk of cryptorchidism among these boys was 1.78% (1.57%—2.00%). This is similar to the prevalence of cryptorchidism at three months of age of 1.8% reported in Oxford, 1984–88 [147].

8.7.1 Discussion of disease risk among siblings

The risk of orchidopexy in male siblings was higher in those belonging to case sibships than control sibships by a factor of four. A previous study reported an elevated risk of 6.2% for undescended testis among brothers of index subjects [165]; here the risk among brothers was also high at 7.2%.

Some congenital anomalies like Noonan's syndrome are known to be associated with undescended testis and to have an increased risk of re-occurrence among siblings [212]. Congenital syndromes like these could not contribute greatly to the familial association seen here because the risk among siblings was estimated after removing boys with major congenital anomalies. This, however, does not rule out genetic causes for the sibling association, as has been hypothesised [159, 162]. Boys who were part of twin or higher order deliveries were also removed from the analysis so eliminating this as a possible cause of the aggregation among siblings.

It is possible that the sibling association was an artefact caused by, for example, parents becoming more aware about undescended testis, and its risks, after having had one child diagnosed and operated upon. The brothers of an affected boy may then be examined more closely and treated more vigorously and at an earlier age, perhaps causing a retractile testis to be mistakenly treated as an undescended testis. It would seem unlikely, however, that such a bias would operate on a scale to produce the strong clustering within sibships seen here. Reports in the literature of familial associations [159, 163, 165] also support the conclusion that clustering within sibships is real.

The sibling association, if real, need not necessarily have a direct genetic cause. Siblings share the same mother and similar prenatal environments and exposures, and these may contribute to the familial clustering. Disentangling environmental and genetic causes, however, is difficult and twins may be a useful group to study. In none of the 22 like-sex twin pairs, excluded from these analyses, were both boys affected. The number of twins, however, was small and an examination of a larger series, by zygosity, might provide some insights into the familial association.

Table 8.14: Odds ratios for cryptorchidism diagnosed at orchidopexy for risk factors present in sibling born immediately before cases and controls: index matching variables and sex of sibling

Risk factor	Cases (total=496) number	Controls (total=3124) number	Odds ratio*	95% confidence interval
Year of birth of index case or control				
1970–74	108	767	0.85	0.66–1.08
1975–79	223	1341	1.00	baseline
1980–86	165	1016	0.97	0.78–1.20
			† LRS[2]= 1.87, p =0.393; Trend LRS[1]= 0.84, p =0.360	
Hospital district of birth of index case or control				
Oxfordshire	155	922	1.00	baseline
West Berkshire	341	2202	0.92	0.75–1.13
			LRS[1]= 0.62, p =0.432	
Sex of sibling				
Boy	258	1659	1.00	baseline
Girl	238	1465	1.04	0.86–1.26
			LRS[1]= 0.19, p =0.661	

* all variables adjusted for other variables in the table

† LRS[n]: Log-likelihood Ratio Statistic with n degrees of freedom

8.8 Risk factors in siblings

The immediately previous and subsequent siblings of the cases and controls were identified, as described in section 7.8. One sibling was recorded as being born on the same day as the index subject, and after closer examination this record appeared to be a duplicate of the index record and was discarded. Fifteen siblings were born within 200 days of the index delivery at impossible or highly improbable values for the inter-delivery interval [247]. Possibly either the date of delivery was wrong or the child was linked to the wrong mother. These records were discarded from the analysis. Any siblings that were part of a twin or higher order delivery or had a major congenital anomaly diagnosed at birth were removed from the analysis.

8.8.1 Results

Immediately prior deliveries

Table 8.14 shows odds ratios for the matching variables, year of birth and hospital of birth of the index case or control. There were no significant associations with these variables, nor

Table 8.15: Odds ratios for cryptorchidism diagnosed at orchidopexy for risk factors present in sibling born immediately before cases and controls: birth weight and gestational age

Risk factor in sibling	Cases (total=496) number	Controls (total=3124) number	Odds ratio*	95% confidence interval	Odds ratio*†	95% confidence interval
Birth weight (kg) of sibling						
≤2.4	27	160	0.99	0.64–1.52	0.93	0.59–1.46
2.5–2.9	87	504	1.00	0.76–1.32	1.00	0.76–1.32
3.0–3.4	207	1215	1.00	baseline	1.00	baseline
3.5–3.9	140	946	0.87	0.69–1.09	0.86	0.68–1.10
4.0 or more	34	280	0.72	0.49–1.05	0.72	0.48–1.07
Missing	1	19				
			‡ LRS[4]= 4.18, p =0.382; Trend LRS[1]= 2.83, p =0.093		LRS[4]= 3.56, p =0.469; Trend LRS[1]= 1.87, p =0.171	
Gestational age (weeks) of sibling						
≤36	28	148	1.30	0.82–2.05	1.29	0.81–2.05
37–38	84	417	1.37	1.03–1.84	1.37	1.02–1.83
39–40	198	1342	1.00	baseline	1.00	baseline
41–42	122	796	1.10	0.85–1.41	1.08	0.84–1.40
43 or more	20	97	1.46	0.86–2.50	1.39	0.81–2.39
Missing	44	324				
			LRS[4]= 6.13, p =0.190; Trend LRS[1]= 0.60, p =0.440		LRS[4]= 5.41, p =0.248; Trend LRS[1]= 0.62, p =0.432	
§ Birth weight for gestational age of sibling						
LGA	26	241	0.63	0.40–0.99	0.67	0.43–1.06
AGA	366	2249	1.00	baseline	1.00	baseline
SGA	59	307	1.31	0.96–1.78	1.31	0.95–1.79
Missing	45	327				
			LRS[2]= 8.21, p =0.017; Trend LRS[1]= 7.76, p =0.005		LRS[2]= 6.33, p =0.042; Trend LRS[1]= 6.13, p =0.013	

* adjusted for period and hospital of index birth, and sex of sibling
† also adjusted for same risk factor in index child
‡ LRS[n]: Log-likelihood Ratio Statistic with n degrees of freedom
§ LGA: Large for gestational age
§ AGA: Appropriate for gestational age
§ SGA: Small for gestational age

was there an association with the sex of the previously born sibling and risk of undescended testis.

Table 8.15 shows odds ratios for birth weight, gestational age and birth weight for gestational age for the previously born sibling of the index cases or controls, in relation to risk of undescended testis at the index delivery and adjusted for the matching variables and the sex of the sibling. There was no significant association with risk of cryptorchidism and the previous sibling's birth weight. Nor was there a statistically significant association with

Table 8.16: Odds ratios for cryptorchidism diagnosed at orchidopexy for risk factors present in sibling born immediately before cases and controls: other risk factors

Risk factor in sibling	Cases (total=496) number	Controls (total=3124) number	Odds ratio*	95% confidence interval	Odds ratio*†	95% confidence interval
Social class at birth of sibling						
I	43	239	1.13	0.78–1.64	1.85	1.03–3.32
II	68	490	0.86	0.63–1.17	0.92	0.60–1.41
III	209	1229	1.00	baseline	1.00	baseline
IV	59	395	0.94	0.67–1.30	1.08	0.73–1.58
V	35	177	1.26	0.83–1.92	1.67	1.01–2.78
Other	7	65	0.85	0.38–1.92	1.01	0.35–2.94
Missing	50	381				
Not collected	25	148				
			‡ LRS[5]= 3.42, p =0.636		LRS[5]= 8.77, p =0.119	
Pre-eclampsia at birth of sibling						
No mention	421	2696	1.00	baseline	1.00	baseline
Yes	75	428	1.11	0.85–1.45	1.02	0.77–1.37
			LRS[1]= 0.55, p =0.459		LRS[1]= 0.02, p =0.880	
Presentation of sibling						
Not breech	191	1276	1.00	baseline	1.00	baseline
Breech	16	52	1.93	1.07–3.50	1.95	1.07–3.56
Missing	1	10				
Not collected	288	1786				
			LRS[1]= 4.20, p =0.040		LRS[1]= 4.28, p =0.039	
Caesarean section for sibling						
No	460	2965	1.00	baseline	1.00	baseline
Yes	36	159	1.43	0.98–2.08	1.62	1.01–2.59
			LRS[1]= 3.24, p =0.072		LRS[1]= 3.80, p =0.051	

* adjusted for period and hospital of index birth, and sex of sibling
† also adjusted for same risk factor in index child
‡ LRS[n]: Log-likelihood Ratio Statistic with n degrees of freedom

gestational age. Birth weight for gestational age in the previous sibling was significantly associated with risk of cryptorchidism in the index cases. There was a strong trend with greater risk of undescended testis among those boys who had a small for gestational age sibling. After adjusting for birth weight for gestational age at the index delivery the overall association and trend was still statistically significant and the odds ratios were little changed in magnitude.

Table 8.16 presents odds ratios for social class, pre-eclampsia, presentation and caesarean section. There was no overall association with social class at the siblings' delivery and the risk of cryptorchidism at the index delivery. The trend across groups I–V was not significant

(p=0.723). After adjusting for social class at the index delivery the odds ratios for groups I and V became significant, but overall the association was not significant and neither was the test for trend (p=0.674).

There was no significant association with pre-eclampsia but risk of cryptorchidism was significantly raised if the previous sibling presented in the breech position. This association was essentially unchanged after adjusting for presentation at the index delivery. There was also a raised but not significant association with caesarean section, which after adjusting for caesarean section during the index delivery was still raised[1].

[1]The log-likelihood ratio statistic p-value for the adjusted odds ratio for caesarean section falls on the wrong side of the conventional α=0.05 significance level to be statistically significant, yet the 95% confidence interval excludes 1.00. The apparent incongruity is a result of the different methods used to construct the confidence intervals and used to calculate the log-likelihood ratio statistic. Throughout this work log-likelihood ratio test p-values have been used, where appropriate, because this method is to be preferred to that used to estimate the 95% confidence intervals [271].

Table 8.17: Odds ratios for cryptorchidism diagnosed at orchidopexy for risk factors present in sibling born immediately after cases and controls: index matching variables and sex of sibling

Risk factor	Cases (total=652) number	Controls (total=3783) number	Odds ratio*	95% confidence interval
Year of birth of index case or control				
1970–74	281	1527	1.10	0.91–1.33
1975–79	237	1421	1.00	baseline
1980–86	134	835	0.97	0.77–1.22
			† LRS[2]= 1.67, p =0.433; Trend LRS[1]= 1.54, p =0.214	
Hospital district of birth of index case or control				
Oxfordshire	185	1165	1.00	baseline
West Berkshire	467	2618	1.12	0.93–1.34
			LRS[1]= 1.41, p =0.235	
Sex of sibling				
Boy	338	1947	1.00	baseline
Girl	314	1836	0.98	0.83–1.16
			LRS[1]= 0.05, p =0.830	

* all variables adjusted for other variables in the table
† LRS[n]: Log-likelihood Ratio Statistic with n degrees of freedom

Immediately subsequent deliveries

Table 8.17 presents odds ratios for the matching variables and sex of the next born sibling. There were no significant association with the matching variables or with the sex of the sibling.

Table 8.18 presents odds ratios for birth weight, gestational age and birth weight for gestational age. There was a significant association and trend between the birth weight of the next born sibling and risk of cryptorchidism in the index subjects. Risk was highest among index subjects who had low birth weight siblings. Adjusting for the birth weight at the index delivery weakened the association, but there was still a significantly raised risk among subjects with a low birth weight sibling. There was no statistically significant association with gestational age, but there was a tendency for risk to be highest among subjects with a subsequent premature sibling. There were no significant associations with birth weight for gestational age.

Table 8.19 presents odds ratios for social class, pre-eclampsia, presentation and caesarean section. The social class of the subsequently born sibling was not related to risk of

Table 8.18: Odds ratios for cryptorchidism diagnosed at orchidopexy for risk factors present in sibling born immediately after cases and controls: birthweight and gestational age

Risk factor in sibling	Cases (total=652) number	Controls (total=3783) number	Odds ratio*	95% confidence interval	Odds ratio*†	95% confidence interval
Birth weight (kg) of sibling						
≤2.4	37	115	2.01	1.35–2.99	1.66	1.10–2.51
2.5–2.9	95	513	1.15	0.89–1.49	1.08	0.83–1.41
3.0–3.4	229	1432	1.00	baseline	1.00	baseline
3.5–3.9	224	1276	1.10	0.90–1.34	1.14	0.93–1.40
4.0 or more	64	435	0.92	0.68–1.24	0.98	0.71–1.34
Missing	3	12				
			‡ LRS[4]= 12.70, p =0.013; Trend LRS[1]= 4.57, p =0.033		LRS[4]= 6.75, p =0.150; Trend LRS[1]= 0.79, p =0.374	
Gestational age (weeks) of sibling						
≤36	34	124	1.49	0.97–2.29	1.33	0.86–2.06
37–38	88	567	0.85	0.65–1.11	0.79	0.60–1.03
39–40	314	1731	1.00	baseline	1.00	baseline
41–42	139	801	1.03	0.82–1.29	1.04	0.83–1.31
43 or more	23	129	0.83	0.48–1.42	0.82	0.48–1.41
Missing	54	431				
			LRS[4]= 5.78, p =0.216; Trend LRS[1]= 0.15, p =0.699		LRS[4]= 6.33, p =0.176; Trend LRS[1]= 0.05, p =0.832	
§ Birth weight for gestational age sibling						
LGA	59	392	0.85	0.63–1.15	0.91	0.67–1.25
AGA	479	2695	1.00	baseline	1.00	baseline
SGA	57	259	1.11	0.79–1.54	0.98	0.69–1.38
Missing	57	437				
			LRS[2]= 1.66, p =0.436; Trend LRS[1]= 1.59, p =0.207		LRS[2]= 0.33, p =0.847; Trend LRS[1]= 0.12, p =0.733	

* adjusted for period and hospital of index birth, and sex of sibling
† also adjusted for same risk factor in index child
‡ LRS[n]: Log-likelihood Ratio Statistic with n degrees of freedom
§ LGA: Large for gestational age
§ AGA: Appropriate for gestational age
§ SGA: Small for gestational age

cryptorchidism among cases and controls. The was no evidence to suggest a trend across groups I–V (p=0.547, and p=0.844 after adjusting for social class at the index delivery). There was a raised but not significant risk of cryptorchidism if the sibling's delivery was associated with pre-eclampsia. There was also a raised risk if the sibling presented in the breech position, but this was not significant. There was no significant association with caesarean section.

Table 8.19: Odds ratios for cryptorchidism diagnosed at orchidopexy for risk factors present in sibling born immediately after cases and controls: other risk factors

Risk factor in sibling	Cases (total=652) number	Controls (total=3783) number	Odds ratio*	95% confidence interval	Odds ratio*†	95% confidence interval
Social class at birth of sibling						
I	54	328	0.93	0.67–1.28	1.17	0.72–1.91
II	117	688	0.86	0.67–1.10	0.82	0.58–1.16
III	280	1456	1.00	baseline	1.00	baseline
IV	81	445	0.99	0.74–1.31	1.02	0.74–1.42
V	35	188	0.93	0.61–1.42	0.82	0.50–1.36
Other	8	107	0.53	0.24–1.16	0.59	0.24–1.46
Missing	54	420				
Not collected	23	151				
			‡ LRS[5]= 4.13, p =0.531		LRS[5]= 4.32, p =0.504	
Pre-eclampsia at birth of sibling						
No	579	3441	1.00	baseline	1.00	baseline
Yes	73	342	1.28	0.98–1.68	1.21	0.91–1.61
			LRS[1]= 3.17, p =0.075		LRS[1]= 1.72, p =0.190	
Presentation of sibling						
Not breech	478	2829	1.00	baseline	1.00	baseline
Breech	15	72	1.36	0.68–2.72	1.21	0.59–2.46
Missing	5	34				
Not collected	154	848				
			LRS[1]= 0.70, p =0.403		LRS[1]= 0.25, p =0.614	
Caesarean section for sibling						
No	614	3550	1.00	baseline	1.00	baseline
Yes	38	233	0.96	0.67–1.37	0.64	0.40–1.03
			LRS[1]= 0.05, p =0.818		LRS[1]= 3.56, p =0.059	

* adjusted for period and hospital of index birth, and sex of sibling
† also adjusted for same risk factor in index child
‡ LRS[n]: Log-likelihood Ratio Statistic with n degrees of freedom

8.8.2 Discussion of risk factors in siblings

The problems associated with the interpretation of these results was discussed in section 7.8.3.

Birth weight and gestation

Unaffected siblings of cases were more likely to be low birth weight than the siblings of controls but this was limited to the later born siblings. There was, perhaps, a similar pattern with gestational age. Low birth weight was identified as a risk factor for cryptorchidism in the original matched case-control study, and birth weight is known to repeat between deliveries to the same woman [249] so a correlation between index and sibling deliveries would be expected. What was unusual was that the correlation was only apparent in the next born sibling, and remained after adjusting for the index delivery. This suggests that the index and subsequent deliveries were different to previous deliveries and that a permanent change may have occurred around the time of the index delivery. These results must be interpreted with caution because, for example, not all cases and controls have older or younger siblings and family size may be influenced by previous complications of pregnancy. Both cases and controls, however, might be expected to be similar in relation to these factors, so little bias would be expected.

Having a small for gestational age sibling was associated with increased risk of cryptorchidism, but only for the siblings born before the index delivery. The same pattern was seen for breech presentation and caesarean section, although the latter was not significant. Again, interpretation of differences between previous and subsequent deliveries must be made with care but this result also suggests that previous and subsequent deliveries were in some way different.

Social class

The association between orchidopexy and social class was not apparent among siblings of cases and controls. This is in contrast to the association seen for siblings of cases and controls with undescended testis diagnosed at birth and with the results from the original orchidopexy case-control study where the relative risks were lower in social class group I.

Social class as used here, although usually considered as a fixed attribute, can change between deliveries because it is defined by occupation. It is hard, however, to imagine type of occupation being sufficiently in flux to show an association among index cases and controls and yet for the association to be absent among their siblings. The significance of

this is uncertain and these results should be confirmed in other studies.

8.9 Conclusion to cryptorchidism studies

Immaturity at delivery or symmetric growth retardation, either because of a premature delivery or because the baby developed slowly *in-utero*, may result in cryptorchidism at birth because the testes have not been given sufficient time to descend while *in-utero*. The baby may catch up in development *ex-utero* and the testes may descend within the first few months after birth [144]. Siblings were not at greatly increased risk of undescended testes at birth which suggests agents external to the mother may be the cause of the immaturity.

It was postulated that asymmetric growth retardation in the third trimester, perhaps due to problems of placental perfusion, may arrest testicular descent *in-utero* such that natural descent does not occur, or may compromise the testes such that they ascend in later childhood. Male siblings of cases were also at increased risk of undescended testis that required an orchidopexy, possibly because they share the same uterine environment or because there is a genetic component to the condition.

With birth weight and gestation there appeared to be more than simple tracking of these characteristics across pregnancies. The significance of the changes between previous and subsequent deliveries is uncertain and these results need confirmation.

The association with social class differed from that seen with testicular cancer [240] and suggests differences in aetiology that deserve to be explored further.

Assuming intra-uterine growth retardation affects the later stages of descent and oestrogens are important in the initial stages, it would be useful to know how important were the established risk factors for cryptorchidism stratified by the different types of maldescent (i.e. testes that remain in the abdomen, inguinal canal, or high scrotum, and for bi-lateral versus uni-lateral maldescent). Better measures of endogenous and exogenous, and bio-available oestrogens during pregnancy, and direct measures of placental function would also be worth examining in relation to the different degrees of maldescent.

8.9.1 Suggestions for future research

The findings of these studies, and their limitations, suggest further areas for future work into the aetiology of cryptorchidism:

- if possible, studies should consider the position or degree of maldescent;
- better measures of intra-uterine growth retardation should be obtained in future studies;

- direct measures oestrogens and placental function should be considered in relation to cryptorchidism;
- the association with social class should be confirmed;
- maternal diabetes should be examined further, preferably by type of diabetes;
- the role of ascending and retractile testes should be examined in relation to the aetiology cryptorchidism;
- large studies of twins may help in partitioning genetic and environmental causes of cryptorchidism.

Most of these suggestions would also apply to studies of testicular cancer.

Part IV

Inguinal Hernia

Chapter 9

Brief Review of the Inguinal Hernia Literature

9.1 Inguinal hernia in children

The mechanisms involved in testicular descent, which were described in section 6.1, are also important when considering indirect inguinal hernia. Briefly, the processus vaginalis is an outpouching of the peritoneal cavity that extends through the internal inguinal ring down the inguinal canal to the scrotum during the third to seventh month of gestation [272]. The gubernaculum, a fibrous cord that connects the testis to the developing genital swelling in the groin, expands and dilates the inguinal canal to a size which will allow the testis and epididymis to pass through. A pocket of peritoneum, the processus vaginalis, hangs over the gubernaculum, and when the gubernaculum shrinks and disappears the processus vaginalis extends into the scrotum so the testis may descend behind it [141]. After the testis has passed through to the scrotum the processus vaginalis fuses [141]. The processus vaginalis normally obliterates from its origin at the internal ring through to the scrotum where a remnant, called the tunica vaginalis, remains attached to the testis [273]. In girls there is minimal development of the gubernaculum and the gonads (ovaries) remain within the pelvis; the inguinal canal is narrow and a shallow diverticulum of peritoneum may persist, which in girls is called the canal of Nuck [273].

The literature and reported current opinion on inguinal hernia in childhood is usually based on experience from studies which were predominantly made up of male cases, although this is not always explicitly stated. The following sections, therefore, usually refer to inguinal hernia in boys, or groups dominated by boys; information solely relating to girls is sparse.

9.2 Formation of inguinal hernia and hydrocele

Inguinal hernia in children is usually indirect [274, 275], that is, the internal orifice is the deep inguinal ring. When the processus vaginalis or canal of Nuck fails to obliterate the entire processus and tunica vaginalis may remain open to the peritoneal cavity and abdominal contents may enter and form a complete inguinal hernia. In boys the hernia may extend to the base of the scrotum, and in girls into the labium majus. More commonly the processus closes from a point just above the descended testis to a short distance below the internal ring, but abdominal contents may enter at this point and form a hernia [276–279]. In infants the contents of the hernia sac is usually small intestine, although in girls it may also contain fallopian tube and ovary [276].

When the processus vaginalis narrows, but remains patent with the peritoneal cavity, lubricating fluid formed by the serosa of the peritoneal cavity may enter and form a communicating hydrocele [274]. If the processus narrows but does not obliterate at one or more points just above the testis to a short distance below the internal ring, fluid may be trapped in the tunica vaginalis or spermatic cord [276–279].

9.2.1 Frequency of a patent processus

In a large study of children with one clinically apparent inguinal hernia it was concluded that in 40% of cases the processus in the contralateral groin would obliterate just before or during the first few months after birth; a further 20% would have obliterated by two years of age with the remaining 40% patent or open to the peritoneal cavity [280]. It was suggested that sometime in later life about half of these might develop a clinically apparent inguinal hernia [280]. It is not clear how the above conclusions relate to the general population because the study was based upon children presenting with an existing anomaly, i.e. an inguinal hernia.

A summary of autopsy studies by Woolley [276] suggested that at birth the processus vaginalis was open to the peritoneal cavity in 80–94% of those bodies examined and by one year of age 57% were still open. In adults without clinical inguinal hernia part or all of the processus vaginalis has been found in 15–37% of specimens. Woolley's figures were, however, based upon studies from the 18th–19th century and it is unclear as to what degree of obliteration was considered as complete or if the counts refer to persons or groins.

Even if the processus vaginalis involutes by obliteration in 90% of children [273], it is clear that a considerable proportion of infants have the potential for an inguinal hernia or hydrocele.

9.3 Inguinal herniotomy or herniorrhaphy

Inguinal herniotomy or herniorrhaphy is a common surgical operation in childhood. In the age group 0–4 years it makes up 12% of all operations amongst boys and 3% amongst girls [35]. The presence of an inguinal hernia in the paediatric age group is an indication for surgical repair because of the risks associated with incarceration or strangulation [277]. Hydroceles are common in the first few months of life and may simply be observed because they have a tendency to resolve spontaneously [277]. Many will disappear by age one year and surgery is only required if the hydrocele persists beyond two years of age [274].

9.3.1 Age at operation

The number of cases of inguinal hernia in childhood is highest during the first year of life [272] and about one third of cases in childhood are operated upon before six months of age (for a summary of studies see Bronsther [278]). In one large series, 80% of children were seen within six weeks after symptoms began and 90% within six months [278]. Inguinal hernia may appear after childhood, when the incidence begins to rise in adult life [276, 281], but these are not discussed here.

9.4 Incidence and prevalence in children

In Newcastle, in 1953–57, the cumulative incidence of repaired inguinal hernia to age 12 years was 1.0%, approximately 12:1 in favour of boys [282]. The right side predominated, estimated at 63.5% of cases, with the left side making up 29.0%, and 7.5% being bilateral. This distribution was similar to an earlier series from the Great Ormond Street Hospital for Sick Children, where the male-female ratio was 9:1, and 62% of inguinal herniae were on the right side, 20% on the left side, and 18% were bilateral [283].

In Budapest, between 1962–66, the prevalence of inguinal hernia to age three years, again defined by operation, was 1.1%, with a sex ratio of 8:1 in favour of boys [284]. There were 57% of herniae on the right side, 26% on the left, and 17% were bilateral.

Other studies, usually based upon paediatric surgical series, give a male to female ratio of around 8.5:1 [278]. The proportion of inguinal herniae on the right side averaged 56.9%, with 27.5% on the left side, and 15.6% bilateral [278].

It has been suggested that the predominance of right sided inguinal herniae is related to the later descent of the right testis, relative to the left testis, and the delayed obliteration of the processus vaginalis on that side [273, 283]. Consistent with this is evidence which

suggests that right sided hernia occur more frequently in boys than girls [278], and that bilateral herniae are more common among preterm babies [285].

9.5 Risk factors for inguinal hernia in childhood

Inguinal hernia is associated with congenital syndromes like chromosome 13 and 18 trisomy, and soft tissue defects like focal dermal hypoplasia [212]. Cerebral palsy has also been associated with an increased incidence of inguinal hernia [286].

There is an association between inguinal hernia and congenital cytomegalic inclusion disease (CID) [287]. The large spleen and liver associated with CID do not appear to be relevant to the aetiology of inguinal hernia because in other conditions where organs are enlarged the incidence of inguinal hernia is not raised [287]. One explanation offered was that CID and inguinal hernia are both secondary to abnormal connective tissue [287]. Alternatively, the failure of the processus vaginalis to close fully may be analogous to the arrested closure of a patent ductus or a cardiac septal foramen that is associated with the congenital rubella syndrome [287].

The most important risk factor for inguinal hernia is very low birth weight and prematurity [285, 288, 289]. Epidemiological studies clearly demonstrate an association with prematurity and low birth weight [217, 282, 284], but there are few epidemiological studies of other risk factors for inguinal hernia in childhood.

Being part of a twin delivery has been associated with inguinal hernia [217, 284]. There is evidence that risk of inguinal hernia was raised among first born children [282], but in a larger study the association was only present after controlling for maternal age [284]. Inguinal hernia has been weakly associated with older maternal and paternal age [284], but an earlier, smaller study failed to show an association with maternal age [282]. In Hungary a relative peak in births during January–March was found among cases of inguinal hernia [284], although a smaller study in Newcastle did not find any evidence for a seasonal pattern [282].

There is no evidence that parental occupation is associated with inguinal hernia [284]. Mother's Quetelet index was not associated with inguinal hernia [217]. There was evidence that progestin use, but not oestrogen use, was associated with inguinal hernia [217]. Breech labour has also been identified as a risk factor [217].

9.6 Inguinal hernia, cryptorchidism and testicular cancer

Inguinal hernia and cryptorchidism often co-exist [24, 217], so it is not surprising to find inguinal hernia significantly associated with a raised risk of testicular cancer [189, 192, 201], or raised but not significantly so [10, 191, 193, 194, 196, 202, 290]. In a review of the epidemiology of testicular cancer Buetow concluded that the relative risks observed are consistent with a two- to threefold elevation in risk [183]. In the studies that also looked at risk with cryptorchidism [10, 189, 191–194, 196, 201, 202], however, the relative risks were smaller for inguinal hernia and testicular cancer than for cryptorchidism and testicular cancer. This suggests that the association between inguinal hernia and testicular cancer may be confounded by cryptorchidism. Supporting this is the observation that the association between inguinal hernia and testicular cancer is reduced if risk of testicular cancer is evaluated in boys without cryptorchidism [193, 196, 202]. In addition, a study based on a Swedish cohort of patients with cryptorchidism found almost no association between testicular cancer and inguinal hernia [205].

Chapter 10

Inguinal Hernia in Children

10.1 Introduction

An inguinal hernia in an infant is an indication for urgent surgery [277], such that most children with this condition will be captured by routine data systems at this point in time. The examination and diagnosis that leads to a surgical decision to operate is likely to have been made carefully. An operation to correct an inguinal hernia, therefore, was used to define cases of inguinal hernia in this case-control study of the prevalence of inguinal hernia and the association with prenatal exposures.

10.2 Children with a record of a repair of inguinal hernia

The Oxford Record Linkage Study (ORLS) identified 2128 boys and 388 girls up to and including five years of age, from general hospital files, who had a record of a repair of an inguinal hernia during 1970-87, and had also been born during 1970–86. By limiting the study to young children the vast majority of the herniae will be indirect [275]. Boys who had a record of an orchidopexy were subsequently removed and boys or girls with major congenital anomalies or who were part of twin or higher order deliveries were also excluded from the analysis. Each case was individually matched with up to eight controls on sex, year and hospital of delivery. Over 99% of cases had four or more matched controls. There were 1701 boys (with 12436 controls) and 347 girls (with 2577 controls) in the case group and these described in more detail in appendix J.

10.3 Identifying risk factors for inguinal hernia in boys

10.3.1 Birth weight and gestation

Table 10.1 shows prevalence ratios for inguinal hernia in boys, as defined by operation, in relation to birth weight, gestation, birth weight for gestational age, size of baby's head and retention in a special care baby unit.

The prevalence of inguinal hernia was highest among low birth weight boys, and decreased up to birth weights of 3.5–3.9 kg but not thereafter. A similar pattern was seen for gestational age and inguinal hernia; the prevalence was highest among premature boys and decreased up to 41–42 weeks.

Section 5.3.1 described the reference distribution used to derive birth weight for gestational age. Prevalence of inguinal hernia was raised amongst boys who were small for their gestational age. There was also a significant trend with birth weight for gestational age but this was mainly due to the increased prevalence among small for gestational age boys. There was a trend towards a higher prevalence of inguinal hernia with decreasing size of baby's head, and like birth weight and gestation, the prevalence increased sharply among the smallest babies. After adjusting for birth weight there was no overall association with size of baby's head ($p=0.604$), nor was the trend with size of baby's head statistically significant ($p=0.215$).

Boys who were retained within a special care baby unit had an increased prevalence of inguinal hernia. After adjusting for birth weight the association was weaker but still significant (adjusted prevalence ratio: 1.48; 95% confidence interval: 1.16–1.89).

Further analysis of birth weight and gestational age

Table 10.2 gives further details about the prevalence of inguinal hernia and the relation between birth weight and gestation, and birth weight and being small for a given gestational age. To avoid over-stratification of the data the highest two birth weight groups were collapsed. No cell used in the analysis contained less than five cases.

Birth weight remained significantly associated with inguinal hernia even after adjustment for gestation (heterogeneity: $p<0.001$; trend: $p<0.001$). The trend to greater prevalence at lower birth weights was apparent for all categories of gestational age. After adjusting for birth weight, gestational age was still significantly associated with inguinal hernia (heterogeneity: $p<0.001$; trend: $p<0.001$). There was no statistical evidence for an interaction between birth weight and gestational age ($p=0.291$).

Table 10.1: Prevalence ratios for boys with hernia operation: birth weight, gestational age, birth weight for gestational age, size of baby's head and retention in special care baby unit

Risk factor	Cases (total=1701) number	percent	Controls (total=12436) number	percent	Prevalence ratio	95% confidence interval	p-value
Birth weight (kg)							
≤2.4	166	9.8	423	3.4	2.93	2.40 – 3.58	<0.001
2.5–2.9	273	16.2	1541	12.4	1.31	1.12 – 1.53	<0.001
3.0–3.4	611	36.2	4575	36.9	1.00	baseline	
3.5–3.9	461	27.3	4274	34.5	0.80	0.71 – 0.91	<0.001
4.0 or more	178	10.5	1586	12.8	0.83	0.70 – 0.99	0.041
Not known	12		37				
* LRS[4]= 156.38, p <0.001; Trend LRS[1]= 117.37, p <0.001							
Gestation (completed weeks from date of last menstrual period)							
≤36	174	11.4	525	4.8	2.52	2.08 – 3.06	<0.001
37–38	302	19.8	2013	18.2	1.13	0.97 – 1.30	0.108
39–40	711	46.5	5398	48.9	1.00	baseline	
41–42	298	19.5	2702	24.5	0.84	0.72 – 0.97	0.017
43 or more	44	2.9	394	3.6	0.86	0.62 – 1.19	0.371
Not known	172		1404				
LRS[4]= 101.68, p <0.001; Trend LRS[1]= 72.02, p <0.001							
† Birth weight for gestational age							
LGA	147	9.6	1087	9.9	1.02	0.85 – 1.22	0.847
AGA	1181	77.3	8982	81.4	1.00	baseline	
SGA	199	13.0	960	8.7	1.56	1.32 – 1.84	<0.001
Not known	174		1407				
LRS[2]= 25.82, p <0.001; Trend LRS[1]= 14.28, p <0.001							
Size of head (cm)							
20.0–34.0	179	23.2	941	15.9	1.73	1.38 – 2.16	<0.001
34.1–35.0	186	24.1	1422	24.0	1.22	0.98 – 1.51	0.077
35.1–36.0	214	27.8	1787	30.1	1.12	0.90 – 1.38	0.306
36.1 or more	192	24.9	1783	30.1	1.00	baseline	
Not known	120		655				
Not collected	810		5848				
LRS[3]= 24.50, p <0.001; Trend LRS[1]= 21.59, p <0.001							
Retention in special care baby unit							
No	1536	90.3	11944	96.0	1.00	baseline	
Yes	165	9.7	492	4.0	2.64	2.19 – 3.18	<0.001
LRS[1]= 90.24, p <0.001							

* LRS[n]: Log-likelihood Ratio Statistic with n degrees of freedom
† LGA: Large for Gestational Age (above 90th percentile for birth weight)
† AGA: Appropriate for Gestational Age (between 10th and 90th percentile for birth weight)
† SGA: Small for Gestational Age (below 10th percentile for birth weight)
Cases individually matched with up to 8 controls on year of birth, sex and hospital of delivery

Table 10.2: Prevalence ratios for gestation and birth weight for gestational age by birth weight for boys

	Prevalence ratios (95% confidence intervals)					
	Birth weight (kg)				Adjusted for birth weight	
	≤2.4	2.5–2.9	3.0–3.4	3.5 or more		
Gestation (weeks)						
<36	4.10 (3.07–5.46)	1.66 (1.13–2.43)	1.72 (1.11–2.67)	1.22 (0.59–2.51)	1.57 (1.25–1.98)	Trend p<0.001
37–38	1.93 (1.20–3.11)	1.33 (1.02–1.73)	1.04 (0.83–1.30)	0.86 (0.64–1.16)	1.01 (0.87–1.17)	
39–40	1.70 (0.98–2.94)	1.18 (0.91–1.55)	1.00 baseline	0.91 (0.77–1.08)	1.00 baseline	
41 or more	3.84 (1.77–8.35)	1.40 (0.98–2.01)	0.84 (0.67–1.07)	0.69 (0.57–0.85)	0.85 (0.74–0.98)	
Adjusted for gestation	2.36 (1.84–3.02)	1.26 (1.06–1.49)	1.00 baseline	0.86 (0.76–0.98)		
			Trend: p<0.001			
*** Birth weight for gestational age**						
LGA	†	†	1.45 (0.72–2.92)	0.92 (0.74–1.13)	1.14 (0.93–1.40)	Trend p=0.033
AGA	3.67 (2.68–5.03)	1.43 (1.16–1.76)	1.00 baseline	0.82 (0.71–0.93)	1.00 baseline	
SGA	2.62 (1.97–3.48)	1.28 (1.03–1.59)	0.77 (0.38–1.55)	†	0.83 (0.67–1.03)	
Adjusted for birth weight for gestational age	3.37 (2.63–4.32)	1.48 (1.22–1.78)	1.00 baseline	0.81 (0.71–0.93)		
			Trend: p<0.001			

† too few or no cases in this category for appropriate analysis
* LGA: Large for gestational age
* AGA: Appropriate for gestational age
* SGA: Small for gestational age

Birth weight was still associated with an increased prevalence of inguinal hernia even after adjustment for birth weight for gestational age (heterogeneity: p<0.001; trend: p<0.001). Overall, birth weight for gestational age was no longer statistically significantly associated with inguinal hernia after adjustment for birth weight (heterogeneity: p=0.097) but there was evidence for a significant trend (p=0.033). After adjustment for birth weight, however, the trend between birth weight for gestational age and inguinal hernia was in the opposite direction to the unadjusted trend. Within any stratum of approximately constant birth weight it is those babies who have the highest gestational ages that will be classified as

Table 10.3: Prevalence ratios for boys with hernia operation: maternal age and parity

Risk factor	Cases (total=1701) number	percent	Controls (total=12436) number	percent	Prevalence ratio	95% confidence interval	p-value
Maternal age (years)							
≤19	143	8.4	977	7.9	1.07	0.88 – 1.30	0.508
20–24	522	30.7	3630	29.2	1.05	0.93 – 1.19	0.455
25–29	632	37.2	4611	37.1	1.00	baseline	
30–34	300	17.6	2381	19.2	0.92	0.79 – 1.06	0.243
35 or over	103	6.1	816	6.6	0.91	0.73 – 1.14	0.420
Not known	1		21				
* LRS[4]= 4.29, p= 0.368; Trend LRS[1]= 3.91, p= 0.048							
Parity (before this pregnancy)							
0	752	44.4	5170	41.6	1.00	baseline	
1	578	34.1	4478	36.1	0.89	0.79 – 1.00	0.052
2	236	13.9	1842	14.8	0.88	0.75 – 1.03	0.108
3 or more	129	7.6	923	7.4	0.95	0.78 – 1.16	0.622
Not known	3		14				
Not collected	3		9				
LRS[3]= 4.82, p= 0.185; Trend LRS[1]= 2.06, p= 0.151							

ast LRS[n]: Log-likelihood Ratio Statistic with n degrees of freedom
Cases individually matched with up to 8 controls on year of birth, sex and hospital of delivery

small for their gestational age. Consequently, after adjustment for birth weight, small for gestation age was acting as a proxy measure for relatively high gestational age—hence the reversed trend.

10.3.2 Maternal age and parity

Table 10.3 shows that there was a significant trend of risk of inguinal hernia with maternal age, with risk raised most among sons of teenage mothers. Adjusting for birth weight eliminated the trend (p=0.343).

It is known from the study of migration bias (results presented in chapter 3) that children of young mothers are more likely to migrate than those of older mothers, and subsequently there may be a proportionately greater deficit of young mothers among the case group; the control group will be unaffected because controls were selected at birth. Based on earlier calculations 3 the true prevalence ratio for the sons of the teenage mothers would be about 1% larger than that in table 10.3, and for maternal ages 30–34 years, it would be about 2% smaller; the other prevalence ratios would remain essentially unchanged. Thus the trend with maternal age, corrected for the migration bias, would be a little steeper but only by a

small amount.

Table 10.3 also shows that boys born to parous mothers had a reduced prevalence of inguinal hernia when compared to sons of nulliparous mothers, although overall this was not statistically significant. After adjustment for birth weight the association vanished (heterogeneity: p=0.897; trend: p=0.684).

Differential migration may have biased the strength of the association between maternal parity and inguinal hernia in sons in a similar way to that described for maternal age. Migration rates are higher than average among mothers of low parity, and subsequently there may be a proportionately greater deficit of nulliparous women among the case group. The effect of correcting for migration bias would be to increase the difference between nulliparity and parity 2 or 3 by around 3%.

10.3.3 Social class and feeding at discharge

Table 10.4 shows that there was a significant association between social class of the head of household and inguinal hernia. There was a significant trend across groups I–V (p=0.014), with the prevalence lowest among those in group I and II but similar across groups III to V. The lowest prevalence, however, was in the group classified to 'other occupations'. This group was made up of students, armed forces personnel, and after 1972, housewives. Adjusting for birth weight weakened the trend (heterogeneity: p<0.001; trend p=0.084).

Migration bias would be expected to produce a pattern similar to that seen in table 10.4 in the absence of any real association between social class and inguinal hernia. High social class families have been shown to be more mobile than families from others social class groups 3 such that there may be a deficit of inguinal hernia cases from the high social class group relative to the other groups. This difference in being able to ascertain cases would bias any comparison of the prevalence between social class groups.

Calculations show that correcting for migration bias would reduce the trend with social class such that prevalence in groups I and II would still be lower than in group III, but to a lesser degree. The prevalence ratio in the group 'other occupations' would be less extreme but still low, around 0.61 instead of 0.51. The adjustment for migration bias shows that the relation between social class and inguinal hernia was not as strong as it first appeared to be but that it probably cannot be attributed completely to migration bias.

There was no statistically significant association between feeding at discharge and inguinal hernia.

Table 10.4: Prevalence ratios for boys with hernia operation: social class and feeding at discharge

Risk factor	Cases (total=1701) number	percent	Controls (total=12436) number	percent	Prevalence ratio	95% confidence interval	p-value
Social class							
I	133	9.2	1098	10.5	0.78	0.64 – 0.95	0.013
II	285	19.7	2224	21.4	0.83	0.71 – 0.96	0.013
III	668	46.2	4369	42.0	1.00	baseline	
IV	218	15.1	1384	13.3	1.03	0.87 – 1.21	0.744
V	82	5.7	578	5.6	0.91	0.71 – 1.17	0.469
Other occupations	61	4.2	761	7.3	0.51	0.38 – 0.67	<0.001
Not known	157		1306				
Not collected	97		716				
* LRS[5]= 35.02, p <0.001							
Feeding at discharge							
Breast	696	67.6	5300	69.7	1.00	baseline	
Artificial	315	30.6	2192	28.8	1.09	0.94 – 1.26	0.257
Complement	18	1.7	114	1.5	1.18	0.71 – 1.96	0.524
Not known	33		133				
Not collected	639		4697				
LRS[2]= 1.55, p= 0.460							

* LRS[n]: Log-likelihood Ratio Statistic with n degrees of freedom
Cases individually matched with up to 8 controls on year of birth, sex and hospital of delivery

Table 10.5: Prevalence ratios for boys with hernia operation: presentation at delivery

Risk factor	Cases (total=1701) number	percent	Controls (total=12436) number	percent	Prevalence ratio	95% confidence interval	p-value
Presentation							
Breech	51	4.9	242	3.2	1.59	1.17 – 2.17	0.003
Vertex (anterior)	905	86.5	6832	89.2	1.00	baseline	
Vertex (posterior)	55	5.3	360	4.7	1.15	0.86 – 1.54	0.346
Others	35	3.3	224	2.9	1.19	0.83 – 1.71	0.348
Not known	17		88				
Not collected	638		4690				
* LRS[3]= 9.12, p= 0.028							

* LRS[n]: Log-likelihood Ratio Statistic with n degrees of freedom
Cases individually matched with up to 8 controls on year of birth, sex and hospital of delivery

10.3.4 Presentation

Breech presentation once labour has been established (table 10.5) was associated with an increased prevalence of inguinal hernia whereas vertex and the other remaining forms of

Table 10.6: Prevalence ratios for boys with hernia operation: pre-eclampsia and eclampsia during pregnancy

Risk factor	Cases (total=1701) number	Cases (total=1701) percent	Controls (total=12436) number	Controls (total=12436) percent	Prevalence ratio	95% confidence interval	p-value
Pre-eclampsia and eclampsia							
No mention	1437	84.5	10724	86.2	1.00	baseline	
Yes	264	15.5	1712	13.8	1.15	1.00 – 1.33	0.057
* LRS[1]= 3.53, p= 0.060							

* LRS[n]: Log-likelihood Ratio Statistic with n degrees of freedom
Cases individually matched with up to 8 controls on year of birth, sex and hospital of delivery

presentation were not. After adjusting for birth weight the prevalence of inguinal hernia was lower but still significantly raised for boys presenting in the breech position (adjusted prevalence ratio: 1.41; 95% CI: 1.03–1.94). Prevalence was also raised for breech delivery relative to vaginal delivery (not shown in the table, prevalence ratio: 1.74; 95% CI: 1.24–2.45) but this too was less pronounced after adjusting for birth weight (adjusted prevalence ratio: 1.48; 95% CI: 1.05–2.09).

10.3.5 Pre-eclampsia

As shown in table 10.6, any mention of pre-eclampsia or eclampsia during the mother's pregnancy was associated with a raised prevalence of inguinal hernia, but this was of borderline statistical significance. Adjusting for birth weight further reduced the association (adjusted prevalence ratio: 1.11; 95% CI: 0.96–1.29). The following results for albuminuria and maximum blood pressure, which contribute to a diagnosis of pre-eclampsia, are not shown in table 10.6. There was no significant association or trend with inguinal hernia and albuminuria (heterogeneity: p=0.429; trend p=0.193), and there was only weak evidence for an association with maximum systolic (heterogeneity: p=0.068; trend p=0.993) and diastolic (heterogeneity: p=0.088; trend: p=0.803) blood pressure.

10.3.6 Other complications of pregnancy

Table 10.7 shows that vomiting during pregnancy was not associated with a raised prevalence of inguinal hernia. Maternal blood transfusion was associated with a raised prevalence of inguinal hernia, as was any mention of haemorrhage, abruptio placentae or placenta praevia, but Rhesus incompatibility between mother and child (not shown in the table) was not

Table 10.7: Prevalence ratios for boys with hernia operation: selected complications of pregnancy

Risk factor	Cases (total=1701) number	percent	Controls (total=12436) number	percent	Prevalence ratio	95% confidence interval	p-value
Vomiting during pregnancy							
No mention	1564	91.9	11423	91.9	1.00	baseline	
Yes	137	8.1	1013	8.1	1.00	0.80 – 1.24	0.972
* LRS[1]= 0.00, p= 0.972							
Blood transfusion (mother)							
No	1538	96.1	11351	97.0	1.00	baseline	
Yes	63	3.9	351	3.0	1.33	1.01 – 1.75	0.043
Not known	1		11				
Not collected	99		723				
LRS[1]= 3.86, p= 0.049							
Haemorrhage, abruptio placentae, placenta praevia							
No mention	1513	88.9	11278	90.7	1.00	baseline	
Yes	188	11.1	1158	9.3	1.22	1.03 – 1.45	0.019
LRS[1]= 5.34, p= 0.021							
Diabetes							
No mention	1699	99.9	12416	99.8	1.00	baseline	
Yes	2	0.1	20	0.2	0.74	0.17 – 3.15	0.680
LRS[1]= 0.18, p= 0.668							

* LRS[n]: Log-likelihood Ratio Statistic with n degrees of freedom
Cases individually matched with up to 8 controls on year of birth, sex and hospital of delivery

(prevalence ratio: 1.06; 95% CI: 0.88–1.27). There was no significant association between maternal diabetes and inguinal hernia in sons, although only two mothers of cases had diabetes mentioned on their maternity record.

10.3.7 Other risk factors

Table 10.8 presents results for selected other perinatal risk factors. The prevalence of inguinal hernia was not significantly raised among boys delivered by caesarean section. The prevalence of inguinal hernia among boys whose mothers smoked during pregnancy was significantly higher than that among boys whose mothers did not. This association was still significant after adjusting for social class (adjusted prevalence ratio: 1.39; 95% CI: 1.17–1.65) or birth weight (adjusted prevalence ratio: 1.29; 95% CI: 1.10–1.52). There were no overall significant associations between inguinal hernia and a diagnosis of obesity during pregnancy, or maternal body mass index. There was a significant trend towards

Table 10.8: Prevalence ratios for boys with hernia operation: other risk factors

Risk factor	Cases (total=1701) number	percent	Controls (total=12436) number	percent	Prevalence ratio	95% confidence interval	p-value
Caesarean section							
No mention	1550	91.1	11484	92.3	1.00	baseline	
Yes	151	8.9	952	7.7	1.18	0.98 – 1.42	0.074
* LRS[1]= 3.09, p= 0.079							
Smoking during pregnancy							
No	575	68.2	4581	75.4	1.00	baseline	
Yes	268	31.8	1492	24.6	1.45	1.24 – 1.70	<0.001
Not known	123		955				
Not collected	735		5408				
LRS[1]= 20.77, p <0.001							
Diagnosis of obesity							
No mention	1691	99.4	12329	99.1	1.00	baseline	
Yes	10	0.6	107	0.9	0.69	0.36 – 1.32	0.259
LRS[1]= 1.41, p= 0.235							
Body Mass Index (kg/m^2)							
≤19.9	67	8.2	515	8.7	0.85	0.65 – 1.13	0.269
20.0–24.9	502	61.2	3348	56.6	1.00	baseline	
25.0–29.9	199	24.3	1629	27.5	0.83	0.69 – 0.98	0.033
30.0–34.5	45	5.5	354	6.0	0.87	0.62 – 1.20	0.385
35.0 or more	7	0.9	73	1.2	0.67	0.31 – 1.48	0.324
Not known	100		802				
Not collected	781		5715				
LRS[4]= 6.10, p= 0.192; Trend LRS[1]= 2.07, p= 0.150							
Apgar score							
10–8 (good)	1133	76.2	8663	79.2	1.00	baseline	
7–4	262	17.6	1667	15.2	1.21	1.05 – 1.40	0.009
3–0 (bad)	91	6.1	604	5.5	1.32	0.97 – 1.79	0.073
Not known	118		786				
Not collected	97		716				
LRS[2]= 8.94, p= 0.011; Trend LRS[1]= 8.67, p= 0.003							

* LRS[n]: Log-likelihood Ratio Statistic with n degrees of freedom
Cases individually matched with up to 8 controls on year of birth, sex and hospital of delivery

higher prevalence of inguinal hernia with poorer Apgar score, but adjusting for birth weight weakened this association (heterogeneity: p=0.170; trend; p=0.077).

Other risk factors were also examined but are not shown because none of the results were statistically significant or notable. For example, there was no association between inguinal hernia and maternal height, weight, systolic or diastolic blood pressure at the first ante-natal visit. Nor were there associations with episiotomy, duration of labour, mother's

blood group, failure of contraceptive or resuscitation of baby with oxygen. There was no evidence of a seasonal pattern in the month of birth of the cases, either when testing for departure from a uniform distribution (p=0.150) or when fitting a sinusoidal seasonal pattern (p=0.228).

Table 10.9: Prevalence ratios for boys with hernia operation: birth weight by age at operation

	Age at operation					All ages
	0–90 days	91–180 days	181 days <1 year	1–2 years	3–5 years	0–5 years
Birth weight (kg)						
≤2.4	5.55 (3.57–8.64)	6.04 (4.05–9.01)	2.18 (1.26–3.78)	1.00 (0.59–1.68)	2.08 (1.28–3.39)	2.93 (2.40–3.58)
2.5–2.9	1.49 (1.05–2.10)	1.76 (1.22–2.54)	0.94 (0.61–1.46)	1.35 (1.01–1.80)	1.08 (0.77–1.51)	1.31 (1.12–1.53)
3.0–3.4	1.00 baseline	1.00 baseline	1.00 baseline	1.00 baseline	1.00 baseline	1.00 baseline
3.5–3.9	0.78 (0.57–1.05)	0.89 (0.65–1.23)	0.75 (0.54–1.04)	0.72 (0.57–0.92)	0.91 (0.70–1.19)	0.80 (0.71–0.91)
4.0 or more	0.38 (0.22–0.66)	0.83 (0.52–1.30)	)0.90 (0.57–1.41)	1.19 (0.89–1.61)	0.72 (0.49–1.07)	0.83 (0.70–0.99)
* LRS[4]	92.91	95.13	12.67	19.42	13.23	156.38
p-value	<0.001	<0.001	0.013	<0.001	0.010	<0.001
Trend LRS[1]	79.33	70.80	6.51	2.71	9.84	117.37
p-value	<0.001	<0.001	0.011	0.100	0.002	<0.001

* LRS[n]: Log-likelihood Ratio Statistic with n degrees of freedom
Cases individually matched with up to 8 controls on year of birth, sex and hospital of delivery

10.3.8 Stratification by age of operation

Birth weight

Table 10.9 shows the association between birth weight and inguinal hernia stratified by age at operation. The association between birth weight and inguinal hernia was strongest among those boys operated on by age 180 days (i.e. before six months of age.) At older ages the association with birth weight was not as pronounced but, with the possible exception of ages 1–2 years, there remained an association between higher prevalence and lower birth weight. Overall the difference in the pattern of prevalence ratios between age groups was significant ($p<0.001$). The trend with birth weight was also significantly different by age group ($p<0.001$).

Gestational age

Table 10.10 shows a similar association between gestational age and age at operation. The association with gestational age was strongest at younger ages of operation, and at older

Table 10.10: Prevalence ratios for boys with hernia operation: gestational age by age at operation

	Age at operation					All ages
	0–90 days	91–180 days	181 days <1 year	1–2 years	3–5 years	0–5 years
Gestational age (completed weeks)						
≤36	3.65 (2.36–5.63)	6.12 (4.11–9.11)	2.03 (1.21–3.42)	1.14 (0.73–1.77)	1.74 (1.09–2.78)	2.52 (2.08–3.06)
37–38	1.72 (1.24–2.38)	1.20 (0.85–1.70)	0.94 (0.63–1.40)	0.91 (0.69–1.21)	1.10 (0.81–1.51)	1.13 (0.97–1.30)
39–40	1.00 baseline	1.00 baseline	1.00 baseline	1.00 baseline	1.00 baseline	1.00 baseline
41–42	0.79 (0.54–1.15)	0.72 (0.49–1.07)	0.74 (0.51–1.07)	0.76 (0.58–0.99)	1.15 (0.86–1.54)	0.84 (0.72–0.97)
42 or more	1.07 (0.53–2.14)	1.23 (0.61–2.47)	0.57 (0.22–1.47)	0.82 (0.43–1.56)	0.75 (0.36–1.59)	0.86 (0.62–1.19)
* LRS[4]	44.77	91.17	12.72	5.34	6.29	101.68
p-value	<0.001	<0.001	0.013	0.254	0.178	<0.001
Trend LRS[1]	36.22	57.18	9.00	2.57	1.76	72.02
p-value	<0.001	<0.001	0.003	0.109	0.185	<0.001

* LRS[n]: Likelihood Ratio Statistic with n degrees of freedom
Cases individually matched with up to 8 controls on year of birth, sex and hospital of delivery

ages it was weaker and no longer statistically significant. Overall the difference in the pattern of the prevalence ratios was significant ($p<0.001$), as was the difference in the trend with gestational age ($p<0.001$).

Special care baby unit

A similar pattern was seen with being retained in a special care baby unit. Table 10.11 shows that being retained in a special care baby unit was more strongly associated with an operation for inguinal hernia at younger than at older ages. The interaction, or difference between the prevalence ratios across age groups, was significant ($p<0.001$).

Social class

The association between social class and inguinal hernia is shown by age at operation in table 10.12. At the younger ages there was little evidence for an association between social class and inguinal hernia, but at older ages there was a relatively lower prevalence of inguinal hernia among social class group I, and also in the group classified to 'other

Table 10.11: Prevalence ratios for boys with hernia operation: retention in special care baby unit by age at operation

	Age at operation					All ages
	0–90 days	91–180 days	181 days <1 year	1–2 years	3–5 years	0–5 years
Retention in special care baby unit						
No	1.00 baseline	1.00 baseline	1.00 baseline	1.00 baseline	1.00 baseline	1.00 baseline
Yes	4.66 (3.17–6.83)	6.18 (4.25–8.99)	2.10 (1.23–3.58)	0.89 (0.55–1.43)	1.79 (1.10–2.90)	2.64 (2.19–3.18)
* LRS[1]	53.87	80.55	6.61	0.24	4.97	90.24
p-value	<0.001	<0.001	0.010	0.627	0.026	<0.001

* LRS[n]: Log-likelihood Ratio Statistic with n degrees of freedom
Cases individually matched with up to 8 controls on year of birth, sex and hospital of delivery

Table 10.12: Prevalence ratios for boys with hernia operation: social class by age at operation

	Age at operation					All ages
	0–90 days	91–180 days	181 days <1 year	1–2 years	3–5 years	0–5 years
Social class						
I	1.00 (0.66–1.50)	1.18 (0.75–1.86)	0.66 (0.37–1.17)	0.71 0.48–1.06)	0.50 (0.31–0.80)	0.78 (0.64–0.95)
II	0.82 (0.58–1.16)	0.78 (0.54–1.13)	0.76 (0.52–1.13)	1.05 0.79–1.39)	0.69 (0.49–0.95)	0.83 (0.71–0.96)
III	1.00 baseline	1.00 baseline	1.00 baseline	1.00 baseline	1.00 baseline	1.00 baseline
IV	0.79 (0.52–1.21)	1.18 (0.79–1.76)	0.81 (0.52–1.27)	1.19 0.88–1.62)	1.09 (0.77–1.54)	1.03 (0.87–1.21)
V	0.71 (0.37–1.36)	0.84 (0.44–1.58)	1.32 (0.75–2.34)	0.94 0.59–1.49)	0.85 (0.49–1.46)	0.91 (0.71–1.17)
Other occupations	0.61 (0.35–1.06)	0.83 (0.45–1.52)	0.66 (0.35–1.25)	0.34 0.18–0.64)	0.30 (0.14–1.62)	0.51 (0.38–0.67)
* LRS[5]	5.19	4.67	6.57	20.80	26.28	35.02
p-value	0.394	0.458	0.254	<0.001	<0.001	<0.001

* LRS[n]: Log-likelihood Ratio Statistic with n degrees of freedom
Cases individually matched with up to 8 controls on year of birth, sex and hospital of delivery

occupations'. Overall the interaction between age at operation and social class was not significant (p=0.099), but the trend across social class groups I to V was different at different ages (p<0.001).

Part of the difference between the age groups for the association between social class and inguinal hernia may be attributed to migration bias. Few boys with an inguinal hernia present at 0–90 days after birth will have had the chance to migrate out of Oxfordshire or West Berkshire before they were operated upon. Boys presenting with an inguinal hernia at older ages, however, may have had the chance to migrate out of the study region and so be operated upon in a hospital outside of the ascertainment of the ORLS. Chapter 3 showed that social class I families and those in the group 'other occupations' were more mobile than the other classes. The result would be a deficit of cases, and hence a lower prevalence, in social class I and the 'other occupations' relative to the other groups. Thus the association between social class and inguinal hernia would be least affected by migration bias at younger ages, and most affected at older ages. Calculations show, however, that correcting for the migration bias would not be able to account for most of the social class association with inguinal hernia.

Presentation at delivery and maternal blood transfusion

There was a significant interaction between presentation and age at operation (p=0.027), as shown in table 10.13. Breech presentation was a strong risk factor for inguinal hernia when the age at operation was 91 days to 1 year, but was weaker at older ages.

There was a significant interaction between maternal blood transfusion and age group for inguinal hernia (p=0.029). As shown in table 10.13, maternal blood transfusion only statistically significantly associated with inguinal hernia for operations at ages 1–2 years.

Other risk factors

There were no significant interactions between the other previously identified risk factors for inguinal hernia and age at operation: smoking (p=0.265); haemorrhage, abruptio placentae, placenta praevia (p=0.483); and Apgar score (heterogeneity: p=0.477; trend: p=0.242).

Table 10.13: Prevalence ratios for boys with hernia operation: presentation and maternal blood transfusion by age at operation

	Age at operation					All ages
	0-90 days	91–180 days	181 days <1 year	1–2 years	3–5 years	0–5 years
Presentation						
Breech	1.10 (0.54–2.24)	2.19 (1.16–4.11)	3.87 (1.94–7.72)	1.45 (0.69–3.02)	0.81 (0.36–1.80)	1.59 (1.17–2.17)
Vertex (anterior)	1.00 baseline	1.00 baseline	1.00 baseline	1.00 baseline	1.00 baseline	1.00 baseline
Vertex (posterior)	1.38 (0.75–2.56)	1.57 (0.88–2.81)	1.59 (0.73–3.48)	0.92 (0.48–1.77)	0.67 (0.32–1.40)	1.15 (0.86–1.54)
Other	1.02 (0.43–2.41)	0.99 (0.39–2.53)	2.60 (1.05–6.40)	1.66 (0.91–3.02)	0.40 (0.12–1.31)	1.19 (0.83–1.71)
* LRS[3]	1.04	7.01	16.38	3.42	4.32	9.12
p-value	0.791	0.072	<0.001	0.331	0.229	0.028
Maternal blood transfusion						
No	1.00 baseline	1.00 baseline	1.00 baseline	1.00 baseline	1.00 baseline	1.00 baseline
Yes	1.30 (0.70–2.42)	1.65 (0.87–3.12)	1.23 (0.53–2.84)	2.14 (1.34–3.41)	0.56 (0.27–1.17)	1.33 (1.01–1.75)
LRS[1]	0.64	2.12	0.23	8.90	2.79	3.86
p-value	0.424	0.146	0.634	0.003	0.095	0.049

* LRS[n]: Log-likelihood Ratio Statistic with n degrees of freedom

Cases individually matched with up to 8 controls on year of birth, sex and hospital of delivery

10.4 Multivariate analyses

10.4.1 Selection of risk factors

The previous section identified low birth weight, short gestational age, retention in a special care baby unit, social class, breech presentation, maternal blood transfusion, and smoking during pregnancy as risk factors for inguinal hernia in boys. These variables were included in the multivariate analyses, and the results were also adjusted for maternal age and, where appropriate, parity.

Although parity was not identified as a risk factor in the univariate analyses it was of *a-priori* interest to stratify on it in the analyses for the same reasons as in the study of cryptorchidism: first and subsequent pregnancies may be hormonally and endocrinologically different from each other.

Being small for gestational age, size of baby's head, haemorrhage, abruptio placentae, placenta praevia, and Apgar score were also associated with risk of inguinal hernia. These variables, however, were not significant after adjusting for birth weight and, therefore, were not included in the multivariate analyses.

10.4.2 Multivariate model

Table 10.14 presents results of multivariate analyses with stratification by parity, using similar methods to those described in section 7.4.2. Any 'missing data' or 'not collected' data items were grouped into one exposure level, except for birth weight and parity where there were too few missing values to make a useful category. All exposure levels used in the analyses contained at least five cases.

The difference between the risk of inguinal hernia between 'nulliparous' and 'parous' was assessed by testing the statistical interaction between parity and the risk factor. Most of the differences were likely to be due to chance variation. At $p<0.15$, a level sometimes used to test for interactions [239], there was a suggestion that two interactions with parity (birth weight and gestational age) were worth further consideration.

Each variable in table 10.14 was adjusted for all other variables in the table. Changes of more than $\pm 10\%$ from the unadjusted prevalence ratios to the multivariate adjusted values are commented upon below.

10.4.3 Multivariate results

There were downward changes of 24%–38% from unadjusted to adjusted values for the prevalence ratios for low birth weight (≤2.4 kg) in each of the three analyses presented in table 10.14. Birth weight, and the trend with birth weight, remained significantly associated with inguinal hernia even after adjustment for the other variables in the model. The interaction between birth weight and parity (p=0.103) was suggestive of a difference in prevalence ratios for inguinal hernia by parity. More specifically, the difference by parity for the group '2.5–2.9 kg' was significant (p=0.034).

For gestational age there were downward changes, from unadjusted to adjusted prevalence ratios, of 42%–44% for prematurity (≤36 weeks gestation), and downward changes of 8%–16% for the next shortest length of gestation (37–38 weeks). Overall, gestational age remained significantly associated with inguinal hernia expect in the 'nulliparous' group, where risk was raised at low and high gestational ages. The interaction between gestational age and parity (p=0.049) was suggestive of a difference by parity. In particular, there was a noticeable difference by parity for gestational ages of 43 or more weeks (p=0.008).

The prevalence ratios for inguinal hernia and being retained in a special care baby unit decreased by 48%–51% from their unadjusted values. Among the sons of nulliparous mothers risk was significantly raised with retention in a special care baby unit, but this was not significant among sons of parous mothers. There was, however, no strong evidence for an interaction by parity (p=0.378).

Overall maternal age was not significantly associated with inguinal hernia and none of the adjusted prevalence ratios changed by more than 10% from their unadjusted values. Among parous mothers there was a significantly raised risk among teenage mothers and a significant trend with age. The interaction with parity (p=0.068) was suggestive of a difference in prevalence ratios by parity.

Social class remained significantly associated with inguinal hernia when stratified by parity, but this was mostly due to the low prevalence in the group 'other occupations'. In the 'parous' group the greatest changes were 12% downward and 11% upward from unadjusted to adjusted values for social class groups I and V respectively, but all other changes were less than 10% in magnitude. The prevalence ratios were similar by parity and there was no evidence for an interaction (p=0.517). The trends across groups I–V were not significant (nulliparous: p=0.093; parous: p=0.974; all parities: p=0.161).

The prevalence ratios associated with breech presentation decreased by 16%–24% from their unadjusted values. Breech presentation was no longer significantly associated with

inguinal hernia. Although the risk was raised among sons of parous mothers but not nulliparous mothers, there was no evidence for an interaction (p=0.344).

Maternal blood transfusion was not significantly associated with inguinal hernia after adjusting for the other risk factors in the multivariate analyses presented in table 10.14. The prevalence ratio for blood transfusion was reduced by 9%–16% in the multivariate analyses when compared to the unadjusted values. There was no indication of interaction with parity (p=0.393).

The prevalence ratios for maternal smoking during pregnancy decreased by 11% from the unadjusted to adjusted value in the 'parous' group; the other changes were less than 10%. Only the risks for 'parous' and 'all parities' were significantly raised and the interaction between parity and smoking was not significant (p=0.425).

Table 10.14: Multivariate analysis: prevalence ratios for boys with inguinal hernia—stratification by maternal parity

Risk factor	Nulliparous		Parous		All parities	
	Prevalence ratio	95% confidence interval	Prevalence ratio	95% confidence interval	Prevalence ratio	95% confidence interval
Parity						
Nulliparous					1.00	baseline
Parous					0.95	0.85–1.06
					* LRS[1]= 0.82, p=0.364	
Birth weight (kg)						
≤2.4	2.08	1.38–3.13	2.39	1.56–3.69	1.99	1.53–2.59
2.5–2.9	1.44	1.12–1.86	1.03	0.81–1.31	1.20	1.03–1.41
3.0–3.4	1.00	baseline	1.00	baseline	1.00	baseline
3.5–3.9	0.94	0.75–1.18	0.81	0.68–0.97	0.84	0.74–0.96
4.0 or more	1.03	0.73–1.45	0.91	0.72–1.16	0.89	0.74–1.07
	LRS[4]= 19.45, p=0.001 Trend LRS[1]= 12.16, p=0.001		LRS[4]= 24.11, p<0.001 Trend LRS[1]= 10.24, p=0.001		LRS[4]= 42.79, p<0.001 Trend LRS[1]= 29.73, p<0.001	
Gestation (weeks)						
≤36	1.49	1.02–2.16	1.23	0.84–1.79	1.46	1.16–1.85
37–38	0.94	0.72–1.24	1.06	0.86–1.31	1.01	0.87–1.18
39–40	1.00	baseline	1.00	baseline	1.00	baseline
41–42	0.90	0.71–1.14	0.75	0.60–0.93	0.84	0.72–0.97
43 or more	1.44	0.89–2.31	0.55	0.31–0.95	0.85	0.61–1.18
† Missing	0.95	0.67–1.35	0.81	0.61–1.08	0.86	0.70–1.05
	LRS[5]= 9.05, p=0.107		LRS[5]= 9.05, p=0.016		LRS[5]= 21.93, p=0.001	
Retention in special care baby unit						
No	1.00	baseline	1.00	baseline	1.00	baseline
Yes	1.66	1.10–2.52	1.12	0.74–1.68	1.31	1.01–1.70
	LRS[1]= 5.63, p=0.018		LRS[1]= 0.25, p=0.614		LRS[1]= 4.14, p=0.042	

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Table 10.14: continued from previous page

Risk factor	Nulliparous		Parous		All parities	
	Prevalence ratio	95% confidence interval	Prevalence ratio	95% confidence interval	Prevalence ratio	95% confidence interval
Maternal age (years)						
≤19	0.82	0.61–1.10	1.63	1.03–2.59	1.02	0.82–1.26
20–24	0.93	0.75–1.16	1.03	0.85–1.25	1.02	0.89–1.16
25–29	1.00	baseline	1.00	baseline	1.00	baseline
30–34	1.16	0.86–1.57	0.88	0.72–1.07	0.95	0.82–1.11
35 or over	0.95	0.52–1.73	0.89	0.67–1.17	0.90	0.72–1.14
	LRS[4]= 3.84, p=0.428 Trend LRS[1]= 2.92, p=0.087		LRS[4]= 24.11, p<0.001 Trend LRS[1]= 10.24, p=0.001		LRS[4]= 1.43, p=0.839 Trend LRS[1]= 1.16, p=0.281	
Social class						
I	0.78	0.55–1.11	0.83	0.62–1.12	0.84	0.68–1.03
II	0.84	0.64–1.10	0.94	0.76–1.17	0.89	0.76–1.04
III	1.00	baseline	1.00	baseline	1.00	baseline
IV	1.17	0.87–1.58	0.99	0.78–1.25	1.01	0.86–1.20
V	0.92	0.59–1.43	0.68	0.47–0.98	0.85	0.66–1.09
Other	0.52	0.33–0.79	0.52	0.35–0.78	0.49	0.37–0.65
† Missing	0.75	0.53–1.04	0.73	0.54–0.99	0.74	0.60–0.91
	LRS[6]= 21.13, p=0.007		LRS[6]= 16.81, p=0.010		LRS[6]= 36.21, p<0.001	
Presentation						
Breech	0.88	0.51–1.53	1.50	0.92–2.45	1.30	0.94–1.79
Not breech	1.00	baseline	1.00	baseline	1.00	baseline
† Missing	0.74	0.23–2.32	1.51	0.72–3.17	1.29	0.75–2.22
	LRS[2]= 0.32, p=0.850		LRS[2]= 3.27, p=0.195		LRS[2]= 3.14, p=0.208	
Maternal blood transfusion						
No	1.00	baseline	1.00	baseline	1.00	baseline
Yes	0.83	0.53–1.29	1.38	0.89–2.14	1.22	0.92–1.62
† Missing	1.12	0.22–5.62	2.17	0.19–24.54	1.54	0.45–5.32
	LRS[2]= 0.53, p=0.766		LRS[2]= 2.30, p=0.317		LRS[2]= 2.25, p=0.325	
Smoking during pregnancy						
No	1.00	baseline	1.00	baseline	1.00	baseline
Yes	1.18	0.89–1.57	1.41	1.11–1.78	1.32	1.12–1.55
† Missing	0.91	0.47–1.75	1.04	0.64–1.68	0.88	0.62–1.25
	LRS[2]= 1.28, p=0.528		LRS[2]= 9.64, p=0.008		LRS[2]= 12.29, p=0.002	

* LRS[n]: Log-likelihood Ratio Statistic with n degrees of freedom
† Missing includes 'Not known' and 'Not collected'
All variables adjusted for other variables in table
Cases individually matched with up to 8 controls on year of birth, sex and hospital of delivery

Analysis by age at operation

Table 10.15 presents results stratified by age at operation. The first two and last two age groups previously used in the univariate analysis by age at operation were each combined to avoid over-stratification of the data. No exposure level contained less than five cases. Maternal blood transfusion was not included in the analysis because it was not associated with inguinal hernia in the previous multivariate analysis. Presentation was retained because in an earlier univariate analysis (table 10.13) because it exhibited an interesting association by age at operation. The results were also adjusted for maternal age and parity.

Low birth weight, short gestational age and retention in a special care baby unit were all significantly associated with risk of inguinal hernia in the youngest age group. The trend with gestational age, excluding the missing value level, was significant (p=0.001). For ages 181 days to less than one year there were no significant associations with these three variables. Risk was raised for low birth weight and premature boys, but neither of the trends were significant (gestational age trend, excluding the missing value level: p=0.133). Among the older children, aged one to five years at operation, there was a significant trend with birth weight, but not with gestational age (gestational age trend, excluding the missing value level: p=0.246), or with retention in a special care baby unit.

At ages 0–180 days and 181 days to less than one year there were no significant associations with social class (trends across groups I to V: p=0.130 and p=0.121 respectively). At ages one to five years there was a significant association with social class and the trend across groups I to V was significant (p=0.014). As mentioned in section 10.3.8 calculations showed that the bias caused by migration would not have been able to account for the association between social class and inguinal hernia at older ages.

Risk of inguinal hernia with breech presentation was only significantly raised among those boys operated upon at 181 days to less than one year of age. The only statistically significant association with maternal smoking was seen in the oldest age group, although risk was raised in the other two age groups.

Table 10.15: Multivariate analysis: prevalence ratios for boys with inguinal hernia—by age at operation

Risk factor	Age at operation					
	0–180 days		181 days–<1 year		1–5 years	
	Prevalence ratio	95% confidence interval	Prevalence ratio	95% confidence interval	Prevalence ratio	95% confidence interval
Parity						
Nulliparous	1.00	baseline	1.00	baseline	1.00	baseline
Parous	0.96	0.79–1.16	0.86	0.63–1.17	0.97	0.83–1.14
* LRS[4]= 0.21, p=0.643			LRS[4]= 0.89, p=0.345		LRS[4]= 0.13, p=0.716	
Birth weight (kg)						
≤2.4	2.88	1.96–4.24	1.66	0.77–3.58	1.34	0.85–2.09
2.5–2.9	1.38	1.06–1.80	0.92	0.58–1.44	1.19	0.95–1.50
3.0–3.4	1.00	baseline	1.00	baseline	1.00	baseline
3.5–3.9	0.90	0.72–1.13	0.81	0.57–1.14	0.82	0.68–0.98
4.0 or more	0.66	0.46–0.94	1.03	0.64–1.66	1.01	0.80–1.29
LRS[4]= 41.72, p<0.001 Trend LRS[1]= 33.64, p<0.001			LRS[4]= 3.99, p=0.407 Trend LRS[1]= 0.65, p=0.420		LRS[4]= 11.52, p=0.021 Trend LRS[1]= 4.82, p=0.028	
Gestation (weeks)						
≤36	1.90	1.32–2.75	1.45	0.77–2.73	1.19	0.82–1.72
37–38	1.22	0.95–1.56	0.86	0.56–1.31	0.93	0.75–1.16
39–40	1.00	baseline	1.00	baseline	1.00	baseline
41–42	0.75	0.57–0.99	0.73	0.50–1.07	0.92	0.76–1.12
43 or more	1.09	0.66–1.79	0.61	0.24–1.59	0.79	0.48–1.29
† Missing	0.86	0.60–1.22	1.02	0.62–1.74	0.81	0.61–1.07
LRS[5]= 22.12, p=0.001			LRS[5]= 5.98, p=0.308		LRS[5]= 4.84, p=0.436	
Retention in special care baby unit						
No	1.00	baseline	1.00	baseline	1.00	baseline
Yes	1.99	1.37–2.89	0.94	0.42–2.12	0.91	0.59–1.40
LRS[1]= 12.49, p<0.001			LRS[1]= 0.02, p=0.881		LRS[1]= 0.18, p=0.669	
Maternal age (years)						
≤19	1.03	0.72–1.48	1.04	0.60–1.82	1.04	0.77–1.42
20–24	1.14	0.92–1.43	0.78	0.54–1.12	1.02	0.85–1.23
25–29	1.00	baseline	1.00	baseline	1.00	baseline
30–34	0.91	0.70–1.18	0.81	0.53–1.21	0.99	0.80–1.22
35 or over	0.79	0.53–1.18	1.10	0.61–1.98	0.95	0.69–1.32
LRS[4]= 4.33, p=0.363 Trend LRS[1]= 3.06, p=0.081			LRS[4]= 3.27, p=0.515 Trend LRS[1]= 0.14, p=0.711		LRS[4]= 0.22, p=0.994 Trend LRS[1]= 0.21, p=0.646	
Social class						
I	1.26	0.91–1.76	0.59	0.32–1.09	0.65	0.48–0.89
II	1.00	0.76–1.31	0.75	0.50–1.13	0.89	0.72–1.10
III	1.00	baseline	1.00	baseline	1.00	baseline
IV	0.98	0.73–1.33	0.78	0.49–1.24	1.12	0.89–1.41
V	0.64	0.40–1.03	1.18	0.65–2.14	0.87	0.61–1.25
Other	0.70	0.45–1.08	0.61	0.32–1.17	0.33	0.20–0.53
† Missing	0.99	0.70–1.40	0.46	0.24–0.88	0.69	0.52–0.92
LRS[6]= 9.08, p=0.169			LRS[6]= 11.38, p=0.077		LRS[6]= 41.99, p<0.001	
Presentation						
Breech	1.23	0.74–2.04	2.74	1.31–5.73	1.06	0.61–1.82
Not breech	1.00	baseline	1.00	baseline	1.00	baseline
† Missing	1.78	0.78–4.04	2.46	0.90–6.74	0.40	0.09–1.67
LRS[2]= 2.29, p=0.318			LRS[2]= 8.78, p=0.012		LRS[2]= 2.15, p=0.342	
Smoking during pregnancy						
No	1.00	baseline	1.00	baseline	1.00	baseline
Yes	1.20	0.92–1.57	1.34	0.85–2.13	1.37	1.07–1.74
† Missing	0.78	0.42–1.44	0.89	0.30–2.62	0.95	0.59–1.53
LRS[2]= 2.86, p=0.239			LRS[2]= 1.70, p=0.427		LRS[2]= 6.69, p=0.035	

* LRS[n]: Log-likelihood Ratio Statistic with n degrees of freedom
† Missing includes 'Not known' and 'Not collected'
All variables adjusted for other variables in table
Cases individually matched with up to 8 controls on year of birth, sex and hospital of delivery

10.5 Discussion of case-control study in boys

Low birth weight, short gestation, retention in a special care baby unit, low social class and smoking during pregnancy were identified as risk factors for inguinal hernia to age five years among boys, after univariate and multivariate analyses. Analyses by parity showed some differences by parity in the pattern of risk of inguinal hernia with birth weight, gestational age and maternal age. Breech presentation, maternal blood transfusion and a mention of haemorrhage, abruptio placenta, or placenta praevia were also identified as risk factors, but after adjusting for the above variables they showed no significant associations with inguinal hernia. The age at which the subject was operated upon strongly modified the association between risk of inguinal hernia and both birth weight and gestational age. In multivariate analyses, birth weight, gestational age and retention in a special care baby unit were more strongly associated with risk of inguinal hernia at younger than older ages at operation.

Previous studies of risk factors for inguinal hernia have usually been smaller, mainly examined birth weight and gestational age, and not looked at other risk factors in detail, and not by age at operation. Some of the results of this study, therefore, are new and may give insights into the aetiology of inguinal hernia, and its relation to cryptorchidism and testicular cancer. First, however, it is necessary to consider the limitations of this study and potential artefactual explanations for the observed results.

10.5.1 The operation for inguinal hernia

This study used a mention of an operation for inguinal hernia in children up to and including five years of age to define cases. There was a concurrent diagnosis of inguinal hernia among 99% of the cases, which provided corroboration that the mention of the operation was not a coding or data extraction error. Excluding the 20 boys without a corresponding diagnosis of inguinal hernia would not have changed the results materially, although the absence of a diagnosis code does not imply the operation code for these boys was necessarily in error.

An inguinal hernia is an indication for surgery [277] and most cases are operated upon within weeks or a few months of symptoms first being notified to medical personnel [278]. Retractile or undescended testis and torsion of the spermatic cord or testis may be mistaken for an inguinal hernia [275], but before a child is operated upon the diagnosis of inguinal hernia will be carefully confirmed because this operation is not a trivial procedure. Some cases may not be true herniae in the sense that no protrusion of organ or tissue occurs, but instead fluid builds up in the inguinal canal or scrotum; a hydrocele that does not absorb and disappear will need similar treatment to an inguinal hernia [275]. Since 99% of

cases had a concurrent diagnosis of inguinal hernia, it seems likely that the overwhelming majority of cases were herniae rather than hydrocele.

Ascertaining cases with a mention of a repair of an inguinal hernia from routine general hospital records, therefore, was likely to have selected cases with true inguinal herniae. In addition, by limiting the cases to those operated upon up to age five years the vast majority of the herniae will have been indirect inguinal hernia [275].

The hernia operation was a marker for a patent processus vaginalis and the formation of an inguinal hernia that would eventually lead to diagnosis and operation by age five years. Not all children with a patent processus vaginalis will develop an inguinal hernia that is diagnosed and operated upon by age five years: the processus may fuse before an inguinal hernia can form; an inguinal hernia may occur occasionally but not be clinically diagnosed, and the processus may fuse at a later date; or the processus may be patent but an inguinal hernia may not occur by age five years. The risk factors identified in this study, therefore, were a mixture of those for a patent processus vaginalis and those that cause an inguinal hernia to occur and be operated upon.

Boys with cryptorchidism

Undescended testes and inguinal hernia often co-exist [217] because they have similar aetiology, and perhaps also in routine data sources because diagnosis or surgery to correct one leads to a greater chance of diagnosis or surgery for the other. It is possible, therefore, that a study of risk factors for inguinal hernia may also identify some of the risk factors for cryptorchidism, because in a proportion of cases both conditions are identified. To concentrate this study on risk factors for inguinal hernia, boys with a record of an orchidopexy were excluded from the case (and control) group. A mention of an orchidopexy was used as the exclusion criterion because it was considered a more reliable diagnosis of undescended testis than a diagnostic code recorded in case notes.

The aetiology of inguinal hernia among the boys with cryptorchidism may be different to that among boys without it. About 11% of boys were excluded because of an operation for undescended testis, so this group would make up only a small proportion of all boys with inguinal hernia. Groups like this, however, deserve careful further study because they might be made up of cases of inguinal hernia that would not have been operated upon in the absence of cryptorchidism, or they might represent cases that have a special causal association with cryptorchidism. In the context of this study, however, they represent a small proportion of all possible cases and are not considered further.

10.5.2 Migration bias

The influence of the bias due to migration has been discussed previously in relation to the study of children with diabetes (section 5.4.1) and undescended testes (section 8.5.2). Within this study migration bias most strongly influenced the association between inguinal hernia and social class, but previous work presented in chapter 3 allowed the size of the bias to be estimated. The other perinatal variables were not greatly influenced by migration bias.

10.5.3 Advantages and disadvantages of routine data

The advantages and disadvantages of routine data were discussed in section 5.4.3 and apply equally to this study.

10.5.4 Risk factors

Immaturity at birth

Low birth weight, short gestation and retention in a special care baby unit were all associated with increased risk of inguinal hernia. Each of these variables can be considered as a measure of immaturity at birth, and similar associations have been reported elsewhere [217, 282, 284, 285, 288, 289]. It is immature babies that would be more likely to have a patent processus vaginalis, and hence potential for an inguinal hernia.

These measures of immaturity were most strongly related to inguinal hernia among boys operated upon within six months of birth. A similar association was seen in a study in Newcastle, where the cases operated upon early in life were, on average, smaller at birth than those operated upon at later ages [282]. Premature babies that remain in hospital, perhaps in a special care baby unit, will be seen frequently by medical staff. If an inguinal hernia forms it is likely to be recognised for what it is, and appropriate action can be taken when the baby is old enough to be operated upon. Immaturity at birth, therefore, is a major predisposing factor for an inguinal hernia, and the difference by age at operation may reflect opportunity for diagnosis and subsequent operation.

Social class

Among the cases operated upon at younger ages there were no strong associations with social class. At older ages risk was decreased in social class group I and the group 'other occupations'. Migration bias would have acted to produce such an association but calculations

showed that it could probably not have accounted for all of this association. Alternatively, parents in social class group I (which contains doctors) may be more likely to notice a hernia early and to act if they discover it in their child; this in turn may lead to an operation at young age, hence the relative deficit of cases in group I at older ages. This observation, however, needs confirmation because in the one study that looked at risk by parental occupation no evidence was found for an association with inguinal hernia [284].

Smoking

Maternal smoking during pregnancy has previously been associated with raised risk of inguinal hernia in offspring [291, 292]. After adjusting for, among other things, birth weight, gestation, maternal age, parity and social class, such an association was also seen in this study.

Women who smoke during pregnancy are likely to be smokers after pregnancy, and in this environment the baby may be prone to coughing which might lead to increased or more frequent abdominal pressure resulting in an inguinal hernia. An implication of this is that sons of smokers may exhibit their inguinal hernia at an earlier age than sons of mothers who did not smoke. Maternal smoking, however, was an equally important risk factors at all ages, suggesting that smoking did not act merely to uncover a potential inguinal hernia at an early age.

Alternatively in adults, it has been suggested that smoking may be related to a defect or weakness in connective tissue and, hence, inguinal hernia [293]. Maternal smoking, however, influences other factors associated with pregnancy, like pre-eclampsia [294] and birth weight [295], and is related to some congenital malformations [291, 292]. Maternal smoking, therefore, may potentially act in a variety of ways to cause an inguinal hernia.

Further discussion

These findings will be discussed further in section 10.8, after the results for inguinal hernia among girls have been presented.

10.6 Identifying risk factors in girls

10.6.1 Birth weight and gestation

Table 10.16 shows prevalence ratios for inguinal hernia in girls in relation to birth weight, gestation, birth weight for gestational age, size of baby's head and retention in a special care baby unit.

There was an increased prevalence with low birth weight and short gestational ages, both resulting in significant overall associations and trends. After adjusting gestational age for birth weight, the overall association with gestational age was no longer significant (p=0.531) and the trend with gestational age was weaker and not significant (p=0.149). There was a strong trend in risk of inguinal hernia in relation to birth weight for gestational age, but this was mostly due to the raised prevalence among small for gestational age babies. After adjusting for birth weight the association was reversed, with highest risk among the large for gestational age babies, but this was not statistically significant.

Prevalence of inguinal hernia was raised among girls with a small head size, but this was not statistically significant. Adjusting for birth weight reduced the raised prevalence among babies with small heads (adjusted prevalence ratio: 0.75; 95% CI: 0.38–1.46). Being retained in a special care baby unit was significantly associated with an increased prevalence of inguinal hernia. After adjusting for birth weight the prevalence was still raised but this no longer significant (adjusted prevalence ratio: 1.41; 95% CI: 0.76–2.59).

These results were essentially similar to the results for boys in the magnitude of the prevalence ratios, but the smaller number of cases reduced the statistical significance of the results.

Table 10.16: Prevalence ratios for girls with hernia operation: birth weight, gestational age, birth weight for gestational age, size of baby's head and retention in special care baby unit

Risk factor	Cases (total=347) number	percent	Controls (total=2577) number	percent	Prevalence ratio	95% confidence interval	p-value
Birth weight (kg)							
≤2.4	38	11.0	96	3.7	3.21	2.10 – 4.89	<0.001
2.5–2.9	86	24.9	448	17.5	1.59	1.19 – 2.14	0.002
3.0–3.4	132	38.2	1066	41.6	1.00	baseline	
3.5–3.9	73	21.1	751	29.3	0.79	0.58 – 1.07	0.126
4.0 or more	17	4.9	203	7.9	0.67	0.39 – 1.14	0.141
Not known	1		13				
LRS[4]= 47.96, p <0.001; Trend LRS[1]= 43.33, p <0.001							
Gestation (completed weeks from date of last menstrual period)							
≤36	26	8.5	76	3.3	2.46	1.53 – 3.95	<0.001
37–38	55	17.9	342	15.0	1.23	0.88 – 1.71	0.232
39–40	155	50.5	1170	51.3	1.00	baseline	
41–42	60	19.5	585	25.6	0.78	0.57 – 1.07	0.122
43 or more	11	3.6	108	4.7	0.74	0.38 – 1.41	0.355
Not known	40		296				
LRS[4]= 19.64, p= 0.001; Trend LRS[1]= 16.79, p <0.001							
Birth weight for gestational age							
LGA	27	8.8	236	10.4	0.95	0.62 – 1.45	0.808
AGA	219	71.3	1819	79.8	1.00	baseline	
SGA	61	19.9	225	9.9	2.14	1.56 – 2.93	<0.001
Not known	40		297				
LRS[2]= 21.00, p <0.001; Trend LRS[1]= 15.31, p <0.001							
Size of head (cm)							
20.0–34.0	65	36.5	370	26.9	1.55	0.91 – 2.65	0.110
34.1–35.0	47	26.4	454	33.0	0.93	0.53 – 1.62	0.795
35.1–36.0	45	25.3	354	25.7	1.14	0.65 – 1.98	0.653
36.1 or more	21	11.8	199	14.5	1.00	baseline	
Not known	26		146				
Not collected	143		1054				
LRS[3]= 6.89, p= 0.076; Trend LRS[1]= 2.81, p= 0.094							
Retention in special care baby unit							
No	317	91.4	2497	96.9	1.00	baseline	
Yes	30	8.6	80	3.1	3.03	1.94 – 4.73	<0.001
LRS[1]= 20.48, p <0.001							

LRS[n]: Likelihood Ratio Statistic with n degrees of freedom
LGA: Large for Gestational Age (above 90th percentile for birth weight)
AGA: Appropriate for Gestational Age (between 10th and 90th percentile for birth weight)
SGA: Small for Gestational Age (below 10th percentile for birth weight)
Cases individually matched with up to 8 controls on year of birth, sex and hospital of delivery

Table 10.17: Prevalence ratios for girls with hernia operation: maternal age and parity

Risk factor	Cases (total=347) number	Cases (total=347) percent	Controls (total=2577) number	Controls (total=2577) percent	Prevalence ratio	95% confidence interval	p-value
Maternal age (years)							
≤19	23	6.6	184	7.1	0.78	0.49 – 1.25	0.308
20–24	92	26.5	726	28.2	0.80	0.61 – 1.05	0.113
25–29	149	42.9	937	36.4	1.00	baseline	
30–34	62	17.9	567	22.0	0.69	0.50 – 0.94	0.020
35 or over	21	6.1	161	6.3	0.82	0.50 – 1.34	0.431
Not known	0		2				
LRS[4]= 6.38, p= 0.173; Trend LRS[1]= 0.10, p= 0.750							
Parity (before this pregnancy)							
0	150	43.4	1064	41.4	1.00	baseline	
1	129	37.3	917	35.6	1.00	0.77 – 1.29	0.979
2	50	14.5	375	14.6	0.95	0.67 – 1.34	0.763
3 or more	17	4.9	217	8.4	0.55	0.32 – 0.93	0.025
Not known	1		2				
Not collected	0		2				
LRS[3]= 6.11, p= 0.107; Trend LRS[1]= 3.06, p= 0.080							

LRS[n]: Likelihood Ratio Statistic with n degrees of freedom
Cases individually matched with up to 8 controls on year of birth, sex and hospital of delivery

10.6.2 Maternal age and parity

There was no trend or association between prevalence of inguinal hernia in girls and maternal age, as shown in table 10.17. Adjusting for birth weight made little change to this. There was a significantly lower prevalence of inguinal hernia among girls born to mothers in the highest parity group, but overall the association and trend was not significant. Adjusting for birth weight made little change to this (adjusted prevalence ratio for parity 3 or more: 0.54; 95% CI: 0.31–0.94). As with boys, the bias due to migration was not strong enough to materially change the interpretation of these results.

Apart from the low prevalence associated with high parity these results were similar to those amongst boys.

10.6.3 Social class and feeding at discharge

Table 10.18 shows the association between inguinal hernia in girls and social class and feeding at discharge. There was an overall significant association with social class, but this was limited to the group 'other occupations'; among social class groups I to V the overall association and trend were not significant (p=0.420, p=0.771 respectively). Correcting for

Table 10.18: Prevalence ratios for girls with hernia operation: social class and feeding at discharge

Risk factor	Cases (total=347) number	Cases (total=347) percent	Controls (total=2577) number	Controls (total=2577) percent	Prevalence ratio	95% confidence interval	p-value
Social class							
I	45	14.8	261	12.0	1.23	0.84 – 1.78	0.289
II	56	18.4	458	21.0	0.85	0.61 – 1.18	0.325
III	135	44.4	937	43.0	1.00	baseline	
IV	43	14.1	273	12.5	1.11	0.77 – 1.61	0.568
V	20	6.6	111	5.1	1.20	0.72 – 2.00	0.481
Other occupations	5	1.6	141	6.5	0.25	0.10 – 0.61	0.002
Not known	23		251				
Not collected	20		145				
LRS[5]= 19.09, p= 0.002							
Feeding at discharge							
Breast	179	75.8	1261	71.9	1.00	baseline	
Artificial	53	22.5	468	26.7	0.80	0.58 – 1.11	0.183
Complement	4	1.7	24	1.4	1.22	0.42 – 3.54	0.715
Not known	4		13				
Not collected	107		811				
LRS[2]= 2.01, p= 0.365							

LRS[n]: Likelihood Ratio Statistic with n degrees of freedom
Cases individually matched with up to 8 controls on year of birth, sex and hospital of delivery

the bias due to migration would give prevalence ratios of 1.33, 0.89, 1.00, 1.09, 1.16, for groups I to V, and 0.30 for 'other occupations'; similar changes where seen among boys. These changes, however, were small with respect to the confidence intervals surrounding the estimated prevalence ratios, and the interpretation of the results is unchanged. There was no significant association with feeding at discharge, as shown in table 10.18.

10.6.4 Presentation and pre-eclampsia

The prevalence ratio for inguinal hernia was raised among girls presenting in the breech position (1.63; 95% CI: 0.95–2.80), which was similar to that for boys presenting in the breech position (1.59; 95% CI: 1.17–2.17), but because of the small numbers of cases the result for girls was not statistically significant. Adjusting for birth weight reduced the strength of the association with breech presentation (adjusted prevalence ratio: 1.29; 95% CI: 0.73–2.26). Prevalence of inguinal hernia was raised for breech delivery relative to vaginal delivery, but this was not significant (1.41; 95% CI: 0.73–2.71).

Table 10.19: Prevalence ratios for girls with hernia operation: presentation at delivery and pre-eclampsia

Risk factor	Cases (total=347) number	percent	Controls (total=2577) number	percent	Prevalence ratio	95% confidence interval	p-value
Presentation							
Breech	17	7.2	79	4.5	1.63	0.95 – 2.80	0.078
Vertex (anterior)	202	85.6	1535	87.5	1.00	baseline	
Vertex (posterior)	9	3.8	88	5.0	0.76	0.38 – 1.54	0.447
Others	8	3.4	52	3.0	1.18	0.55 – 2.51	0.668
Not known	4		15				
Not collected	107		808				
LRS[3]= 3.78, p= 0.286							
Pre-eclampsia and eclampsia							
No mention	312	89.9	2243	87.0	1.00	baseline	
Yes	35	10.1	334	13.0	0.73	0.50 – 1.07	0.107
LRS[1]= 2.76, p= 0.096							

LRS[n]: Likelihood Ratio Statistic with n degrees of freedom
Cases individually matched to 8 controls on year of birth, sex and hospital of delivery

As with boys, there was no significant association with pre-eclampsia or eclampsia.

10.6.5 Other risk factors

Table 10.20 shows results for selected other risk factors. Unlike the results for boys where there were raised risks, there were no significant associations with haemorrhage, abruptio placentae and placenta praevia, or with maternal blood transfusion. There was a raised risk if the mother had diabetes recorded on her maternity record, but the number of such subjects was small and the result was not significant.

There was a raised, but not significant, risk with caesarean section and maternal smoking during pregnancy. Overall there was no significant association with Apgar score, but there was a significantly raised prevalence among those girls with the poorest score. Adjusting for birth weight reduced this association (adjusted prevalence ratio for Apgar score 3–0: 1.59; 95% CI: 0.80–3.19). Not shown in the table, there was no evidence for a seasonal distribution in the births of cases relative to the controls (heterogeneity p=0.135; sinusoidal pattern p=0.358).

There were no significant associations among the other risk factors examined (maternal height, weight, systolic or diastolic blood pressure at the first ante-natal visit, episiotomy, duration of labour, mother's blood group, failure of contraceptive or resuscitation of baby

Table 10.20: Prevalence ratios for girls with hernia operation: other risk factors

Risk factor	Cases (total=347) number	Cases (total=347) percent	Controls (total=2577) number	Controls (total=2577) percent	Prevalence ratio	95% confidence interval	p-value
Haemorrhage, abruptio placentae, placenta praevia							
No mention	313	90.2	2335	90.6	1.00	baseline	
Yes	34	9.8	242	9.4	1.04	0.70 – 1.52	0.856
LRS[1]= 0.03, p= 0.856							
Diabetes							
No mention	345	99.4	2574	99.9	1.00	baseline	
Yes	2	0.6	3	0.1	4.92	0.82 – 29.47	0.081
LRS[1]= 2.53, p= 0.111							
Caesarean section							
No mention	318	91.6	2406	93.4	1.00	baseline	
Yes	29	8.4	171	6.6	1.27	0.84 – 1.93	0.254
LRS[1]= 1.24, p= 0.265							
Smoking during pregnancy							
No	140	72.2	1078	75.5	1.00	baseline	
Yes	54	27.8	350	24.5	1.20	0.86 – 1.68	0.293
Not known	26		196				
Not collected	127		953				
LRS[1]= 1.09, p= 0.297							
Blood transfusion (mother)							
No	321	98.2	2348	96.8	1.00	baseline	
Yes	6	1.8	78	3.2	0.55	0.24 – 1.27	0.163
Not known	148		3				
Not collected	20		148				
LRS[1]= 2.29, p= 0.130							
Apgar score							
10–8 (good)	247	81.5	1912	82.8	1.00	baseline	
7–4	38	12.5	310	13.4	0.95	0.66 – 1.37	0.785
3–0 (bad)	18	5.9	86	3.7	2.18	1.12 – 4.25	0.022
Not known	24		124				
Not collected	20		145				
LRS[2]= 4.85, p= 0.089; Trend LRS[1]= 1.57, p= 0.210							

LRS[n]: Likelihood Ratio Statistic with n degrees of freedom
Cases individually matched to 8 controls on year of birth, sex and hospital of delivery

with oxygen).

10.7 Multivariate analysis

10.7.1 Selection of risk factors

The previous section identified low birth weight, and after adjusting for birth weight, retention in a special care baby unit and social class as risk factors for inguinal hernia in girls to age five years. Other variables, like gestational age, birth weight for gestational age and Apgar score, were significant in the univariate analysis but once adjusted for birth weight they were no longer significantly associated with inguinal hernia. Some variables, like maternal age, parity and presentation at delivery were not significantly associated with inguinal hernia either before or after adjusting for birth weight. The relatively small number of cases, however, made it difficult to detect small or moderate increases in risk as statistically significant. The approach adopted, therefore, was to use the same set of risk factors that were used in table 10.15 from the study of inguinal hernia among boys.

10.7.2 Multivariate results

Table 10.21 presents the results from the multivariate model. The variables in the table were adjusted for all the other variables shown. There was a downward change of 26% for low birth weight ($\leq$2.4 kg) and changes of less than 5% for the other groups when the adjusted prevalence ratios were compared with the unadjusted ones. Birth weight, however, remained significantly associated with risk of inguinal hernia among girls. There were no statistically significant associations with gestational age; excluding the missing value level the trend with gestational age was not significant (p=0.144). In the two groups of shortest gestational ages the prevalence ratios were reduced by 43% and 21% respectively, and, although not statistically significant, prevalence was still raised at $\leq$36 weeks of gestation.

The adjusted prevalence ratio for retention in a special care baby unit decreased by 57% from its unadjusted value and was not statistically significant. There were no significant associations with maternal age and none of the prevalence ratios changed by more than 10%. The only large change in the prevalence ratios for social class was of 13% for group V. Overall social class was significantly associated with risk of inguinal hernia but this was mostly limited to the 'other' and 'missing' groups. Across groups I to V the trend with social class was not significant (p=0.717).

The adjusted prevalence ratio for breech presentation decreased by 30% from its unadjusted value. There were no significant associations with presentation. The prevalence ratio for the 'missing' group for smoking during pregnancy increased by 12% from its unadjusted

Table 10.21: Multivariate analysis: prevalence ratios for girls with inguinal hernia

Risk factor	Cases (total=345) number	percent	Controls (total=2558) number	percent	Prevalence ratio	95% confidence interval	p-value
Parity							
Nulliparous	150	43.5	1057	41.3	1.00	baseline	
Parous	195	56.5	1501	58.7	0.92	0.72 – 1.19	0.545
* LRS[1]= 0.37, p=0.545							
Birth weight (kg)							
≤2.4	38	11.0	96	3.8	2.40	1.34 – 4.31	0.003
2.5–2.9	86	24.9	447	17.5	1.53	1.13 – 2.07	0.006
3.0–3.4	131	38.0	1064	41.6	1.00	baseline	
3.5–3.9	73	21.2	749	29.3	0.82	0.60 – 1.11	0.202
4.0 or more	17	4.9	202	7.9	0.70	0.41 – 1.20	0.193
LRS[4]= 20.60, p<0.001; Trend LRS[1]= 18.90, p<0.001							
Gestation (weeks)							
≤36	26	7.5	76	3.0	1.44	0.81 – 2.56	0.212
37–38	54	15.7	339	13.3	0.96	0.67 – 1.36	0.815
39–40	155	44.9	1166	45.6	1.00	baseline	
41–42	60	17.4	582	22.8	0.83	0.60 – 1.15	0.263
43 or more	11	3.2	106	4.1	0.74	0.38 – 1.44	0.377
† Missing	39	11.3	289	11.3	1.08	0.71 – 1.65	0.712
LRS[5]= 4.31, p=0.506							
Retention in special care baby unit							
No	316	91.6	2480	97.0	1.00	baseline	
Yes	29	8.4	78	3.0	1.28	0.67 – 2.42	0.457
LRS[1]= 0.55, p=0.460							
Maternal age (years)							
≤19	23	6.7	184	7.2	0.81	0.49 – 1.36	0.429
20–24	92	26.7	724	28.3	0.77	0.57 – 1.04	0.085
25–29	147	42.6	928	36.3	1.00	baseline	
30–34	62	18.0	564	22.0	0.69	0.50 – 0.95	0.023
35 or over	21	6.1	158	6.2	0.89	0.54 – 1.48	0.652
LRS[4]= 6.47, p= 0.167; Trend LRS[1]= 0.01, p=0.908							
Social class							
I	45	13.0	261	10.2	1.28	0.86 – 1.89	0.228
II	56	16.2	453	17.7	0.88	0.62 – 1.25	0.477
III	133	38.6	928	36.3	1.00	baseline	
IV	43	12.5	273	10.7	1.03	0.70 – 1.51	0.872
V	20	5.8	111	4.3	1.09	0.64 – 1.85	0.747
Other	5	1.4	141	5.5	0.24	0.10 – 0.61	0.003
† Missing	43	12.5	391	15.3	0.56	0.33 – 0.95	0.031
LRS[6]= 22.48, p= 0.001							
Presentation							
Breech	17	4.9	77	3.0	1.20	0.67 – 2.13	0.542
Not breech	218	63.2	1667	65.2	1.00	baseline	
† Missing	110	31.9	814	31.8	2.00	0.61 – 6.54	0.251
LRS[2]= 1.52, p=0.468							
Smoking during pregnancy							
No	140	40.6	1075	42.0	1.00	baseline	
Yes	53	15.4	347	13.6	1.13	0.79 – 1.61	0.516
† Missing	152	44.1	1136	44.4	1.22	0.58 – 2.55	0.600
LRS[2]= 0.60, p=0.741							

* LRS[n]: Log-likelihood Ratio Statistic with n degrees of freedom
† Missing includes 'Not known' and 'Not collected'
All variables adjusted for other variables in table
Cases individually matched with up to 8 controls on year of birth, sex and hospital of delivery

value, but there were no significant associations with risk of inguinal hernia.

10.7.3 Analysis by age at operation

Table 10.22 presents results stratified by age at operation. There were too few cases to allow the youngest age group to be further sub-divided, as was done for boys. In the social class group 'other occupations' there were only two and three cases respectively among those operated upon at less than one year of age and one to five years of age, and there were only two cases in the gestational age class '4.0 or more' weeks: all other cells contained five or more cases or controls. None of the interactions between age at operation and the exposures under study were reached $p<0.015$.

Birth weight and gestational age

There was a strong trend and association with birth weight among cases operated upon before one year of age. At older ages, one to five years, the overall association was not significant and the trend was weaker but still statistically significant. There was a similar pattern for gestational age. The trend, excluding the 'missing' level, among the youngest group was significant ($p=0.029$), but the trend at older ages was weaker and not significant ($p=0.889$). These results are similar to those seen among boys.

Retention in a special care baby unit, maternal age and parity

There were no significant associations with retention in a special care baby unit, or with maternal age or parity.

Social class

Overall social class was not significantly associated with inguinal hernia among the cases operated upon at the youngest ages, but was so at older ages. The trends across social class groups I to V were not significant (<1 year: $p=0.661$; 1–5 years: $p=0.908$). The prevalence ratio for the group 'other occupations' was significantly low at ages one to five years, and this contributed to the overall significance of social class at these ages. These results were similar to those for boys.

Presentation and smoking during pregnancy

There were no significant associations with presentation at delivery or maternal smoking during pregnancy.

Table 10.22: Multivariate analysis: prevalence ratios for girls with inguinal hernia—by age at operation

Risk factor	Age at operation					
	less than 1 year		1–5 years		All ages	
	Prevalence ratio	95% confidence interval	Prevalence ratio	95% confidence interval	Prevalence ratio	95% confidence interval
Parity						
Nulliparous	1.00	baseline	1.00	baseline	1.00	baseline
Parous	0.93	0.61–1.41	0.91	0.66–1.26	0.92	0.72–1.19
	* LRS[4]= 0.13, p=0.719		LRS[4]= 0.33, p=0.564		LRS[4]= 0.37, p=0.545	
Birth weight (kg)						
≤2.4	4.52	1.73–11.82	1.68	0.77–3.66	2.40	1.34–4.31
2.5–2.9	1.98	1.22–3.22	1.27	0.85–1.91	1.53	1.13–2.07
3.0–3.4	1.00	baseline	1.00	baseline	1.00	baseline
3.5–3.9	0.78	0.45–1.36	0.82	0.56–1.20	0.82	0.60–1.11
4.0 or more	0.42	0.12–1.43	0.76	0.41–1.41	0.70	0.41–1.20
	LRS[4]= 20.37, p<0.001 Trend LRS[1]= 18.80, p<0.001		LRS[4]= 5.62, p=0.229 Trend LRS[1]= 5.37, p=0.021		LRS[4]= 20.60, p<0.001 Trend LRS[1]= 18.90, p=<0.001	
Gestation (weeks)						
≤36	1.53	0.64–3.69	1.28	0.57–2.84	1.44	0.81–2.56
37–38	1.14	0.67–1.97	0.82	0.51–1.33	0.96	0.67–1.36
39–40	1.00	baseline	1.00	baseline	1.00	baseline
41–42	0.59	0.32–1.09	0.98	0.66–1.43	0.83	0.60–1.15
43 or more	0.34	0.08–1.46	1.03	0.48–2.19	0.74	0.38–1.44
† Missing	1.14	0.55–2.34	1.12	0.66–1.90	1.08	0.71–1.65
	LRS[5]= 7.81, p=0.167		LRS[5]= 1.52, p=0.910		LRS[5]= 4.31, p=0.506	
Retention in special care baby unit						
No	1.00	baseline	1.00	baseline	1.00	baseline
Yes	1.00	0.35–2.83	1.51	0.64–3.57	1.28	0.67–2.42
	LRS[1]= 0.00, p=0.999		LRS[1]= 0.88, p=0.349		LRS[1]= 0.55, p=0.460	
Maternal age (years)						
≤19	0.90	0.41–2.01	0.69	0.35–1.38	0.81	0.49–1.36
20–24	0.95	0.57–1.59	0.69	0.48–1.00	0.77	0.57–1.04
25–29	1.00	baseline	1.00	baseline	1.00	baseline
30–34	0.75	0.43–1.31	0.66	0.44–0.99	0.69	0.50–0.95
35 or over	1.12	0.51–2.46	0.77	0.39–1.53	0.89	0.54–1.48
	LRS[4]= 1.34 p=0.854 Trend LRS[1]= 0.02, p=0.895		LRS[4]= 6.25, p=0.181 Trend LRS[1]= 0.02, p=0.902		LRS[4]= 6.47, p=0.167 Trend LRS[1]= 0.01, p=0.908	
Social class						
I	1.91	0.98–3.72	1.04	0.63–1.72	1.28	0.86–1.89
II	1.19	0.65–2.19	0.80	0.52–1.22	0.88	0.62–1.25
III	1.00	baseline	1.00	baseline	1.00	baseline
IV	1.41	0.75–2.66	0.93	0.57–1.52	1.03	0.70–1.51
V	1.43	0.56–3.65	0.92	0.48–1.76	1.09	0.64–1.85
Other	0.28	0.06–1.32	0.21	0.06–0.67	0.24	0.10–0.61
† Missing	1.17	0.52–2.66	0.39	0.19–0.79	0.56	0.33–0.95
	LRS[6]= 9.14, p=0.166		LRS[6]= 18.57, p=0.005		LRS[6]= 22.48, p=0.001	
Presentation						
Breech	1.65	0.64–4.25	0.98	0.46–2.11	1.20	0.67–2.13
Not breech	1.00	baseline	1.00	baseline	1.00	baseline
† Missing	2.98	0.25–35.73	1.92	0.49–7.59	2.00	0.61–6.54
	LRS[2]= 1.68, p=0.432		LRS[2]= 0.79, p=0.674		LRS[2]= 1.52, p=0.468	
Smoking during pregnancy						
No	1.00	baseline	1.00	baseline	1.00	baseline
Yes	1.03	0.57–1.85	1.18	0.75–1.86	1.13	0.79–1.61
† Missing	0.42	0.10–1.80	1.91	0.80–4.58	1.22	0.58–2.55
	LRS[2]= 1.60, p=0.449		LRS[2]= 2.24, p=0.327		LRS[2]= 0.60, p=0.741	

* LRS[n]: Log-likelihood Ratio Statistic with n degrees of freedom
† Missing includes 'Not known' and 'Not collected'
All variables adjusted for other variables in table
Cases individually matched with up to 8 controls on year of birth, sex and hospital of delivery

10.8 Discussion of case-control study for girls

There are no previous epidemiological studies of risk factors for inguinal hernia among girls alone, and where both sexes have been studied together the results were weighted towards the boys because boys out-numbered the girls by at least 8:1 [282, 284]. The results from this study, therefore, may give new insights into the aetiology of inguinal hernia by comparing and contrasting the risk factors among boys and girls.

Section 10.5 discussed some of the issues associated with the use of routine data to study risk factors for inguinal hernia among boys. Most of those comments also apply to the study of risks among girls, and will not be repeated here.

10.8.1 Testicular feminisation

One issue specific to girls is that of testicular feminisation. In one report, two out of 17 girls admitted to hospital for repair of an inguinal hernia had a negative sex-chromatin pattern; in both cases the inguinal masses contained only testicular tissue [296]. The degree to which girls with inguinal hernia represented cases of testicular feminisation in this study is not known but such cases are likely to be rare. It has been suggested that in 1% of hernia operations a testicle is discovered in a phenotypic girl [297]. It seems likely, therefore, that the majority of female cases in this study cannot be attributed to testicular feminisation.

10.8.2 Similarities between boys and girls

Previous epidemiological studies of inguinal hernia [282, 284] have not looked at girls separately. The results among girls were essentially similar to those among boys: risk was strongly associated with low birth weight and possibly prematurity; there tended to be more cases than expected from social class group I among those operated upon at the youngest ages, and the association with birth weight and prematurity was also stronger among those operated upon early. Among boys it was suggested that the differences by age at operation might be attributed to earlier diagnosis, and hence operation, among low birth weight and premature cases and cases born to parents in social class I. The results for girls are consistent with this interpretation.

The risk associated with maternal smoking during pregnancy was not as large as that seen for boys, but the confidence intervals were wide and compatible with a raised risk. There were no other risk factors among girls that were significant or suggested a difference in aetiology between boys and girls.

Common aetiology

The similarities between boys and girls suggests that at least a proportion of cases share a common aetiology and that part of this may be independent of sex related factors. There is, however, a large absolute difference in risk of inguinal hernia by sex, with boys over eight times more likely to be affected [278]. In girls there is minimal development of the gubernaculum [273], but in boys the gubernaculum enlarges the inguinal canal so that the testes may pass through [141]. The mechanism of testicular descent, therefore, appears to predispose boys to an inguinal hernia, but beyond this the factors that cause some boys to actually have an inguinal hernia appear to be the same as those that operate in girls.

In this study it was immaturity that was the strongest risk factor for inguinal hernia within the sexes. It is possible that obliteration of the processus vaginalis needs an *in-utero* stimulus, and that babies that are born too early miss out completely or partially on this stimulus, or that obliteration proceeds more slowly after birth. If this stimulus exists it is probably not related to the hormones thought to be involved in the inguino-scrotal phase of testicular descent [142], because girls too are affected. There is also the possibility that a defect of connective tissue [293], perhaps brought about by maternal smoking during pregnancy, may also increase risk of inguinal hernia in both sexes.

10.9 Risk of inguinal hernia in siblings

The risk of inguinal hernia in siblings of cases and controls was estimated using the affected-sib method [245] as described in section 7.6. Boys with a record of an orchidopexy, and boys and girls with major congenital anomalies or who were part of a multiple delivery were not included in any part of the analysis.

10.9.1 Risk for boys with an affected male sib

The 1701 male cases were part of 1672 sibships made up of 2460 boys without a record of a major congenital malformation, no record of orchidopexy and who were not part of a multiple delivery. There were 1.47 eligible boys per affected sibship. Table 10.23 shows the distribution of affected boys by size of sibship. Overall the risk of inguinal hernia to age five years in boys from sibships with a male case was 6.87% (4.74%–9.47%). Table 10.23 also shows the number of affected boys among sibships containing at least one control boy. Only boys who were eligible to become cases were included. There were 16116 boys in 11250 sibships for an average of 1.43 boys per sibship. Overall the risk of inguinal hernia to age five years in boys from sibships with a male control was 1.34% (1.17%–1.53%). The relative risk for inguinal hernia, for boys who belong to an affected sibships relative to boys who belong to a control sibship, was 5.1.

10.9.2 Risk for girls with an affected female sib

As shown in table 10.23 the risk of inguinal hernia to age 5 years in girls from sibships with a female case was 5.32% (1.96%–10.92%): this was similar to the risk among boys in affected sibships. There were, however, only five sibships which contained two cases; the remaining 337 sibships contained only one case each. There were seven affected girls among 2524 sibships containing at least one control, and overall the risk of inguinal among these girls was 0.19% (0.08%–0.37%). This was 7.1 times smaller than the risk for boys in control sibships. The relative risk for inguinal hernia, for girls who belong to an affected sibships relative to girls who belong to a control sibship, was 28.1.

10.9.3 Discussion of risk in siblings

In Budapest, 1962–66, the reported prevalence of inguinal hernia to age three years was 1.1% [284], and in Newcastle, 1953–57, the cumulative risk to age 12 years was 1.0% [282]. These risks, however, are for boys and girls combined, and should be compared with the

Table 10.23: Number of sibships with r boys (or girls) with inguinal hernia in sibship of boys (or girls) of size s

Sibship size (s)	Number of sibships: Number of affected same-sex children in sibship (r) 0	1	2	3	4	5	6	7	Total	Risk (%)
Male sibships with at least one male case										
1	—	1006							1006	—
2	—	518	18						536	6.50
3	—	107	9	0					116	7.38
4	—	10	2	0	0				12	10.20
5	—	2	0	0	0	0			2	0.00
6	—	0	0	0	0	0	0		0	—
7	—	0	0	0	0	0	0	0	0	—
Total	—	1643	29	0	0	0	0	0	1672	6.87
								95% confidence interval		(4.74–9.47)
Male sibships with at least one male control										
1	7177	123							7300	1.58
2	3126	73	0						3199	1.84
3	597	16	0	0					613	2.24
4	113	3	0	0	0				116	2.41
5	17	1	0	0	0	0			18	0.00
6	3	0	0	0	0	0	0		3	0.00
7	1	0	0	0	0	0	0	0	1	0.00
Total	11034	216	0	0	0	0	0	0	11250	1.34
								95% confidence interval		(1.17–1.53)
Female sibships with at least one female case										
1	—	197							197	—
2	—	110	2						112	3.51
3	—	27	3	0					30	9.38
4	—	2	0	0	0				2	0.00
5	—	1	0	0	0	0			1	0.00
Total	—	337	5	0	0	0	0	0	342	5.33
								95% confidence interval		(1.96–10.92)
Female sibships with at least one female control										
1	1589	5							1594	0.31
2	738	2	0						740	0.14
3	155	0	0	0					155	0.00
4	26	0	0	0	0				26	0.00
5	9	0	0	0	0	0			9	0.00
Total	2517	7	0	0	0	0	0	0	11250	0.19
								95% confidence interval		(0.08–0.37)

average risk of 0.8% among male and female controls seen in this study. In this study and each of the cited studies [282, 284] inguinal hernia was defined by operation, but there are differences in the age groups used, and this study excluded a high risk group from

the analysis, boys with an orchidopexy. The comparison of cumulative risk, therefore, must be made with caution, but the results here are broadly similar to the two previous studies [282, 284]. Among the controls the absolute risk in boys was seven times larger than that in girls. This is in accord with the reported ratio of boys to girls of 8.5:1 [278], although this would also include the high risk group of boys with a record of an orchidopexy.

It is worth noting that, unlike cryptorchidism [147], orchidopexy [167] and testicular cancer [298], the figures give no indication for a rise in the prevalence of inguinal hernia. Supporting this, an examination of published hospital discharge data from the Hospital In-patient Enquiry for the years 1972, 1978 and 1985 shows no increase in the rate of inguinal hernia operations in England and Wales in boys aged 0–4 years [35, 299, 300].

Among boys born to women in the Collaborative Perinatal Project (USA), 1958–65, the prevalence of inguinal hernia to age seven years was 4.77% [217] in whites and 4.19% in blacks. Unlike the above studies, a diagnosis of inguinal hernia was used to select cases, not an operation, and it may be that this can wholly or partially explain the high reported prevalence in that study.

The risk of inguinal hernia in same-sex siblings was higher in case sibships than control sibships by a factor of five for boys and 28 for girls. Boys and girls who had major congenital malformations or were part of twin or higher order deliveries were removed from these analyses, so these factors cannot account for the clustering of cases within sibships. It is possible that having one child with an inguinal hernia leads to a greater chance that a subsequent child will be brought to medical attention and operated upon at an early age. It seems unlikely, however, that selection forces would be strong enough to produce a clustering within affected sibships as large as that seen here.

Appendix section J.1.3 showed that in six out of 66 (9%) male-male twin sets both boys were affected, and in one out of 10 (10%) female-female twin sets both girls were affected. Although the numbers of twin sets where both children were affected was small, these figures also suggest that there is clustering within sibships. Previous studies, however, have reported an increased risk of inguinal hernia with being part of a twin delivery [217, 284] and the clustering within twins may be due to this.

The clustering within sibships may point to a genetic cause underlying inguinal hernia. Siblings, however, also share the same mother and similar pre- and post-natal environments, and these may contribute to the familial association. Further studies of twins, by sex and zygosity, may give insights into the environmental and genetic causes of inguinal hernia in children.

Table 10.24: Odds ratios for inguinal hernia in boys diagnosed by operation, in relation to risk factors present in siblings born immediately before cases and controls: index matching variables and sex of sibling

Risk factor	Cases (total=566) number	Controls (total=3746) number	Odds ratio*	95% confidence interval
Year of birth of index case or control				
1970–74	107	699	0.95	0.74–1.22
1975–79	215	1344	1.00	baseline
1980–86	244	1703	0.90	0.74–1.09
			† LRS[2]= 1.19, p =0.551; Trend LRS[1]= 0.53, p =0.468	
Hospital district (birth of index)				
Oxfordshire	238	1640	1.00	baseline
West Berkshire	328	2106	1.07	0.89–1.28
			LRS[1]= 0.50, p =0.480	
Sex of sibling				
Boy	309	1928	1.00	baseline
Girl	257	1818	0.88	0.74–1.05
			LRS[1]= 1.92, p =0.165	

* all variables adjusted for other variables in the table
† LRS[n]: Log-likelihood Ratio Statistic with n degrees of freedom

10.10 Risk factors in siblings

The next section examines risk of inguinal hernia in boys in relation to exposures that were present at the delivery of the immediately previous or next sibling of the cases and controls. Each exposure is also adjusted for the same exposure at the index delivery. The methods used were discussed in section 7.8.

10.10.1 Results

Immediately previous deliveries

Table 10.24 shows odds ratios for the matching variables and the sex of the previously born sibling. All the index siblings were boys and so sex of the index was not included. There were no significant associations with the matching variables and although not significant, the prior siblings were less likely to be girls than boys.

Table 10.25 shows odds ratios for birth weight, gestational age and birth weight for gestational age of the sibling in relation to risk of inguinal hernia in the index cases. Risk of inguinal hernia was significantly increased if the prior sibling was low birth weight, but

Table 10.25: Odds ratios for inguinal hernia in boys diagnosed by operation, in relation to risk factors present in siblings born immediately before cases and controls: birth weight and gestational age

Risk factor in sibling	Cases (total=566) number	Controls (total=3746) number	Odds ratio*	95% confidence interval	Odds ratio*†	95% confidence interval
Birth weight (kg) of sibling						
<2.4	47	170	1.84	1.29–2.62	1.31	0.90–1.92
2.5–2.9	99	611	1.10	0.85–1.42	0.97	0.75–1.26
3.0–3.4	226	1512	1.00	baseline	1.00	baseline
3.5–3.9	144	1097	0.87	0.70–1.09	0.94	0.74–1.18
4.0 or more	47	336	0.91	0.65–1.28	1.02	0.71–1.46
Missing	3	20				
			‡ LRS[4]= 15.23, p =0.004; Trend LRS[1]= 10.50, p =0.001		LRS[4]= 2.78, p =0.595; Trend LRS[1]= 0.76, p =0.384	
Gestational age (weeks) of sibling						
≤36	41	171	1.57	1.06–2.35	1.35	0.89–2.03
37–38	89	507	1.24	0.94–1.62	1.18	0.89–1.56
39–40	244	1647	1.00	baseline	1.00	baseline
41–42	114	930	0.86	0.67–1.11	0.91	0.71–1.18
43 or more	25	128	1.62	1.00–2.60	1.77	1.09–2.86
Missing	53	363				
			LRS[4]= 13.31, p =0.010; Trend LRS[1]= 4.21, p =0.040		LRS[4]= 8.95, p =0.062; Trend LRS[1]= 0.81, p =0.368	
§ Birth weight for gestational age sibling						
LGA	45	291	0.98	0.69–1.40	0.93	0.65–1.35
AGA	400	2720	1.00	baseline	1.00	baseline
SGA	66	368	1.17	0.87–1.59	1.08	0.79–1.48
Missing	55	367				
			LRS[2]= 1.10, p =0.577; Trend LRS[1]= 0.77, p =0.381		LRS[2]= 0.42, p =0.810; Trend LRS[1]= 0.42, p =0.518	

* adjusted for period and hospital of index birth, and sex of sibling
† also adjusted for same risk factor in index child
‡ LRS[n]: Log-likelihood Ratio Statistic with n degrees of freedom
§ LGA: Large for gestational age
§ AGA: Appropriate for gestational age
§ SGA: Small for gestational age

this was less apparent and not significant after adjusting for the birth weight of the index case or control. There were significantly increased risks with low and high gestational ages, and the increased risk at high gestation remained after adjusting for the gestational age at the index delivery. There were no significant associations with birth weight for gestational age of the sibling.

Table 10.26 shows that there were no significant associations between social class at the siblings' delivery and inguinal hernia at the index delivery. The trend with social class

Table 10.26: Odds ratios for inguinal hernia in boys diagnosed by operation, in relation to risk factors present in siblings born immediately before cases and controls: other risk factors

Risk factor in sibling	Cases (total=566) number	Controls (total=3746) number	Odds ratio*	95% confidence interval	Odds ratio*†	95% confidence interval
Social class at birth of sibling						
I	37	312	0.77	0.52–1.14	0.75	0.41–1.37
II	87	613	0.96	0.72–1.27	0.79	0.53–1.17
III	211	1420	1.00	baseline	1.00	baseline
IV	77	469	1.06	0.78–1.43	1.02	0.71–1.47
V	35	218	0.93	0.60–1.44	1.08	0.66–1.78
Other	13	101	0.90	0.47–1.73	0.90	0.39–2.06
Missing	66	406				
Not collected	40	207				
			‡ LRS[5]= 2.36, p =0.797		LRS[5]= 2.08, p =0.837	
Presentation of sibling						
Not breech	279	1914	1.00	baseline	1.00	baseline
Breech	10	87	0.81	0.41–1.57	0.76	0.39–1.49
Missing	2	30				
Not collected	275	1715				
			LRS[1]= 0.42, p =0.515		LRS[1]= 0.69, p =0.408	
Caesarean section for sibling						
No	535	3510	1.00	baseline	1.00	baseline
Yes	31	236	0.87	0.59–1.29	0.72	0.45–1.14
			LRS[1]= 0.48, p =0.490		LRS[1]= 2.04, p =0.153	

* adjusted for period and hospital of index birth, and sex of sibling
† also adjusted for same risk factor in index child
‡ LRS[n]: Log-likelihood Ratio Statistic with n degrees of freedom

across groups I–V was not significant either before (p=0.204) or after (p=0.101) adjusting for social class at the index delivery. There was no significant association with presentation at delivery of the previously born sibling.

Table 10.27: Odds ratios for inguinal hernia in boys diagnosed by operation, in relation to risk factors present in siblings born immediately after cases and controls: index matching variables and sex of sibling

Risk factor	Cases (total=690) number	Controls (total=4071) number	Odds ratio*	95% confidence interval
Year of birth of index case or control				
1970–74	245	1490	0.87	0.72–1.05
1975–79	260	1378	1.00	baseline
1980–86	185	1203	0.81	0.66–1.00
			† LRS[2]= 4.33, p =0.115; Trend LRS[1]= 0.29, p =0.590	
Hospital district (of index birth)				
Oxfordshire	313	1765	1.00	baseline
West Berkshire	377	2306	0.92	0.78–1.08
			LRS[1]= 1.04, p =0.307	
Sex of sibling				
Boy	376	2120	1.00	baseline
Girl	314	1951	0.91	0.77–1.07
			LRS[1]= 1.41, p =0.236	

* all variables adjusted for other variables in the table
† LRS[n]: Log-likelihood Ratio Statistic with n degrees of freedom

Immediately subsequent deliveries

Table 10.27 presents odds ratios for the matching factors at the index delivery and sex of the next born sibling. There were no significant associations with year or hospital of birth, or with the sex of the sibling.

There was a raised risk of inguinal hernia among boys with a low birth weight subsequent sibling, but this was not statistically significant, as shown in table 10.28. After adjusting for birth weight at the index delivery this association was reversed and the trend to greater risk at higher birth weights was significant. Cross-tabulation of odds ratios by index and sibling birth weight (not shown here) revealed that risk was uniformly raised across all sibling birth weights if the index was low birth weight ($\leq$2.4 kg) and uniformly low if the index was large. Only at moderate index birth weights (2.5–2.9 kg, 3.0–3.4 kg) did risk increase with increasing sibling birth weight, and this showed up as a reversal in the trend.

There was a significant association between prevalence of inguinal hernia and the subsequent sibling's gestational age, but because risk increased at both short and long gestational ages the trend was not significant. The association remained significant after adjusting for

Table 10.28: Odds ratios for inguinal hernia in boys diagnosed by operation, in relation to risk factors present in siblings born immediately after cases and controls: birth weight and gestational age

Risk factor in sibling	Cases (total=690) number	Controls (total=4071) number	Odds ratio*	95% confidence interval	Odds ratio*†	95% confidence interval
Birth weight (kg) of sibling						
≤2.4	29	137	1.28	0.84–1.96	0.85	0.55–1.32
2.5–2.9	100	553	1.09	0.85–1.40	0.89	0.69–1.15
3.0–3.4	268	1579	1.00	baseline	1.00	baseline
3.5–3.9	217	1337	0.96	0.79–1.17	1.12	0.92–1.37
4.0 or more	74	450	0.96	0.72–1.27	1.31	0.96–1.77
Missing	2	15				
			LRS[4]= 2.41, p =0.661; Trend LRS[1]= 1.86, p =0.173		‡ LRS[4]= 5.84, p =0.211; Trend LRS[1]= 5.68, p =0.017	
Gestational age (weeks) of sibling						
≤36	33	154	1.35	0.89–2.05	1.09	0.71–1.67
37–38	117	588	1.28	1.00–1.63	1.16	0.90–1.48
39–40	294	1849	1.00	baseline	1.00	baseline
41–42	131	844	0.96	0.76–1.22	1.02	0.80–1.29
43 or more	39	139	2.08	1.41–3.07	1.96	1.32–2.92
Missing	76	497				
			LRS[4]= 17.24, p =0.002; Trend LRS[1]= 0.11, p =0.743		LRS[4]= 10.88, p =0.028; Trend LRS[1]= 0.89, p =0.345	
§ Birth weight for gestational age of sibling						
LGA	73	395	1.10	0.83–1.46	1.19	0.89–1.60
AGA	490	2890	1.00	baseline	1.00	baseline
SGA	51	281	1.10	0.79–1.52	0.96	0.68–1.34
Missing	76	505				
			LRS[2]= 0.64, p =0.725; Trend LRS[1]= 0.02, p =0.893		LRS[2]= 1.42, p =0.491; Trend LRS[1]= 1.12, p =0.290	

* adjusted for period and hospital of index birth, and sex of sibling
† also adjusted for same risk factor in index child
‡ LRS[n]: Log-likelihood Ratio Statistic with n degrees of freedom
§ LGA: Large for gestational age
§ AGA: Appropriate for gestational age
§ SGA: Small for gestational age

gestational age at the index delivery, although the raised risk was mostly limited to the group with the largest gestational age. There were no significant associations with birth weight for gestational age.

Table 10.29 shows odds ratios for social class and presentation at delivery for the next sibling born after the index case or control. There was no overall association with social class, nor was the trend across groups I–V significant before (p=0.089) or after (p=0.150) adjusting for social class at the index delivery. There was no significant association with

Table 10.29: Odds ratios for inguinal hernia in boys diagnosed by operation, in relation to risk factors present in siblings born immediately after cases and controls: other risk factors

Risk factor in sibling	Cases (total=690) number	Controls (total=4071) number	Odds ratio*	95% confidence interval	Odds ratio*†	95% confidence interval
Social class at birth of sibling						
I	44	359	0.72	0.50–1.04	0.67	0.40–1.13
II	109	706	0.93	0.73–1.20	0.88	0.62–1.24
III	279	1633	1.00	baseline	1.00	baseline
IV	84	479	0.99	0.74–1.33	0.93	0.66–1.30
V	43	206	1.18	0.79–1.77	1.31	0.83–2.09
Other	24	113	1.12	0.63–2.00	1.12	0.56–2.21
Missing	64	371				
Not collected	43	204				
			‡ LRS[5]= 4.79, p =0.442		LRS[5]= 4.53, p =0.475	
Presentation of sibling						
Not breech	534	3204	1.00	baseline	1.00	baseline
Breech	13	79	0.96	0.49–1.90	0.94	0.47–1.86
Missing	13	35				
Not collected	130	753				
			LRS[1]= 0.01, p =0.912		LRS[1]= 0.03, p =0.857	
Caesarean section for sibling						
No	643	3831	1.00	baseline	1.00	baseline
Yes	47	240	1.15	0.83–1.59	1.04	0.69–1.58
			LRS[1]= 0.70, p =0.404		LRS[1]= 0.04, p =0.843	

* adjusted for period and hospital of index birth, and sex of sibling
† also adjusted for same risk factor in index child
‡ LRS[n]: Log-likelihood Ratio Statistic with n degrees of freedom

presentation at delivery of the next born sibling.

10.10.2 Discussion of risk factors in siblings

As previously discussed (section 7.8.3), the interpretation of the results from the analysis of risk factors present at the delivery of the previous and subsequent siblings needs care. Only the associations with birth weight and gestation were significant and so only these will be discussed here.

Birth weight and gestational age

It might be expected that a case with inguinal hernia, who was more likely to be low birth weight, would be more likely to have a sibling also with low birth weight, because birth weight is known to track across deliveries [249]. This was seen, although after adjusting for the index birth weight the association with the birth weight of the subsequent sibling was reversed. Closer examination revealed that risk was raised uniformly if the index was low birth weight irrespective of the sibling birth weight. At index birth weights of 2.5–2.9 kg and 3.0–3.4 kg risk was raised with *increasing* sibling birth weight. The pattern was such that risk was increased if the index was smaller than the sibling. This suggested that while absolute low birth weight of the index subject was important, relative birth weight may also be important; an index baby of 3.0 kg may, in absolute terms, not be considered small but relative to his subsequent sibling he may have failed to reach his *in-utero* growth potential. Relative birth weight has been shown to be an important concept in relation to perinatal mortality [301].

Risk was also raised with short and long gestational ages of the sibling, and after adjusting for the index gestation the risk with longer gestation was still apparent. Gestational age and birth weight are strongly correlated such that the patterns seen with birth weight would be expected to carry over to gestational age.

It appears, therefore, that an individual baby's risk of inguinal hernia may be determined in part by its birth weight relative to the usual weight of infants born to that mother. In practice it may be difficult to determine if a baby has failed to reach its growth potential if it has no siblings to be compared against. One alternative is to compare birth weight to adult height [20], but this too has limitations. It would be useful, therefore, to develop models of expected birth weight, perhaps based upon birth weight of siblings and parental height, race and their own birth weight.

10.11 Conclusions to inguinal hernia studies

It was shown that the absolute risk for an inguinal hernia in childhood was seven times higher in boys than girls, which was in accord with previous reports [278]. This large absolute difference in risk is probably related to the mechanisms involved in testicular descent, where the processus vaginalis must dilate to accommodate the descending testis [141]; in girls there is less development of this structure [273] and presumably the processus is patent to a lesser degree, or not at all. Beyond the absolute difference in risk boys and girls were similar in relation to the risk factors that reflected immaturity at birth: low birth weight and prematurity.

At birth, in an immature infant, obliteration of the processus vaginalis may be incomplete at the time of delivery. In boys obliteration should take place after the testes have descended down the inguinal canal. Descent down the inguinal canal usually starts around seven or eight months of gestation [143] and final descent into the scrotum is usually complete three to four months after birth [144]. Obliteration of the processus vaginalis *ex-utero* may proceed slowly, or not at all, perhaps because it requires some stimulus from the mother. Inguinal hernia then may be viewed as a direct consequence of immaturity. Alternatively it is possible that the factors that cause an infant to be born immature may also have acted to slow or stop the process of obliteration *in-utero*. Immaturity may then be indirectly related to inguinal hernia. Apart from maternal smoking during pregnancy there was no evidence for other risk factors, like pre-eclampsia, that might support this view. In either case it appears that the association between immaturity and inguinal hernia is probably not related to the sex of the child.

The analysis based on previous and subsequent siblings suggested that immaturity should be evaluated on a relative scale—with reference to the expected birth weight for an offspring of a particular mother. Relative birth weight may not only be important for inguinal hernia but also for other studies of prenatal origins of disease in later life. It might be necessary to develop models for expected birth weight, or expected *in-utero* growth potential.

The prevalence of inguinal hernia in childhood does not appear to be increasing, but further work could be done to verify this. The lack of an increase in prevalence of inguinal hernia is in contrast to cryptorchidism [147, 167] and testicular cancer [298] and suggests there are differences in the aetiology of these conditions. The low risk with high social class also points to possible differences in the aetiology of inguinal hernia and testicular cancer. These results, however, need to be verified.

The possible mechanisms for maternal smoking during pregnancy in relation to inguinal hernia may be related to the way in which smoking causes general birth defects [291, 292], or low birth weight [295], or the way in which it affects the baby's environment after delivery, or to defects in connective tissue [293].

10.11.1 Suggestions for future research

A general conclusion from this work is that risk factors and mechanisms independent of the sex of the child should be considered in relation to inguinal hernia. More specifically:

- large studies of twins may help in partitioning genetic and environmental causes of inguinal hernia;
- relative birth weight may be important in assessing maturity at birth, but models for expected birth weight might need to be developed;
- the lack of an apparent increase in inguinal hernia in childhood should be verified, and this reconciled with the increasing cryptorchidism rate;
- and, the association with social class should be confirmed.

Chapter 11

Final Conclusions

This thesis presented results from studies of three conditions using routine data from the Oxford Record Linkage Study (ORLS). Pre-eclampsia was identified as a risk factor for diabetes in childhood, and although this has been found once before [14] the aetiological significance of the finding remains uncertain. The studies of cryptorchidism suggested that intra-uterine growth retardation in the third trimester may be important in the aetiology of undescended testes that do not spontaneously descend in later life.

Low birth weight, short gestation and smoking during pregnancy were identified as risk factors for inguinal hernia among boys, and among girls the results were similar. This suggested that mechanisms independent of the sex of the child may be involved in the actiology of this condition.

On a more general note this thesis has shown that routine data from the ORLS could be used to identify pre-natal and early life risk factors for diseases in childhood and young adult life. A potential bias due to differential migration of cases and controls was identified, but the methods presented in chapter 3 provided a way to estimate the size of the bias. The results from these studies have led to hypotheses about the aetiology of the selected conditions, and suggested areas for future research.

With further follow-up of the ORLS population rarer diseases and diseases in later life will be able to be studied, in particular cancers, cardiovascular disease, respiratory disease and diabetes in adult life. Future studies would be able to examine some of the hypotheses raised by Barker and his colleagues [1, 2]. In such studies, however, bias due to migration may be a bigger problem than encountered here, but as demonstrated in chapter 3, the size of the bias and its impact can be assessed in this and other studies using a similar design.

It was also shown that ORLS data can be linked to other databases, in this case the Oxfordshire Family Health Services Authority (FHSA) register. Potentially, other linkages

could be made to existing medical databases within hospitals, to obtain more specific information about the condition or disease studied (e.g. laterality and position of maldescent for orchidopexy cases), or to other specialised registers, like those for childhood diabetes.

Linkage to siblings of cases and controls from the studies of cryptorchidism and inguinal hernia made it possible to estimate the risk of siblings being affected. These results need careful interpretation because both genetic and shared environmental conditions may be responsible for clustering within sibships. Identification of siblings also made it possible to look at risk factors for disease in deliveries immediately previous and subsequent to the index delivery. The results from the cryptorchidism studies suggested that permanent changes to the mother may occur around the time of the pregnancy involving the affected child. The results from the inguinal hernia study suggested that relative birth weight, or failure to reach full growth potential *in-utero*, when compared to siblings, may be a risk factor. Information of this type in relation to perinatal variables associated with previous and subsequent pregnancies of the mother should be considered in other studies of the foetal origins of diseases in later life.

Part V

Appendices

Appendix A

Overview of the Oxford Record Linkage Study

A.1 The population covered by the ORLS

Since 1963 the Oxford Record Linkage Study (ORLS) has assembled information so those hospital records relating to the same individual may be linked together. The original area covered by the ORLS included the City of Oxford, the county of Oxfordshire (except Henley Municipal Borough and Rural District), and Abingdon Borough and Rural District in Berkshire; a total population of about 340,000 persons. From 1966 coverage was extended to that part of Berkshire within the Oxford Regional Hospital Board area: a total population of 800,000 persons with about 14,000 births each year.

A.2 Data collected for Oxfordshire and West Berkshire

The ORLS has systematically acquired information from general and psychiatric hospital records, birth and death notifications, and all maternities in Oxfordshire and West Berkshire. Hospital data are collected for patients admitted to National Health Service (NHS) care. Submission of data from hospitals that treat private patients has been inconsistent, but in Britain only a small part of health care is provided by the private sector and that is usually limited to minor conditions.

A.2.1 General hospital records

Relevant information contained in clinical summaries and case notes from general and psychiatric hospitals were extracted and coded by clerical staff in the Records Departments of

the hospitals. These brief abstracts were similar to ones routinely collected elsewhere in England; in the past as the Hospital Activity Analysis (HAA) and currently as the Hospital Episode System. In Oxford recent standards set for HAA data collection were that: records should be available for 99.5% of all discharges; all HAA records should include patient's date of birth, sex, place of residence and a range of other specified items; and a diagnosis on 98%, and patients occupation on 90%, of all records [302].

A.2.2 Birth and death certificates

The Office of Population Censuses and Surveys (OPCS), formerly the General Registrar Office, sends to the ORLS copies of livebirth and stillbirth certificates for all deliveries in the area. Also sent to the ORLS are copies of such certificates for deliveries to women usually resident in the area but who delivered outside it. The ORLS receives death certificates of all persons resident in the area and of all non-residents who die in the area. Also received are death certificates for people usually resident in the area but who die elsewhere, although this is not thought to be complete.

A.2.3 Maternity and delivery records

A detailed description of the pregnancy, labour and delivery, and the subsequent morbidity of mother and infant are abstracted by trained clerks from hospital case notes. For domiciliary deliveries the midwife who delivered the infant sends her notes to the ORLS and clerks then abstract and code relevant information. The level of ascertainment is checked by matching the delivery records with live birth and stillbirth certificates from OPCS.

A.3 Collection of data extended to other health districts

From 1974 the coverage of general hospital and psychiatric hospital records, births, and deaths, was extended to the six districts of Oxfordshire, West Berkshire, East Berkshire, Wycombe, Northampton and Kettering; a total population of about 1.9 million. Information on day cases have been collected since 1976. From 1984 the districts of Aylesbury and Milton Keynes were included in the Study. This brought coverage to the whole of the Oxford Regional Health Authority: a total population of about 2.5 million people. Table A.1 summarises the coverage of the ORLS. Collection of maternity and delivery records did not expand beyond Oxfordshire and West Berkshire.

A.4 How the link is made with existing records

Newly abstracted records were compared with the master file of people already on the ORLS system. The comparison is usually made using a phonetic representation of name (the Soundex code [303]), sex, and date of birth using probability matching [304]. If a match was found the person's file was brought up to date by adding the new record. If no match was found a new file was opened for that person. If only a partial match was made special probabilistic rules were used to decide if the comparison was or was not a match. The details of the comparison were different for different types of linkage, e.g. existing birth record to new hospital record or existing hospital record to new hospital record.

A.5 Validation of information collected by the ORLS

Aggregated statistical returns used for financial resource allocation show that about 5% of paediatric admissions for residents of the six districts occurred outside these districts and that this has not changed appreciably over time [305]. In a validation exercise for a study of total hip replacement 98.8% of operations in one hospital were identified by the ORLS [306]. The ORLS missed 4.5% of total hip replacements, some of which were known to have been undertaken privately. Similarly, in another study about 96% of the diagnostic information on poisoning in adolescents was correctly recorded by the ORLS [307].

A.6 The maternity and delivery records

Maternity and delivery records were extracted from hospital or midwives' notes. Since 1970 the maternity and delivery abstract was stored on a computer file. The data for the period before 1970 have been abstracted but only stored on microfilm.

A.7 Some advantages and disadvantages of the ORLS

The main advantages of using the ORLS are listed below:

- the cases may be easily identified from ORLS records;
- intrinsic to the record linkage system is the ability to link cases to all their hospital records and their delivery record;
- controls may be selected from the same source of delivery files as the cases, ensuring comparability between case and control data records;

- mothers of the cases and controls and may be easily identified, and their maternity records may be extracted;
- siblings of the cases and controls may be easily identified, and their records extracted;
- nearly all the data needed are already coded and on computer;
- data are available for many years;
- the total cost of the study is low;
- large sample sizes are possible within the limitations of the ORLS population size;
- the ORLS has its own quality control measures above those associated with the routine data sources.

There are disadvantages too:

- only data items recorded by the ORLS were available, so limiting the exposures and outcomes that can be studied;
- there was no active follow-up of subjects, deaths were notified to the ORLS but there was no information about migration out of the study area;
- the maximum length of follow-up was limited;
- the size of the population covered by the ORLS was limited.

A.8 Some previous studies based upon ORLS data

The maternity and delivery records have been used previously to describe obstetric practice in the Oxfordshire and West Berkshire area [308]. During 1965–72, for example, there were increases in the rate of induction, episiotomy and the use of forceps; stillbirth rates fell, but the reduction was more apparent among the induced births.

In the early 1970s there were a series of case-control studies, of conditions usually diagnosed in the perinatal period, using ORLS maternity and delivery data from the mid to late 1960s and early 1970s. These studies had a common methodology; usually each case was diagnosed at or soon after birth and matched to three livebirths for maternal age, parity, civil status of mother, social class of the father, hospital and year of delivery and, as closely as possible, for area of residence. There were studies of epilepsy and pregnancy [309], sudden unexpected deaths in infants [310–312], anencephalus [313], and pyloric stenosis [22].

More recently a combination of maternity, delivery and general hospital records was used to investigate the role of prenatal and perinatal factors in the aetiology of cryptorchidism [24].

Table A.1: The Oxford Record Linkage Study area

Year	Study area	Total population	OPCS births and deaths	General hospital discharge records	Maternity and delivery records
1963	Oxford City and County, Abingdon and Banbury	340,000	Oxfordshire	Oxfordshire hospitals for Oxfordshire and Abingdon residents	Oxford City and County, Abingdon and Banbury
1966	above, plus Reading hospitals	800,000	Oxfordshire and West Berkshire	Oxfordshire and West Berkshire hospitals and residents	Oxfordshire and West Berkshire residents in Oxfordshire and West Berkshire hospitals or domiciliary
1974/75	Six districts: Oxfordshire; West Berkshire; East Berkshire; Wycombe; Northampton and Kettering	1,900,000	All of Oxford Regional Health Authority	Six districts' hospitals	⇓
1984	All of Oxford Regional Health Authority (i.e. plus Aylesbury and Milton Keynes)	2,500,000	⇓	All of Oxford Regional Health Authority	⇓

Appendix B

Data Extraction Methods for the Diabetes Study

B.1 Diseases and conditions to be studied

The diseases and conditions to be studied were selected on four main criteria:

- the disease or condition would cause a person to be admitted to hospital and so appear on the Oxford Record Linkage Study (ORLS) files;
- within the ORLS population there would be a sufficient number of cases of the disease or condition to ensure reasonable statistical power for a case-control study;
- there was reason to believe that the disease or condition might have pre-natal origins;
- there were important aetiological reasons to study the diseases (i.e. the causes of childhood onset diabetes are not known, and for cryptorchidism and inguinal hernia there are close links with testicular cancer).

B.1.1 Disease codes for diabetes

The following codes were used to identify cases of diabetes (discharge diagnoses were coded using the International Classification of Diseases (ICD) [314]):

- Diabetes — general hospital discharge diagnosis ICD codes 260 (revision 7) and 250 (revisions 8 and 9).

B.2 Identifying cases for the diabetes study

Staff at the ORLS, identified all people from the ORLS general hospital file who had a hospital discharge diagnosis of diabetes during 1963–87. Only those diabetic subjects with a birth record on the ORLS system were selected. Only subjects born during 1963–86 would have had a birth record available at the time the data was extracted.

Nearly all people born in, and to parents resident in, Oxfordshire or West Berkshire had maternity abstracts routinely collected during 1963–86. A small number of maternity abstracts for births in Oxfordshire and West Berkshire, to parents resident outside of the area, were collected. The rest of the diabetes study was limited to people with a maternity abstract.

For births during 1970–86 information from the maternity abstract was entered onto ORLS computer files. Data items concerning the baby were put into a delivery file and data items concerning the mother were put into a maternity file. For births during 1963–69 data from the maternity abstract were not entered onto the computer system, although the abstracts were still available, either stored on paper or microfilm.

ORLS staff took the file of people identified previously and split it into those born during 1963–69 and 1970–86. For the diabetic subjects born during 1970–86 the following variables to be used for matching were extracted from the subjects' delivery file: date of birth; sex and hospital of delivery. For the diabetic subjects born during 1963–69 matching variables were extracted from the birth record. The birth records had to be used because there was no computerised delivery file for the majority of births during 1963–69. These matching variables were: date of birth, sex and, because hospital of delivery was not available on this record, place of delivery. The maternity form number, the number stamped onto the maternity abstract, was also extracted. Only those diabetic subjects with either a delivery record or a maternity form number were retained.

B.3 Control selection

B.3.1 Births during 1970–86

All livebirths that matched with a birth record of a diabetic subject were selected from the delivery file. The matching was done on sex, year of delivery and hospital of delivery, or if born in a GP unit to another birth from a GP unit. In addition, hospital births had to have been discharged alive from the hospital. ORLS staff further reduced the number of matching livebirths by only selecting those livebirths which had the same last digit of

the system number as the index diabetic subject. The system number is a unique number given to every individual on the ORLS system. Consecutive birth are not necessarily given consecutive system numbers. The result of this selection procedure was to produce a file containing a '1–in–10' sample of livebirths matching to the diabetic subjects.

The file containing the '1–in–10' sample of matching livebirths was sent to the London School of Hygiene and Tropical Medicine (LSHTM) where I selected up to eight matched potential controls for each diabetic subject, at random, using a program written in the C computer language. The random selection was achieved in the following way:

- the livebirths matching to a diabetic subject, but not the index diabetic itself, were numbered 1 to n;
- eight different integers in the range 1 to n were selected using a random number generator;
- up to eight livebirths corresponding to these eight integers were selected as potential controls;
- the diabetic subject and the selected potential controls were given a number identifying their matched set;
- the procedure was repeated for all diabetic subjects.

Some diabetic subjects were matched to less than eight livebirths. When this happened all available livebirths from the '1–in–10' sample were selected as potential controls. Staff at the ORLS then supplied another file of livebirths that matched to these diabetic subjects but without selecting on the last digit of the system number. The extra livebirths necessary to make a matched set of eight potential controls were then selected using the procedure outlined above. In some instances there were still less than eight matching livebirths.

B.3.2 Births during 1963–69

ORLS staff selected all livebirths from the birth record that matched with the birth of a diabetic subject, excluding the index diabetic birth itself. The matching was done on sex, year of delivery and place of delivery.

The number of matching livebirths was further reduced by only selecting those livebirths which had the same last digit of the system number as the index diabetic. The file of livebirths was sent to the LSHTM where I selected up to ten potential controls using a similar procedure as for the 1970–86 births. Only two diabetic subjects did not get their

quota of ten controls. It turned out that these diabetic subjects would not contribute to the study because there was no maternity information available for them, so no extra controls were sought.

B.4 Data extraction from ORLS files

All subjects, the cases with diabetes and the controls, were assembled into one file which contained the unique identifying system number for the subject, the matching variables, a number identifying the matched set to which the diabetic subject or potential control belonged, the number of possible matches from which the potential controls had been selected, the order in which the potential controls had been selected, and for births during 1963–69 the maternity form number.

B.4.1 Maternity and delivery records

For subjects born during 1970–86 information from the maternity abstract had been entered into the delivery file and the maternity file on the ORLS system. For subjects born during 1963–69 the maternity abstract had not been entered onto a computer file. The original forms or copies, however, do still exist. The forms for maternity events during 1963–64 were stored at the ORLS, in filing cabinets, and for maternity events during 1965–69 copies of the forms were stored on microfilm.

Maternity and delivery records 1970–86

ORLS staff extracted selected data items from the computerised delivery file for the subjects born during 1970–86. One of the data items was the mother's system number, which was the link to all the mother's records on the ORLS system. With the mother's system number all the maternity files associated with each mother were found and selected data items were extracted from those files, for events that occurred during 1970–86. These maternity data were not only extracted for the births of diabetic subjects and their potential controls, but also for the births of the siblings of the diabetic subjects and the siblings of the potential controls. Also included were other maternity events the mother may have experienced such as stillbirths and abortions.

There were in total 1526 delivery records and 4215 maternity records in the diabetes study. Four of these maternity records were subsequently deleted because they were duplicates of another four records. These records belonged to one woman.

Maternity and delivery records 1963–69

Using the maternity form number and year of delivery it was possible to find the maternity abstract on the microfilm record. I extracted delivery data for all the diabetics born during 1965–69 and, for practical reasons, for only the first two selected potential controls for each diabetic case. Maternity data associated with those deliveries were also extracted.

Three types of data extraction sheet were used. One for domiciliary deliveries and, because the ORLS maternity abstract used for hospital deliveries was revised after 1967, two for hospital deliveries. The form used for hospital deliveries during 1968–69 was blue or white, the form for hospital deliveries during 1965–67 was green, and the form used for domiciliary deliveries was yellow. Appendix D contains examples of the forms used.

It was not feasible to extract maternity data for any other maternity event the mother may have had. These maternity records had never been entered onto the ORLS computer system, and as a consequence of this they had never been linked to any other records the mother may have had.

For births during 1963–64 the maternity abstracts were stored in filing cabinets at the offices of the ORLS, but it soon became apparent from an attempt to find a few subjects that the paper records were usually not complete—the maternity abstracts were often missing from the place in the file where they should have been. For this reason no delivery or maternity data were extracted for the subjects born during 1963–64.

B.4.2 Microfilm records

I entered data from the microfilm records onto computer, using the computer package Epi-Info [315], at the LSHTM. Logical checks for data entry errors were made and any mistakes that were found were corrected by reference back to the data extraction sheets. A sample of the corrected data was checked against the data extraction sheets by a member of staff at the LSHTM. From a 10% sample of each type of form zero errors were found in any data entry field.

The microfilm datafile for the 1965–69 births was merged with the delivery and maternity datafiles for the 1970–86 births. It was not possible to find equivalent data items for all the variables on both datasets; some items had not been collected in earlier years, and some had had their meaning changed. For example, information about maternal smoking was not available before 1976 and, therefore, did not appear on the 1965–69 datafile. After 1975 'Apgar score' was changed to 'Apgar score at 1 minute' and 'Apgar score at 5 minutes.' In the latter case, following the bridging method employed by the ORLS, the item called

'Apgar score' from the microfilm datafile was bridged to the new item called 'Apgar score at 1 minute'.

B.4.3 General hospital files

Selected data items were extracted for all diabetics and controls from the general hospital file on the ORLS computer system. These items were not extracted for the mothers or the siblings of the diabetic subjects or for the siblings of the potential controls.

There were in total 4560 general hospital records. Twenty-four of these records were subsequently deleted because they were duplicates of another 24 records. These records belonged to two people.

B.4.4 Death certificate records

If deceased, date of death was extracted from the death certificate record of the diabetic subject or potential control. There were in total 67 death certificate records.

B.5 Data management

All data were transferred to the LSHTM's SUN computer system (SunOS Release 4.1.3) where the computer package SAS [316] was used for data management.

Appendix C

Cryptorchidism and Inguinal Hernia Data

C.1 Revised methods

The methods for the studies of cryptorchidism and inguinal hernia were essentially the same as for the diabetes study, described in appendix B, but extra linkages were made to the siblings of the cases and controls. At a later stage some subjects were excluded because they were not eligible for the case-control analyses; during the data extraction subjects were strictly potential cases or controls, but for convenience they will be referred to simply as cases and controls.

The following codes were used to identify cases (discharge diagnoses were coded using the International Classification of Diseases (ICD) [314] and operations were coded using the Classification of Surgical Operations (CSO) [317]):

- Cryptorchidism (at birth) — delivery file diagnosis ICD codes 752.1 (revision 8) and 752.5 (revision 9);

- Cryptorchidism (orchidopexy) — general hospital operation CSO codes 696 (1956 edition) and 648 (1969 edition, 1971 reprint, 1975 reprint);

- Inguinal hernia operation — general hospital operation CSO code 402 (1956 edition) and 410–411 (1969 edition, 1971 reprint, 1975 reprint).

Only cases born during 1970–86 were selected for these studies because this provided an adequate sample size without having to extract manually data from ORLS microfilm records. Controls were selected using the same procedure as described in appendix B.

Unlike the diabetes study there was no follow-up of these subjects with the Oxfordshire Family Health Services Authority.

Delivery, general hospital and death records were extracted for the cases and controls. The mothers of the index cases and controls were identified from the delivery record and all their maternity, general hospital and, if applicable, death records for the years 1970–86 were extracted. It was also possible to extract a mother's delivery record if she had been born during 1970–86 within Oxfordshire or West Berkshire, but because there were only five such mothers these were not analysed further. The siblings born during 1970–86, of the index cases and controls, were identified from the mothers' maternity records and their delivery, general hospital and, if applicable, death records were also extracted.

Duplicate records were removed. Some 'near-duplicate' records were discovered. These appeared to be the same event but with data split across two records. For example, there were admissions with basic identifying information and no further details, followed by a similar admission with lots of data. These 'near duplicate' records were updated with information taken from both records to create one full record.

Appendix D

Microfilm Data Abstraction Forms

16

BC form number □/74268 Maternity form number □/74267

Form version(68) 4 Hospital number □□□6587 NHS number.....

Age (mother) 20

- date of birth (mother) 12-09-48

Address 6080

Place of birth 6083

C/S: Religion 23

Social class 5

Hospital 14

GP 6503

Consultant 342

- date of admission 08-08-69

- date of LMP 20-11-68

- date of booking 06-02-69

Date of booking: No A/N Attendances 31

Parity: POH I & II 000

X-ray: Blood group 35

BP: Albuminuria 441

- BP 150/95

Source: booking: adm 24 hrs 112

Hospital trans from or prev booked -

Flying squad: stage of labour 22

Induction, Hrs between and delievry 52

Episiotomy: transfusion 12

Rhesus incompatability 2

Anaesthetic: Operation 00

Pos on delivery baby I 9

Pos on delivery baby II □

Comp. of preg. 6370

Delivery baby I 325

Delivery baby II □□□

Comp. of Puer. -

Non-obststric disease -

Duration of labour 2

- duration 22:00

- date of delivery 20-08-69

Disposal 1

Stay 21

- date of discharge 29-08-69

PET admitted to rest

ARM Mild PET
failure to dilate

Vacuum ext. & epis

---------- o ----------

NAD
LMP & FLACCID
at birth

BABY I

Sex 1

Weight 39

- birthweight □809

Drugs to baby □

Oxygen 1

Type of feeding □

Blood group 9

Dis/SB. baby Y800

Cause of death/SB □

Result 1

BABY II

Sex □

Weight □

- birthweight □□□□

Drugs to baby □

Oxygen □

Type of feeding □

Blood group □

Dis/SB. baby □□□□

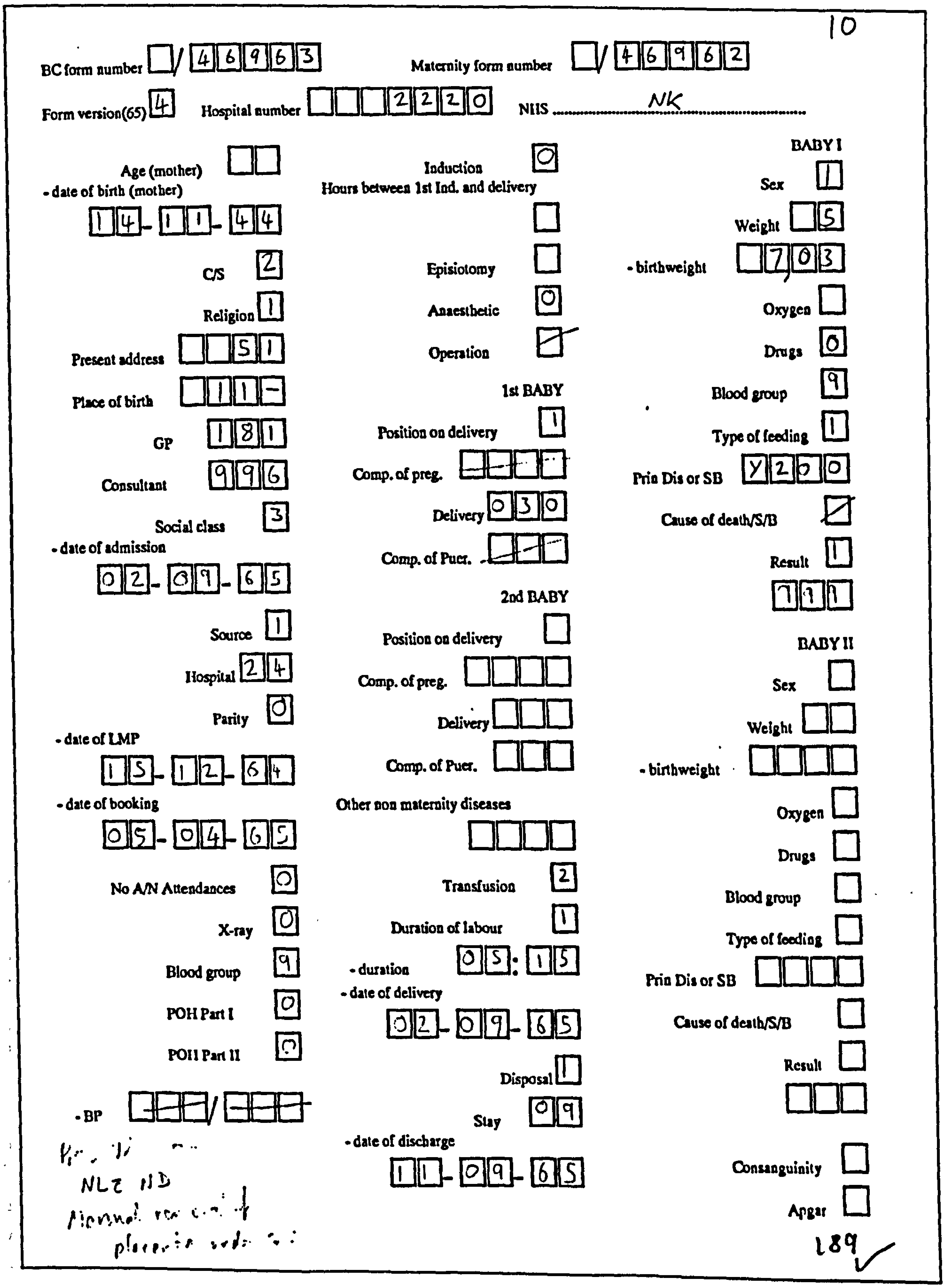
Cause of death/SB □

Result □

Consanguinity 3

Apgar X

Figure D.1: An example of the blue delivery data extraction sheet used for hospital births, 1968–69



10

BC form number [ ]/ 4 6 9 6 3 Maternity form number [ ]/ 4 6 9 6 2

Form version(65) 4 Hospital number [ ][ ][ ] 2 2 2 0 NHS ....NK........

Age (mother) [ ][ ]	Induction 0	BABY I
- date of birth (mother) 14-11-44	Hours between 1st Ind. and delivery [ ]	Sex 1
C/S 2	Episiotomy [ ]	Weight [ ] 5
Religion 1	Anaesthetic 0	- birthweight [ ] 7 0 3
Present address [ ][ ] 5 1	Operation [ ]	Oxygen [ ]
Place of birth [ ] 1 1 -	1st BABY	Drugs 0
GP 1 8 1	Position on delivery 1	Blood group 9
Consultant 9 9 6	Comp. of preg. [ ][ ][ ][ ]	Type of feeding 1
Social class 3	Delivery 0 3 0	Prin Dis or SB Y 2 0 0
- date of admission 02-09-65	Comp. of Puer. [ ][ ][ ]	Cause of death/S/B [ ]
Source 1	2nd BABY	Result 1
Hospital 2 4	Position on delivery [ ]	7 1 1
Parity 0	Comp. of preg. [ ][ ][ ][ ]	BABY II
- date of LMP 15-12-64	Delivery [ ][ ][ ]	Sex [ ]
- date of booking 05-04-65	Comp. of Puer. [ ][ ][ ]	Weight [ ][ ]
No A/N Attendances 0	Other non maternity diseases [ ][ ][ ][ ]	- birthweight [ ][ ][ ][ ]
X-ray 0	Transfusion 2	Oxygen [ ]
Blood group 9	Duration of labour 1	Drugs [ ]
POH Part I 0	- duration 05:15	Blood group [ ]
POH Part II 0	- date of delivery 02-09-65	Type of feeding [ ]
- BP [ ][ ][ ]/[ ][ ][ ]	Disposal 1	Prin Dis or SB [ ][ ][ ][ ]
	Stay 0 9	Cause of death/S/B [ ]
	- date of discharge 11-09-65	Result [ ]
		[ ][ ][ ]
		Consanguinity [ ]
		Apgar [ ]

NLZ ND

189

Figure D.2: An example of the green delivery data extraction sheet used for hospital births, 1965–68

27

BC form number 5/56765. Maternity form number 5/56964

Form version(D) 5 Hospital number NHS .....

Age (mother)

- date of birth (mother) 23-12-44

Place of birth 00/

Present address 00

Civil State 2

GP 367

Social class 3

Husband's occupation

Religion

Ante-natal care 1

- date of LMP 10-02-65

- date of booking 01-07-65

Total visits 6

Parity 1

Blood group 5

POH Part I 0

POH Part II 0

X-ray site 0

BP 33

- BP 130/88

Albuminuria 0

Illness in pregnancy /

LOA SMD

Induction 0

Hours between 1st Ind. and delivery

Episiotomy

Anaesthetic

Operation /

1st BABY

Position on delivery 1

Comp. of preg. ----

Delivery 000

Comp. of Puer. ---

2nd BABY

Position on delivery

Comp. of preg.

Delivery

Comp. of Puer.

Other non-maternity diseases

Duration of labour 1

- duration 04:45

Present at delivery 1

Admitted to hospital 0

Flying squad 0

Transfusion

- date of delivery 01-12-65

BABY I

Sex 1

Weight 5

- birthweight 7,04

Drugs to baby 0

Blood group

Oxygen

Type of feeding 3

Prin Dis or SB 1223

Cause of death/S/B /

Result 1

Apgar

BABY II

Sex

Weight

- birthweight

Drugs to baby

Blood group

Oxygen

Type of feeding

Prin Dis or SB

Cause of death/S/B

Result

Apgar

Consanguinity

98

Figure D.3: An example of the yellow delivery data extraction sheet used for domiciliary births, 1965–69

Appendix E

Migration Bias: Mathematical Details

1. $ID_{(i,j)}$ is the incidence rate for cause i in exposure group j, assumed constant over age and period ($i = 0$ for migration, $i = 1$ for disease under study; $j = 0$ for unexposed group, $j = 1$ for exposed group.)

2. f = proportion of study population exposed at start of study relative to the baseline group.

3. L = proportion of study population that migrate by the end of the study period.

4. RR_{true}, the true disease-exposure relative risk, is the ratio of the disease rate in the exposed group to the disease rate in the unexposed group:

$$RR_{true} = \frac{ID_{(1,1)}}{ID_{(1,0)}}$$

5. The total rate at which subjects are lost from the 'at risk' set in unexposed ($j = 0$) or exposed ($j = 1$) group is given by the sum of the rates for migration and disease:

$$ID_{(\cdot,j)} = ID_{(0,j)} + ID_{(1,j)}$$

6. The migration ($i = 0$) or disease ($i = 1$) rate in the study population at start of study is given by the average rate over the unexposed and exposed groups:

$$ID_{(i,\cdot)} = (1 - f) \times ID_{(i,0)} + f \times ID_{(i,1)}$$

7. The proportion of the study population, (L), that has migrated from the study area in time T is given by 1 minus the proportion of people still left in the study area:

$$L = 1 - \{f \times \exp(-ID_{(0,1)} \times T) + (1 - f) \times \exp(-ID_{(0,0)} \times T)\}$$

8. The odds ratio for migration in relation to exposure, $OR_{migratiom}$, is given by

$$OR_{migration} = \frac{\{1 - \exp(-ID_{(0,1)} \times T)\} \div \exp(-ID_{(0,1)} \times T)}{\{1 - \exp(-ID_{(0,0)} \times T)\} \div \exp(-ID_{(0,0)} \times T)}$$

9. The biased disease-exposure relative risk, RR_{biased}, is given by (see [36], equation 1)

$$RR_{biased} = \frac{\frac{ID_{(1,1)}}{ID_{(\cdot,1)}}\{1 - \exp(-ID_{(\cdot,1)} \times T)\} \div \left[1 - \frac{ID_{(1,1)}}{ID_{(\cdot,1)}}\{1 - \exp(-ID_{(\cdot,1)} \times T)\}\right]}{\frac{ID_{(1,0)}}{ID_{(\cdot,0)}}\{1 - \exp(-ID_{(\cdot,0)} \times T)\} \div \left[1 - \frac{ID_{(1,0)}}{ID_{(\cdot,0)}}\{1 - \exp(-ID_{(\cdot,0)} \times T)\}\right]}$$

A computer spreadsheet program may be used to solve the above equations subject to the constraint that all the equations are in agreement. For example, if f=0.90, L=0.50, $OR_{migration}$=8.00, $ID_{(0,\cdot)}$=2.5 per 100 person-years, and RR_{true}=2.0, then T=28.6 years, $ID_{(0,0)}$=0.48 per 100 person-years, $ID_{(1,0)}$=5.26 per 100,000 person-years, $ID_{(0,1)}$=2.72 per 100 person-years, and $ID_{(1,1)}$=10.53 per 100,000 person-years. This satisfies the equations above and give RR_{biased}=1.487. The bias, relative to RR_{true}, is then 1.487÷2.00, or 74%.

Appendix F

The Diabetes Study

F.1 Children with a hospital diagnosis of diabetes

The Oxford Record Linkage Study (ORLS) identified 330 children, from general hospital files, who had a diagnosis of diabetes during 1965-87 and had been born during 1965–85. Children with cystic fibrosis, major congenital anomalies or who were part of twin or higher order deliveries were excluded from the analyses, as detailed below.

F.1.1 Exclusions from the case group

Diseases known to cause diabetes

Three children with diabetes (0.9%) had diagnoses of cystic fibrosis (of pancreas) that predated the diagnosis of diabetes by six to thirteen years. Cystic fibrosis is a condition which is known to cause diabetes [50] and the aetiology of diabetes in the presence of cystic fibrosis is different to that of idiopathic or 'uncomplicated' diabetes. These three children, therefore, were excluded from the study. None of the control group had a diagnosis of cystic fibrosis. There was no mention of diabetes secondary to other causes, like haemochromatosis, chronic pancreatitis or Cushing's disease.

Major congenital anomalies

The International Classification of Diseases, revision 8 (ICD 8) was used almost exclusively to record malformations for births during 1970–72 but there were a few exceptions where ICD 9 codes were used. ICD 9 was used exclusively during 1973–86. Congenital anomalies coded on the delivery record under ICD 8 were re-coded to their equivalent code under ICD 9.

The classification system of ICD 8 and 9 does not in itself separate major from minor congenital anomalies (for example, xeroderma pigmentosum and birthmarks both have the same four digit level classification *Other specified anomalies of skin*). The approach adopted, therefore, was to identify those congenital anomaly codes that occurred frequently and to decide whether the anomalies within those ICD categories were most likely to be minor or major anomalies. The distinction between minor and major congenital anomalies was partly based upon criteria used by the Liverpool Congenital Malformations Registry [318] and which have been used in other epidemiological studies [319].

Major congenital anomalies were taken to be any condition mentioned under ICD 9 chapter XIV (Congenital Anomalies, ICD 9: 740.0–759.9) less the following common conditions considered to be minor anomalies: accessory auricle (744.1); absence or hypoplasia of umbilical artery (747.5); undescended testicle (752.5); hypospadias and epispadias (752.6); congenital dislocation of hip (754.3) and congenital anomalies of the integument (757.0–757.9). Hydrocele (778.6), part of the congenital anomaly chapter in ICD 8 but not ICD 9, was considered to be a minor anomaly.

There were seven children (2.1%), five boys and two girls, with at least one mention of a major congenital anomaly. The aetiology of diabetes when associated with a major congenital anomaly is likely to be different from that of idiopathic diabetes. For example, diabetes may be one small part of a syndrome like Turner's or Down's [50]. The seven children with major congenital anomalies were therefore excluded from the case group.

Multiple births

Two boys and one girl with diabetes (0.9%) were part of three twin deliveries. These children were also excluded from the main analyses because the aetiology of diabetes in twin or higher order births may be different to that in singletons.

F.2 The cases

The 315 (95.5%) children that remained in the study, after exclusions due to cystic fibrosis, major congenital anomalies or multiple deliveries, became the cases. There were 160 (50.8%) boys and 155 (49.2%) girls. The same exclusion criteria were used when the control group was assembled.

Figures F.1, F.2 and F.3 show the distribution of year of birth, year of ascertainment and age of ascertainment among the 315 cases. The date of ascertainment was the date of the first known hospital diagnosis for diabetes, as recorded by the ORLS. Four cases were

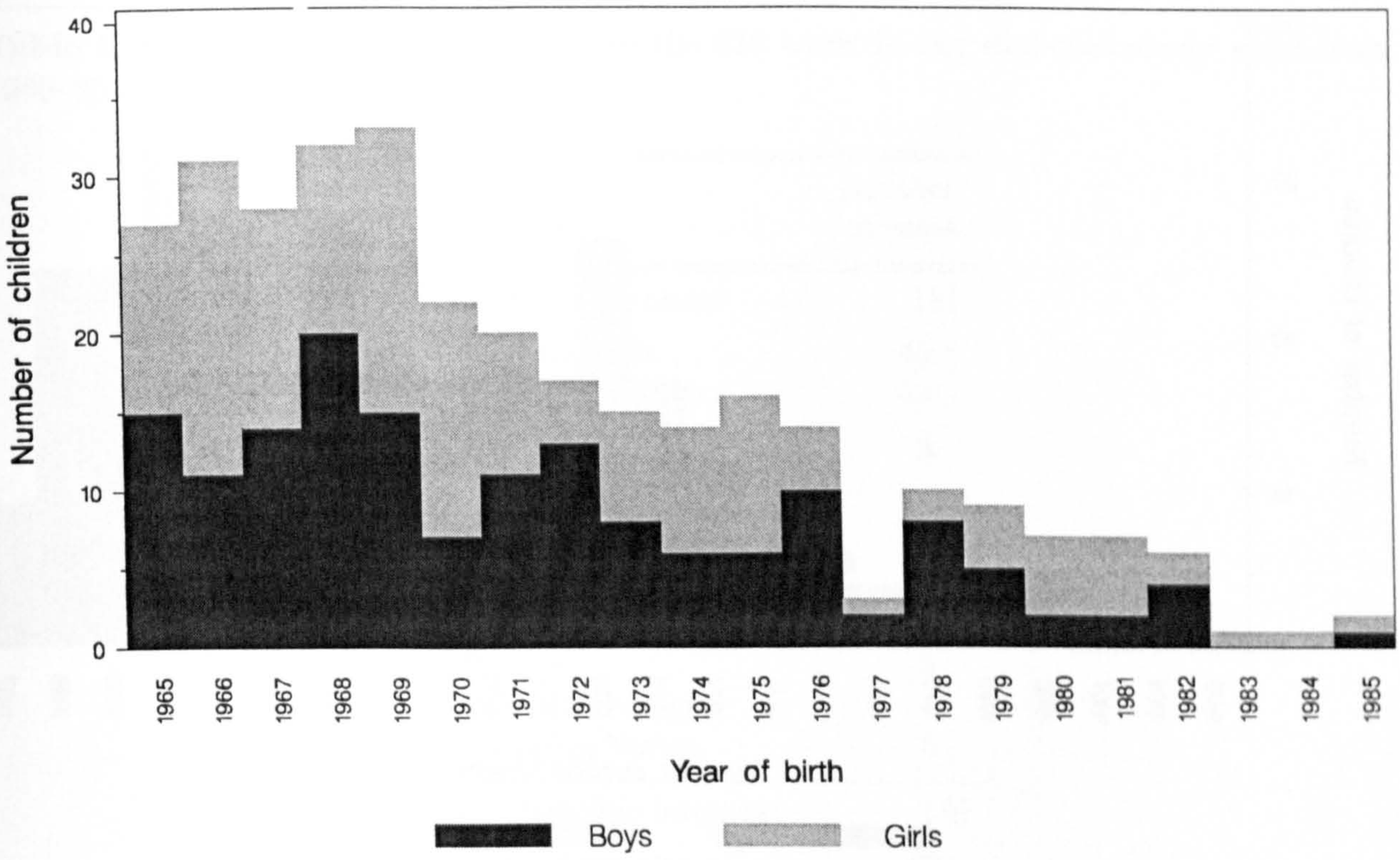


Figure F.1: Year of birth of the 315 cases with diabetes

diagnosed diabetic at birth, followed by cases at 33, 89 and 139 days after birth. Note that since the study period ended in 1987, and children had to have been born during 1965–85 to enter the study, these distributions do not reflect incidence rates. The distributions are biased towards the early years of birth, younger age at ascertainment and later year of ascertainment.

Only three cases were born in 1977 whereas in 1976 and 1978 there were, respectively, 14 and 10 cases born. Remembering that diabetic cases were only selected into this study if there was a delivery abstract present on the ORLS system, such a deficit of cases in one year might be due to a large maternity hospital, or hospitals, not completing or returning to the ORLS, delivery abstracts for births during that year. Cross-tabulation of year of birth by hospital suggested that there were a deficit of cases born in the John Radcliffe hospital in 1977; there were no cases in 1977 whereas in the 1976 and 1978 there were 3 and 6 cases respectively.

F.2.1 Diagnosis of diabetes

Tables F.1 and F.2 list the hospitals where the cases were born and where they were later diagnosed with diabetes. Eighteen (5.7%) of the cases were diagnosed in hospitals outside of Oxfordshire or West Berkshire and 32 (10.2%) deliveries, all during 1965–69, were domiciliary. The 32 domiciliary deliveries represented 21.2% of deliveries between 1965–69, which

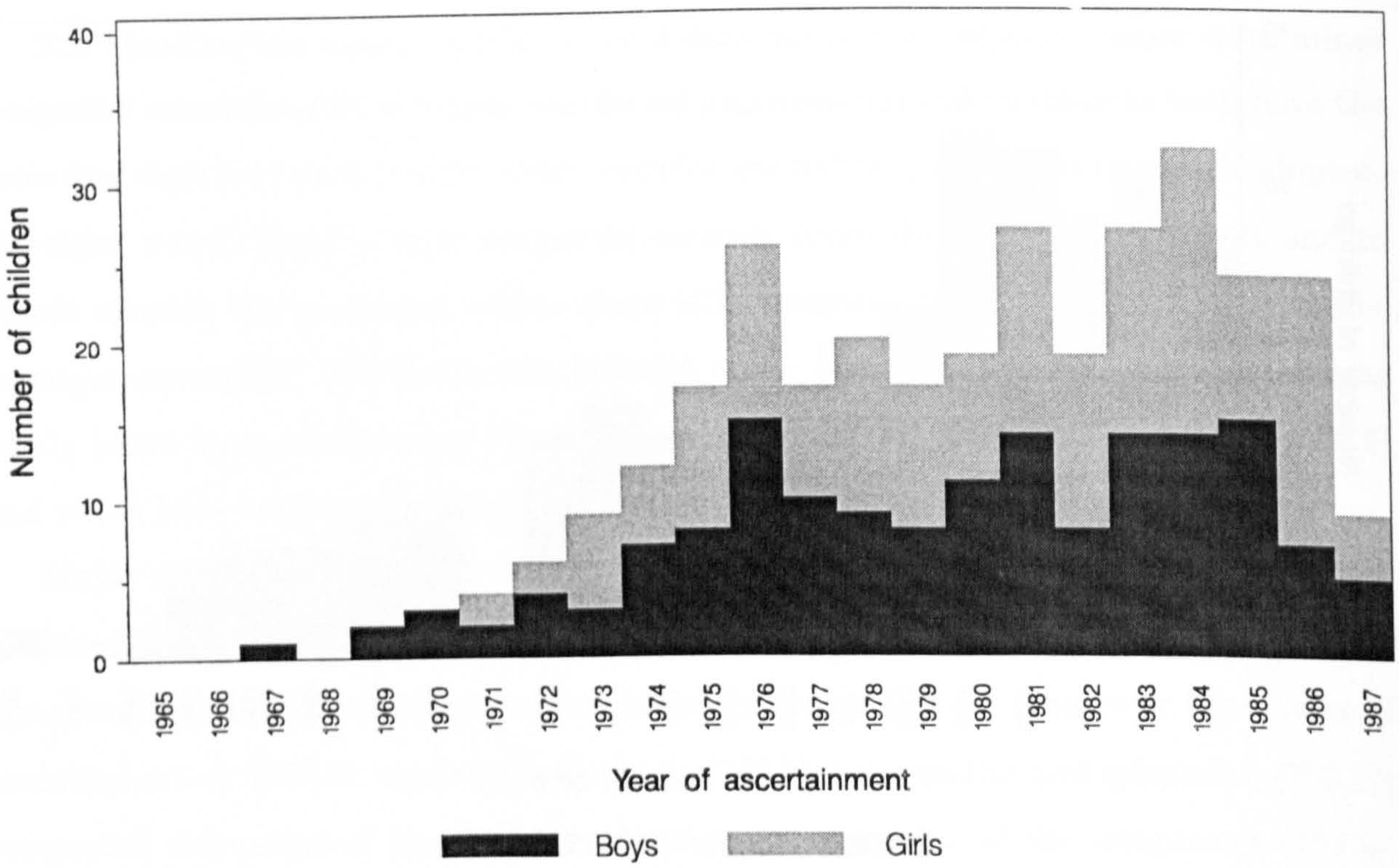


Figure F.2: Year of ascertainment of the 315 cases with diabetes

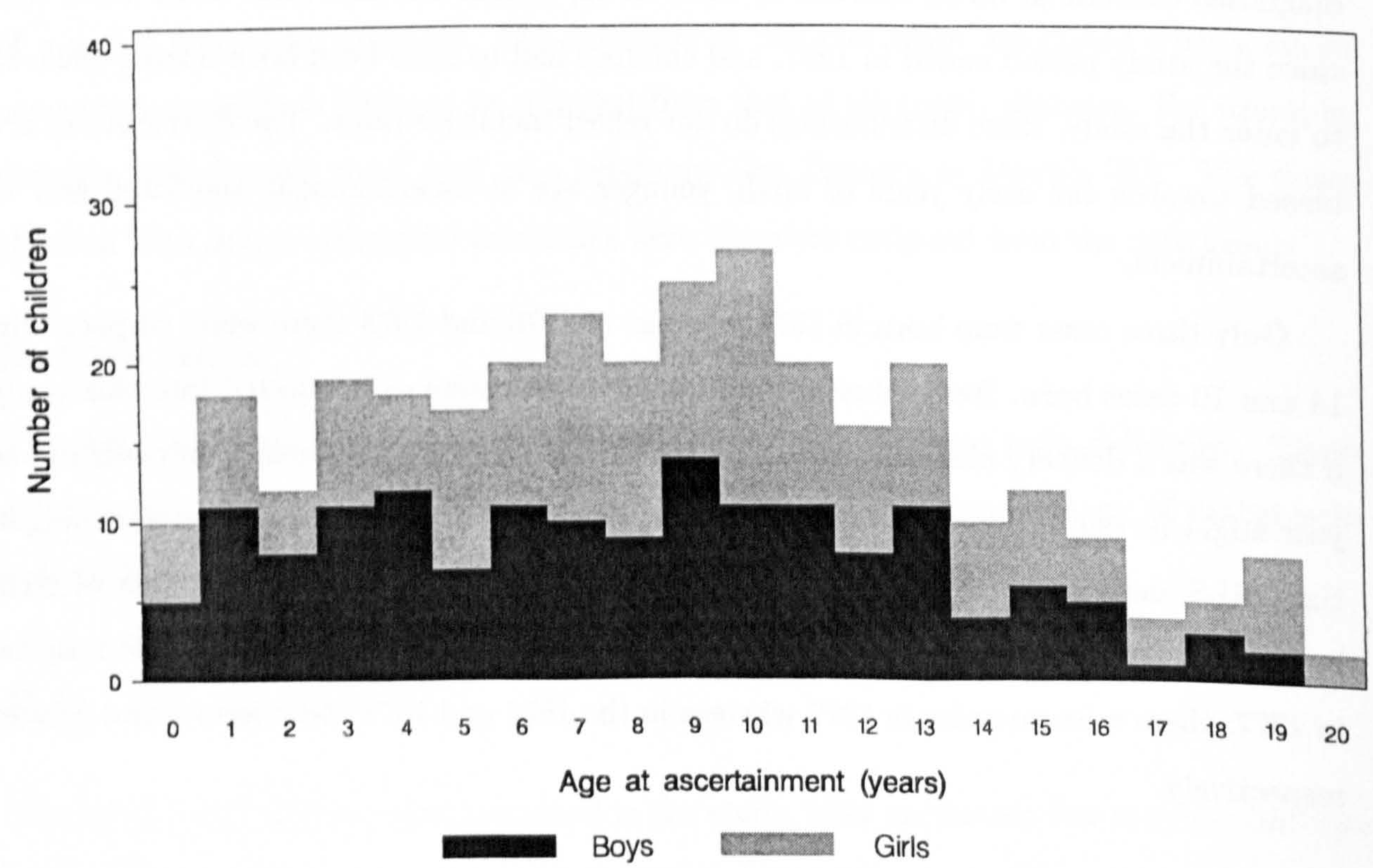


Figure F.3: Age at ascertainment for the 315 cases with diabetes

is similar to the 18.5% reported for all of Oxfordshire and West Berkshire during the same period [308].

Table F.1: Districts and hospitals where the 315 cases in the diabetes study were born, 1965–85

District Hospital		Number of cases
Oxfordshire hospitals		*151*
John Radcliffe		45
Radcliffe Infirmary		42
John Radcliffe	GP unit	8
Churchill		15
Horton Maternity		22
Abingdon		1
Wantage		4
Warren		5
Bicester Cottage		4
Chipping Norton		5
West Berkshire hospitals		*130*
Royal Berkshire		62
Battle		22
Dellwood Maternity		16
Wokingham		13
Sandleford		7
St. George's		4
Townlands		4
Wallingford		2
District not known		*2*
Hospital not known		2
Domiciliary		*32*
Oxfordshire		10
West Berkshire		22
Total		315

F.2.2 Associated diagnoses

During the hospital admission were diabetes was first mentioned two hundred and sixty-two (83.2%) of the children entered as emergency admissions, a further two (0.6%) were admitted for accidents, and four (1.3%) were diagnosed when born in hospital and required special medical attention. The remaining admissions were mostly booked or from the waiting list.

Not including diabetes, there were 77 other diagnoses recorded during the hospital visit when the cases had their (first known) diagnosis of diabetes. Table F.3 lists the diagnoses by broad heading. It was not appropriate to compare the general hospital diagnoses among the cases with those of the controls. Cases, because of their diabetes, were more likely

Table F.2: Districts and hospitals in which the 315 cases with diabetes were ascertained

District Hospital	Number of cases
Oxfordshire	*157*
John Radcliffe	74
Radcliffe Infirmary	29
Churchill	31
Horton General	21
Horton Maternity	1
Slade	1
West Berkshire	*143*
Royal Berkshire	83
Battle	59
Newbury District	1
East Berkshire	*7*
King Edward VII	2
Farnham Park	5
Northampton	*4*
Northampton General	4
High Wycombe	*2*
Wycombe General	1
Amersham General	1
Kettering	*1*
Kettering and District General	1
Aylesbury	*2*
Stoke Mandeville	2
Milton Keynes	*2*
Milton Keynes	2
Total	315

to enter hospital than controls. Once in hospital, diagnoses other than diabetes may be recorded which would not otherwise have been made.

Infectious and parasitic diseases were recorded among eight children. Two children had chicken pox, two had ill defined intestinal infections, two had candidiasis and the remaining two had rubella or an 'other viral disease.' One boy had a diagnosis of a neoplasm, being a 'malignant neoplasm of other endocrine glands and related structures.'

Table F.3: General hospital diagnoses during the index admission when the 315 cases with diabetes were ascertained

ICD 9* code	Discharge diagnosis	Number of diagnoses	
001–139	Infectious and parasitic diseases	9	
140–239	Neoplasms	1	
240–279	Endocrine, nutritional and metabolic diseases and immunity disorders	321	
250	*diabetes mellitus*		*315*
251	*disorders of pancreatic internal secretion other than diabetes mellitus*		*1*
280–289	Diseases of blood and blood forming organs	0	
290–319	Mental disorders	3	
317–319	*mental retardation*		*3*
320–389	Diseases of nervous system and sense organs	10	
345	*epilepsy*		*3*
360-379	*disorders of eye and adnexa*		*3*
380–389	*disorders of the ear and mastoid process*		*4*
390–459	Diseases of the circulatory system	4	
460–519	Diseases of the respiratory system	11	
460–466	*acute respiratory infections*		*5*
474	*chronic disease of tonsils and adenoids*		*1*
493	*asthma*		*1*
520–579	Diseases of the digestive system	9	
540–543	*appendicitis*		*3*
580–629	Diseases of the genitourinary system	5	
630–676	Complications of pregnancy, childbirth and the puerperium	0	
680–709	Diseases of the skin and subcutaneous tissue	0	
710–739	Diseases of the musculoskeletal system and connective tissue	0	
740–759	Congenital anomalies	4	
760–779	Certain conditions originating in the perinatal period	4	
780–799	Signs, symptoms and ill-defined conditions	8	
N800–N999	Injury and poisoning	3	
001–N999	All causes	392	

* International Classification of Diseases, 9th revision

F.2.3 Hospital admissions before and after the admission for diabetes

One hundred and twenty-three of the children with diabetes had 317 prior hospital discharge diagnoses and 184 of the children had 1111 subsequent diagnoses to mid 1987. Table F.4 lists the previous and subsequent diagnoses. Obviously, none of the prior admissions mentioned diabetes but 157 (49.8%) cases had a subsequent admission with a mention of diabetes. Of the seven subsequent admissions for poisoning, four were for the adverse effects of hormones

or synthetic substitutes. In the context of this study it is likely that these four events were related to the insulin treatment that is required by diabetic cases.

There were three children with a prior diagnosis of a neoplasm: one boy with a 'benign neoplasm of skin', and two girls with diagnoses of 'haemangioma and lymphangioma' and a 'malignant neoplasm of brain' respectively. None of these children had a further admission with a mention of a neoplasm.

Six of the children with diabetes had subsequent diagnoses of a neoplasm. One of these children was the same boy that had been previously diagnosed with a 'malignant neoplasm of other endocrine glands and related structures' at the index admission. This boy had in total 13 admissions with this diagnosis over a period of 10 months. One boy had a diagnosis of a 'malignant neoplasm of brain' and another boy had a diagnosis of lipoma. Two boys had diagnoses of polycythaemia, with one of them also having lymphatic leukaemia diagnosed on two other occasions. The remaining girl had a diagnosis of lymphatic leukaemia.

Table F.4: General hospital diagnoses prior to, and subsequent to, the index hospital admission for 315 cases with diabetes

ICD 9* code	Discharge diagnosis	Number of diagnoses Before first diagnosis of diabetes	After
001–139	Infectious and parasitic diseases	12	24
140–239	Neoplasms	3	22
240–279	Endocrine, nutritional and metabolic diseases and immunity disorders	6	680
250	*diabetes mellitus*	*0*	*626*
251	*disorders of pancreatic internal secretion other than diabetes mellitus*	*2*	*46*
280–289	Diseases of blood and blood forming organs	4	1
290–319	Mental disorders	8	15
317–319	*mental retardation*	*8*	*7*
320–389	Diseases of nervous system and sense organs	62	53
345	*epilepsy*	*14*	*11*
360-379	*disorders of eye and adnexa*	*13*	*6*
380–389	*disorders of the ear and mastoid process*	*27*	*22*
390–459	Diseases of the circulatory system	3	6
460–519	Diseases of the respiratory system	71	72
460–466	*acute respiratory infections*	*5*	*36*
474	*chronic disease of tonsils and adenoids*	*32*	*7*
493	*asthma*	*18*	*10*
520–579	Diseases of the digestive system	14	50
540–543	*appendicitis*	*0*	*9*
580–629	Diseases of the genitourinary system	10	31
630–676	Complications of pregnancy, childbirth and the puerperium	0	9
680–709	Diseases of the skin and subcutaneous tissue	5	15
710–739	Diseases of the musculoskeletal system and connective tissue	7	3
740–759	Congenital anomalies	22	9
760–779	Certain conditions originating in the perinatal period	3	2
780–799	Signs, symptoms and ill-defined conditions	32	68
N800–N999	Injury and poisoning	55	51
493	*poisoning*	*3*	*7*
001–N999	All causes	317	1111

* International Classification of Diseases, 9th revision

F.3 The controls

Initially each case born during 1970–85 was matched with up to eight livebirths on sex, hospital (or domiciliary birth) and year of delivery and each case born during 1965–69 was matched with two livebirths on sex, place of delivery (hospital or domiciliary) and year of delivery. This produced a list of 1,612 potential controls. See section B.3 for more details about control selection. None of the potential controls had a diagnosis of cystic fibrosis. The list of potential controls was examined and livebirths were successively excluded from entry to the control group if: they had a major congenital anomaly diagnosed at birth (n=41, 2.5%); they were part of a multiple delivery (n=30, 1.9%,); they were known to have died *before* the date at which their matched case was diagnosed with diabetes (n=15, 0.9%); or they were themselves diagnosed with diabetes *before* the date at which their matched case was diagnosed with diabetes (n=1, 0.1%). The last two conditions were used to try and ensure that the controls had had the same opportunity for diagnosis of diabetes as the cases. Ideally, children should also have been excluded from the control group if they had migrated from the study area before their matched case had been diagnosed with diabetes, but sufficient information about migration was not available to do this. The potential bias caused by migration is discussed in more detail in section 3.

The above selection criteria made it possible to estimate incidence ratios for diabetes in relation to perinatal risk factors. Appendix B.3 discusses control selection in more detail.

The remaining 1525 livebirths became the matched control group. The control group was actually made up of 1520 individuals, of whom five (0.3%) entered into the study more than once, in different matched sets, as controls, and one (0.1%) was later affected and also entered the study as a case. Allowing a control person to become a case and allowing controls to be re-selected was valid in the context of this study design [320, 321]. Table F.5 shows the number of controls in each matched set.

Table F.5: Number of matched sets by number of controls in each matched set for the 315 cases with diabetes and their 1525 matched controls

	Year of birth					
	1965–69		1970–85		1965–85	
Number of controls in matched set	Number of matched sets*	Percent	Number of matched sets	Percent	Number of matched sets	Percent
8			105	62.9	105	33.3
7			47	28.1	47	14.9
6			11	6.6	11	3.5
5			1	0.6	1	0.3
4			0	0.0	0	0.0
3			1	0.6	1	0.3
2	130	87.2	2	1.2	132	41.9
1	18	12.2	0	0.0	18	5.7
Total	148	100.0	167	100.0	315	100.0

* For birth during 1965–69 not more than two controls were matched to each case

Appendix G

Issues Concerning the Selection of Controls

G.1 Introduction

It has been argued that, in aetiologic studies, odds ratios are useful only when they serve as approximations to the incidence ratio for disease in the exposed group relative to the unexposed group [322]. Under the rare disease assumption odds ratios approximate rate ratios and risk ratios, and these are easier to interpret than odds ratios. When the disease is not rare, either because the incidence is high or the study period is so long that the cumulative incidence of disease is not small, the agreement between odds ratios, rate ratios and risk ratios is not good [323]. Appropriate sampling of controls, however, allows direct estimation of the rate ratio, odds ratios, or risk ratio [323, 324]. The rare disease assumption need not be invoked and the investigator is free to choose the measure of association that will be most appropriate for the study [324].

G.1.1 Incidence density sampling

Incidence density sampling is a term used to describe a form of sampling that allows rate ratios to be estimated directly from case-control studies [323]. Controls are selected from the population at risk of disease at the time of onset of each case [323]. The consequences of this are that [320, 325]:

- a control who subsequently develops disease can then serve as a case;
- the same individual can serve as a control for more than one case, provided he or she is disease free at that time.

The study is implicitly stratified on time of disease onset, and as this can usually be considered unique to each case, the method of analysis is that used for matched case-control studies [326].

To apply this sampling scheme it is necessary to determine who is at risk at any point in time, and to sample randomly from that group. In nested case-control studies this is possible because the entire cohort in which the case-control study is nested is under observation. In population based case-control studies this may be possible if the population from which cases arise can be enumerated. In some case-control studies, however, it is not possible to enumerate or even define the population at risk and for practical reasons controls are chosen from some other, possibly ill-defined, population (e.g. hospital controls; neighbourhood controls; historic controls).

G.1.2 Similarities between case-control and cohort studies

The similarities between cohort studies and case-control studies becomes apparent under incidence density sampling. A nested case-control study can be viewed as an alternative and possibly more efficient way to analyse a large cohort study. The case series provides information about numerators, and denominators are provided by sampling a fraction of the cohort—the controls [324, 327]. Exposure data for the entire cohort must potentially be available, but only that portion for the selected cases and controls need be processed. For example, resources may be used more efficiently if only a fraction of the cohort need be interviewed, or have questionnaires coded and entered onto a computerised database, or have biochemical markers of exposure analysed in a laboratory.

In one sense, all case-control studies that can employ incidence density sampling are nested within the cohort of the population at risk. The case series is not compared to the control series, but rather it is supplemented with information about the population at risk [327]. Unfortunately the word 'controls' is often taken to mean not-diseased, but here it takes on a broader meaning and the control group may include diseased individuals, and the same individual more than once [320, 325].

G.1.3 The diabetes study

In the study of diabetes the principles of incidence density sampling were used to select controls because the parameter of interest was considered to be the ratio of disease incidence rates in exposed relative to unexposed groups. Unfortunately it was not possible to enumerate the population at risk each time a case was diagnosed and thus the observed incidence

rate ratios were potentially biased. It was possible, however, to estimate the amount of bias introduced by the compromised sampling scheme, and this bias due to migration was discussed in detail in chapter 3.

G.1.4 Estimating risk ratios or prevalence ratios

In the study of undescended testes diagnosed at birth the parameter of interest was the ratio of disease prevalence among livebirths in exposed relative to unexposed groups. Prevalence is the proportion of the population affected by the disease at a given time [328], and at birth this is the same as the risk of being affected among all livebirths. In the studies of undescended testes diagnosed at orchidopexy and the study of inguinal hernia, each condition was considered to be present, but not necessarily diagnosed, at birth. Prevalence ratios at birth therefore, were, considered to be the parameter of interest. The choice, however, was mostly academic because earlier results based upon incidence ratios were similar to those based upon prevalence ratios.

In the epidemiologic literature the sampling scheme for prevalence or risk ratios, however, is not as clearly expressed as that for incidence rate ratios. It was not clear how controls should be sampled in the matched studies presented in the main part of this thesis. This question was answered by simulating three different control selection schemes and comparing the results with the known prevalence ratio.

G.2 Simulation exercise

G.2.1 Methods

Three sampling schemes were considered for a matched case-control study where the parameter of interest was the prevalence ratio. Each scheme used different criteria for selecting controls from simulated dataset.

1. Sampling from the *whole* population without replacement within matched sets but with replacement between sets:
   - for each case n controls were selected, without replacement from the remaining population (i.e. no person was allowed to enter into the same matched set more than once);
   - the above selection procedure was repeated for each case regardless of who had been previously selected (i.e. a person may be selected more than once, but can only enter into different sets).

Table G.1: The population of 102,000 people which form the basis of the simulation study to examine three sampling schemes

	Simulated dataset			
	Affected	Unaffected	Total	Prevalence
Exposed	400	5000	5400	7.41%
Unexposed	1600	95000	96600	1.66%
Total	2000	100000	102000	1.96%
Proportion exposed	20.00%	5.00%	5.29%	

True prevalence or risk ratio: 7.41/1.66 = 4.47
True prevalence odds ratio: (400*95000)/(5000*1600) = 4.75

2. Sampling from the *unaffected* population without replacement within matched sets but with replacement between sets:

   - similar to the previous scheme, but cases were not allowed to become controls (i.e. controls may appear in different sets but they were disease free at all times during follow-up).

3. Sampling from the *unaffected* population without replacement within *and* between matched sets:

   - similar to the previous scheme (i.e. scheme 2), but as well as excluding affected people from the control group, people were only allowed to enter into one matched set.

To study the effect of these different sampling schemes a dataset was created with 2,000 affected and 100,000 unaffected individuals. In the affected group 20% of people were marked as exposed, and in the unaffected group 5% of people were marked as exposed. The prevalence or risk of being affected was 7.41% in the exposed group and 1.66% in the unexposed group. The prevalence or risk ratio was 4.47 and the odds ratio was 4.75. These figures are presented in table G.1.

All 2,000 cases were selected from the dataset, and up to 10 controls were selected for each case according to the three different sampling schemes. In practice, controls were selected according to sampling scheme 1, and the additional exclusion criteria of schemes 2 and 3 were applied to generate controls groups conforming to these schemes.

Table G.2: Result of 20 simulations for the three different sampling schemes

Sampling scheme‡	Average parameter estimate*	95% confidence interval†
1	4.51	4.43–4.58
2	4.80	4.71–4.89
3	4.95	4.86–5.04

* Transformed mean of 20 conditional logistic regression parameter estimates (β)
† Confidence interval based on sample of 20 parameter estimates
‡ See text for description

Conditional logistic regression was used to estimate the relative risk[1] based on the three sampling schemes. Table G.2 presents results from 20 sampling simulations. The estimated relative risk from sampling scheme 1 was consistent with the true prevalence or risk ratio. The relative risk from sampling scheme 2 was consistent with the true odds ratio. The relative risk from sampling scheme 3 was not consistent with either the prevalence ratio or the odds ratio.

G.3 Conclusions

Sampling scheme 1 was appropriate for estimating prevalence ratios and has been used in the studies of cryptorchidism and inguinal hernia. With the benefit of hindsight it can be seen that this scheme follows naturally from incidence density sampling. Sampling scheme 2 might also have been expected to estimate the odds ratio, and this was also verified. Odds ratios, however, are not as appealing as prevalence ratios and scheme 2 was not used in the studies presented in the main part of this thesis.

Sampling scheme 3 demonstrates that if subjects are not allowed to re-enter into different matched sets the relative risk estimates neither a prevalence ratio nor an odds ratio. It is debatable whether sampling scheme 3 serves any useful purpose, other than to show the direction of association. There would appear to be no good reason to use scheme 3 when schemes 1 and 2 are just as easy to implement.

The statistical efficiency and standard errors for each scheme were not considered, but these were secondary issues to estimating an unbiased relative risk.

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[1] Relative risk is used as a generic term to describe the association between exposure and disease — usually it is a rate ratio or an odds ratio, but it may also be a biased estimate of either of these two measures.

Appendix H

Undescended Testis Diagnosed at Birth

H.1 Boys with a diagnosis of 'undescended testicle' at birth

The Oxford Record Linkage Study (ORLS) identified 1070 boys from delivery records who were born during 1970-86 and had undescended testes recorded at birth. Boys with major congenital anomalies or boys who were part of twin or higher order deliveries were subsequently excluded from the case-control analyses.

H.1.1 Congenital anomalies

Table H.1 shows the frequency with which major congenital anomalies were mentioned on the ORLS delivery record in boys with a diagnosis of cryptorchidism at birth.

There was room to record up to ten malformation diagnoses on the ORLS delivery file, although during 1970–72 only one was routinely recorded. During 1970–72 that single diagnosis had to be 'undescended testicle' if the boy was to be selected into this study. If a boy born during 1970–72 had an undescended testis and a major congenital anomaly it was likely that the more serious condition would take precedence, hence boys with major congenital anomalies born during this period would automatically be excluded from the case group. Classification of congenital anomalies into major and minor anomalies was described in section F.1.1.

Among boys with major anomalies the aetiology of cryptorchidism is likely to be different from that of idiopathic or 'uncomplicated' cryptorchidism. For example, cryptorchidism may be one small part of a syndrome like Down's or Prader-Willi [212–214]. Eighty-four (7.9%) boys, therefore, with at least one mention of a major congenital anomaly were

Table H.1: Major congenital anomalies mentioned at birth among 84 boys with undescended testis diagnosed at birth who had any such anomalies

ICD 9* code	Description of major congenital anomaly	Number of mentions of an anomaly
740.0–740.9	Anencephalus and similar anomalies	0
741.0–741.9	Spina bifida	0
742.0–742.9	Other congenital anomalies of nervous system	1
743.0–743.9	Congenital anomalies of eye	3
744.0, 744.2–744.9	Congenital anomalies of ear, face and neck (*less* accessory auricle)	3
745.0–746.9	Bulbus cordis anomalies and anomalies of cardiac septal closure, *and* Other congenital anomalies of heart	3
747.0–747.4, 747.6–747.9	Other congenital anomalies of circulatory system (*less* absence or hypoplasia of umbilical artery)	13
748.0–748.9	Congenital anomalies of respiratory system	3
749.0–749.9	Cleft palate and cleft lip	3
750.0–750.9	Other congenital anomalies of upper alimentary tract	2
751.0–751.9	Other congenital anomalies of digestive system	2
752.0–752.4, 752.7–752.9	Congenital anomalies of genital system, (*less* undescended testicle *and* hypospadias)	28
753.0–753.9	Congenital anomalies of urinary system	3
754.0–754.2, 754.4–756.9,	Certain congenital anomalies of limbs, *and* Other congenital anomalies of limbs, *and* Other congenital musculoskeletal deformities (*less* congenital dislocation of hip)	36
758.0–759.9	Chromosomal anomalies, *and* Other and unspecified anomalies	6
	Any major congenital anomaly	106

* International Classification of Diseases, 9th revision

subsequently excluded from the case group.

H.1.2 Multiple births

Forty boys (3.7%) were part of a twin delivery. There were no triplet or higher order deliveries but one of the twins with undescended testes also had a mention of a major congenital anomaly. Boys from twin deliveries were also excluded from the main analyses because the aetiology of cryptorchidism in twin or higher order births may be different to that in singletons. The 40 twin boys were part of 37 twin pairs, which were made up of 12 (32.4%) pairs with a female co-twin and 25 (67.6%) pairs with a male co-twin; both boys were affected in three of the like-sex twin pairs. For comparison, in England and Wales during 1974–84 the proportion of liveborn twin boys who were born with a female or a male

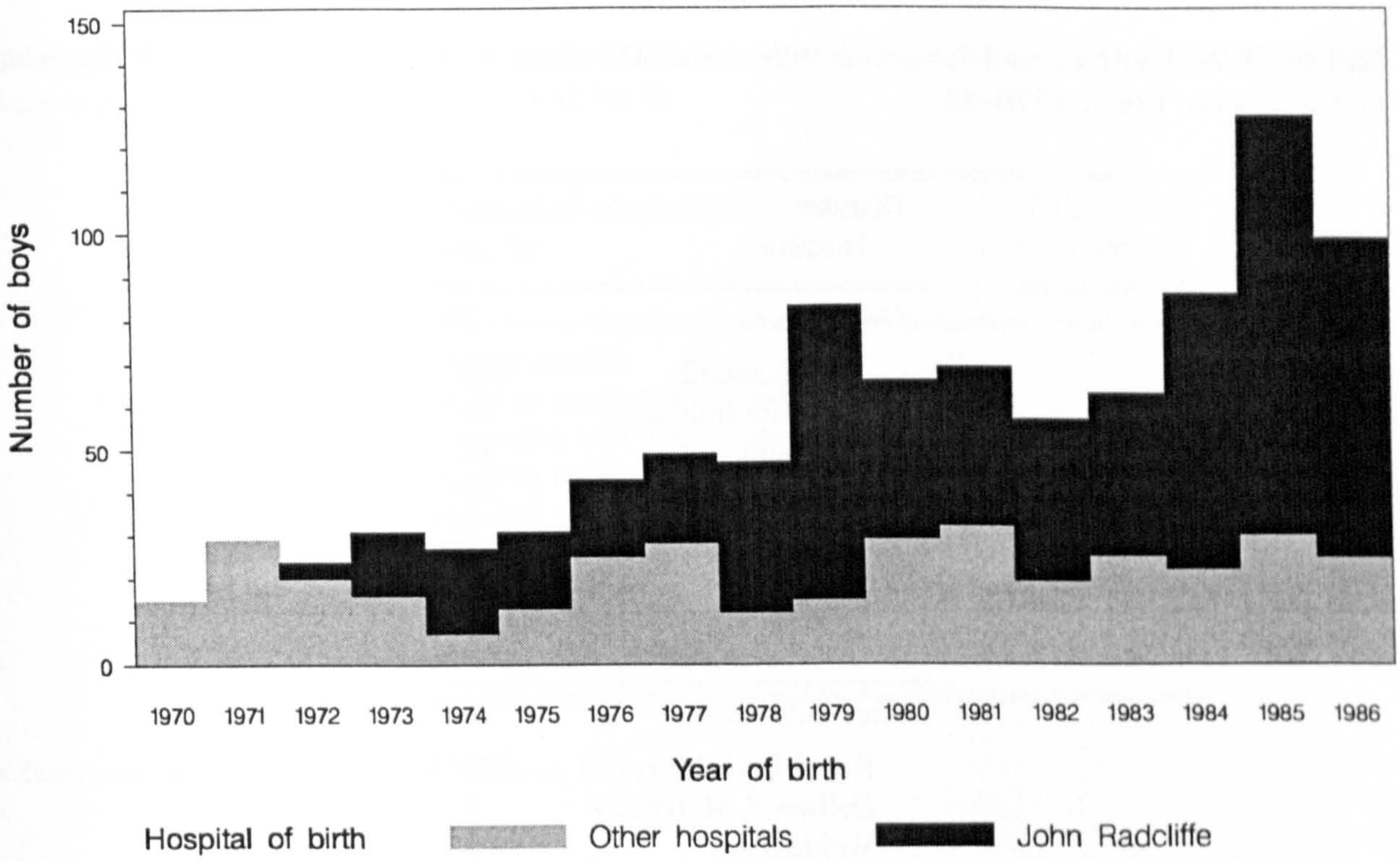

Figure H.1: Year of birth of the 947 cases diagnosed with cryptorchidism at birth

co-twin was 29.4% and 70.6% respectively [329].

Among the 22 male-male twin sets where only one boy was affected there were 11 sets where the co-twin was heavier at birth than the affected twin, 10 sets where the co-twin was lighter and one set where the co-twin's birth weight was unknown. Among the 12 male-female twin sets there were five sets where the female co-twin was heavier and in the remaining seven sets the affected boy was heavier. In 12 of the male-male twin sets the affected twin was born first and in the remaining 10 sets the co-twin was first born. In six of the male-female twin sets the affected boy was born first and in the remaining six sets the female twin was first born. There was no evidence, as suggested by Scorer [146], that it was the smaller twin which was affected, although Scorer's observation related to a study of only five uni-ovular twin pairs.

H.2 The cases

After exclusions for congenital anomalies and multiple deliveries the 947 (88.5%) boys that remained in the study became the cases. The same exclusion criteria were also used when the control group was assembled.

Figure H.1 shows the distribution of year of birth for the 947 cases. It is of interest to note that a special study of cryptorchidism was carried out at the John Radcliffe hospital during

Table H.2: District and hospitals where the 947 cases with undescended testis diagnosed at birth were born, 1970–86

District Hospital	Number of cases
Oxfordshire	*708*
John Radcliffe	585
Radcliffe Infirmary	24
Churchill	14
Horton Maternity	72
Wantage	1
Abingdon	6
Bicester Cottage	4
Chipping Norton	2
West Berkshire	*238*
Royal Berkshire	220
Dellwood Maternity	4
Wokingham	5
Sandleford	7
Townlands	2
Not known	1
Total	947

1984–86 [147]. The John Radcliffe Hospital Cryptorchidism Study Group used standardised criteria to define cryptorchidism and it is possible that during this period these guidelines influenced the way in which cryptorchidism was routinely recorded in that hospital. One hundred and ninety six (20.7%) boys had a record of an orchidopexy by 1987. These boys were also part of the orchidopexy case-control study which is described in chapter 8.

Table H.2 lists the hospitals where the cases were born. Over half the cases (61.8%) were born in the John Radcliffe hospital and nearly one quarter (23.2%) in the Royal Berkshire hospital.

H.2.1 Minor congenital anomalies

By definition, all 947 cases had at least one mention of an undescended testicle, and for those boys born during 1970–72 it was the only congenital anomaly mentioned. There were, however, 69 mentions of other minor anomalies among 67 of the boys born in 1973 or later, as shown in table H.3.

Table H.3: Minor congenital anomalies mentioned at birth among 67 boys from the 947 cases with cryptorchidism diagnosed at birth

ICD 9* code	Description of congenital anomaly	Number of mentions of an anomaly
744.1	Accessory auricle	3
747.5	Absence or hypoplasia of umbilical artery	4
752.6	Hypospadias and epispadias	6
754.3	Congenital dislocation of hip	21
757.0–757.9	Congenital anomalies of the integument	11
778.6	Hydrocele	24
	Any minor congenital anomaly (excluding cryptorchidism)	69

* International Classification of Diseases, 9th revision

H.3 The controls

Each case was matched with up to eight livebirths on sex, hospital and year of delivery. It was not possible to match all cases with eight controls because in some instances there were not enough livebirths that satisfied the matching criteria. A more detailed description of the matching and control selection is given in section B. A list of 7,549 potential controls was created and livebirths were successively excluded from entry to the control group if they had a major congenital anomaly diagnosed at birth (n=343, 4.5%) or they were part of a multiple delivery (n=169, 2.2%, which included four triplets).

The remaining 7,036 livebirths became the matched control group. One-hundred and twelve (1.6%) controls were themselves affected and re-appear in different matched sets as cases. The 7,036 controls were actually only 6,659 individuals, of whom 358 (5.4%) entered the study as controls more than once, in a different matched sets. In nested matched case-control studies an individual can serve as a control for more than one case [321, 330]. This method of control selection allowed the estimation of risk ratios or prevalence ratios. See appendix B.3 for more details. Table H.4 shows the number of controls in each matched set. Over ninety-nine percent of the matched sets contained four or more controls.

Table H.4: Number of matched sets by number of controls in each matched set for the 947 cases and their 7,036 matched controls

Number of controls in matched set	Number of matched sets	Percent
8	538	56.8
7	300	31.7
6	93	9.8
5	13	1.4
4	2	0.2
3	0	0.0
2	0	0.0
1	1	0.1
Total	947	100.0

Appendix I

Undescended Testis Diagnosed at Orchidopexy

I.1 Boys with a record of an orchidopexy

The Oxford Record Linkage Study (ORLS) identified 1570 boys, from general hospital files, who had a record of an orchidopexy during 1970-87 and had been born during 1970-86. Boys with major congenital anomalies or who were part of twin or higher order deliveries were later excluded from the analyses.

I.1.1 Major congenital anomalies

Table I.1 shows the frequency with which major congenital anomalies were mentioned at birth in the 1570 ORLS delivery records for the boys with orchidopexy. Classification of congenital anomalies into major and minor anomalies was as described in section F.1.1.

Among boys with major anomalies the aetiology of cryptorchidism is likely to be different from that of idiopathic or 'uncomplicated' cryptorchidism. For example, cryptorchidism may be one small part of a syndrome like Down's or Prader-Willi [212–214]. The eighty-six (5.5%) boys with at least one mention of a major congenital anomaly were therefore excluded from the case group.

I.1.2 Multiple deliveries

Thirty-five boys, including one with a major congenital anomaly, were part of a twin delivery and another one was part of a triplet delivery. These 36 (2.3%) boys were also excluded from the main analyses because the aetiology of cryptorchidism in twin or higher order births may be different to that in singletons.

Table I.1: Major congenital anomalies mentioned at birth among 86 boys with undescended testis diagnosed at orchidopexy who had any such anomalies

ICD 9* code	Description of major congenital anomaly	Number of mentions of an anomaly
740.0–740.9	Anencephalus and similar anomalies	0
741.0–741.9	Spina bifida	2
742.0–742.9	Other congenital anomalies of nervous system	4
743.0–743.9	Congenital anomalies of eye	0
744.0, 744.2–744.9	Congenital anomalies of ear, face and neck (*less* accessory auricle)	4
745.0–746.9	Bulbus cordis anomalies and anomalies of cardiac septal closure, *and* Other congenital anomalies of heart	4
747.0–747.4, 747.6–747.9	Other congenital anomalies of circulatory system (*less* absence or hypoplasia of umbilical artery)	3
748.0–748.9	Congenital anomalies of respiratory system	1
749.0–749.9	Cleft palate and cleft lip	3
750.0–750.9	Other congenital anomalies of upper alimentary tract	6
751.0–751.9	Other congenital anomalies of digestive system	4
752.0–752.4, 752.7–752.9	Congenital anomalies of genital system, (*less* undescended testicle *and* hypospadias)	27
753.0–753.9	Congenital anomalies of urinary system	0
754.0–754.2, 754.4–756.9,	Certain congenital anomalies of limbs, *and* Other congenital anomalies of limbs, *and* Other congenital musculoskeletal deformities (*less* congenital dislocation of hip)	41
758.0–759.9	Chromosomal anomalies, *and* Other and unspecified anomalies	3
	Any major congenital anomaly	102

* International Classification of Diseases, 9th revision

The 35 twin pairs were made up of 22 (62.9%) sets where the co-twin was male and 13 (37.1%) sets where the co-twin was female; in none of the like-sex twin pairs were both boys affected. For comparison, in England and Wales during 1974–84 the proportions of liveborn twin boys with male and female co-twins were 70.6% and 29.4% respectively [329].

Among the 22 male-male twin sets there were 11 sets where the co-twin was heavier at birth than the affected twin, 10 sets where the co-twin was lighter and one set where the birth weights were the same. Among the 13 male-female twin sets there were six sets where the female co-twin was heavier, six where the affected boy was heavier and one set where the birth weights were not known. In nine of the male-male twin sets the affected twin was born first and in the remaining 13 sets the co-twin was first born. In six of the male-female twin sets the affected boy was born first and in the remaining seven sets the female twin

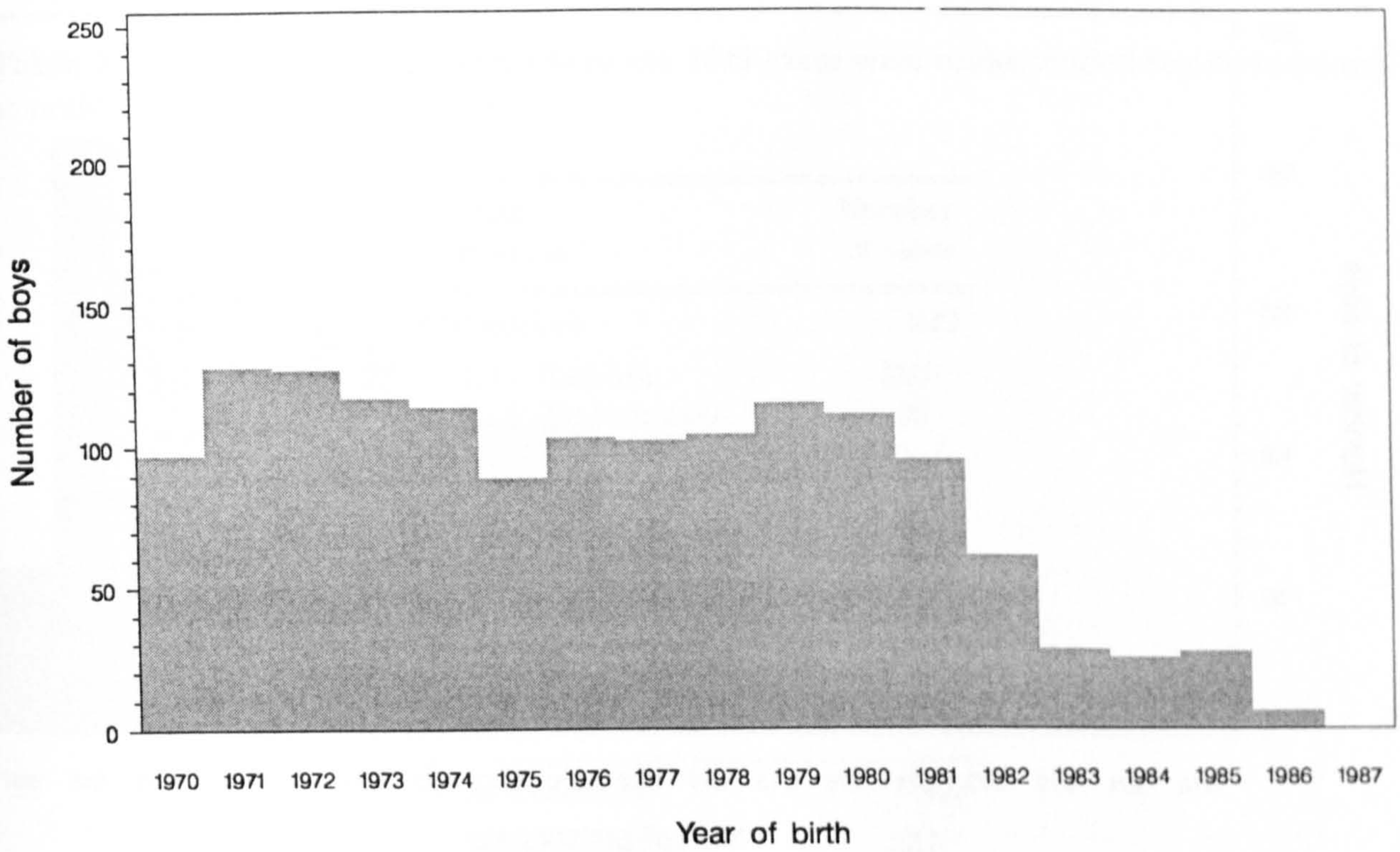

Figure I.1: Year of birth of the 1449 orchidopexy cases

was first born. As in section H.1.2, there was no evidence, as suggested by Scorer [146], that it was the smaller, less mature twin who was more likely to be affected.

I.2 The cases

The 1449 (92.3%) boys that remained in the study, after exclusions for major congenital anomalies and multiple deliveries, became the cases. The same exclusion criteria were used when the control group was assembled.

Figures I.1, I.2 and I.3 show the distribution of year of birth, year of orchidopexy and age at orchidopexy for the 1449 cases. Note that since the study period ended in 1987, and boys had to have been born during 1970–86 to enter the study, these distributions do not reflect incidence rates. Using population estimates for Oxfordshire and West Berkshire it was estimated that the cumulative incidence of orchidopexy to age 14 years was 2.4%.

I.2.1 The orchidopexy

The ORLS hospital files for 1987 were not complete when data for this study was extracted, with fewer and fewer records of orchidopexy from February onwards; the last case was admitted in July 1987, and the deficit of cases in that year can been seen in figure I.2. The reason the ORLS files were incomplete was because records from 1987 onwards had not yet

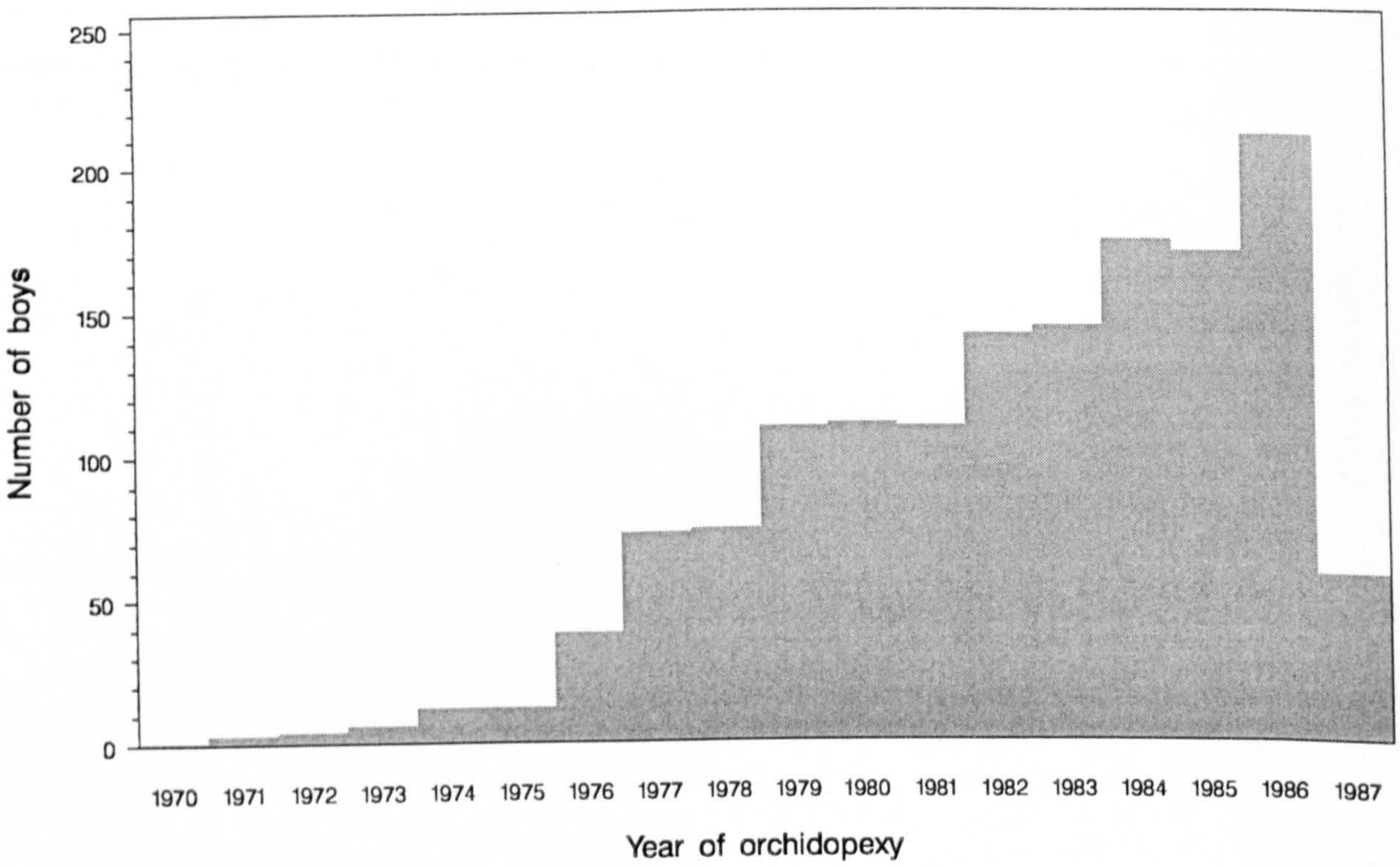

Figure I.2: Year of orchidopexy for the 1449 cases

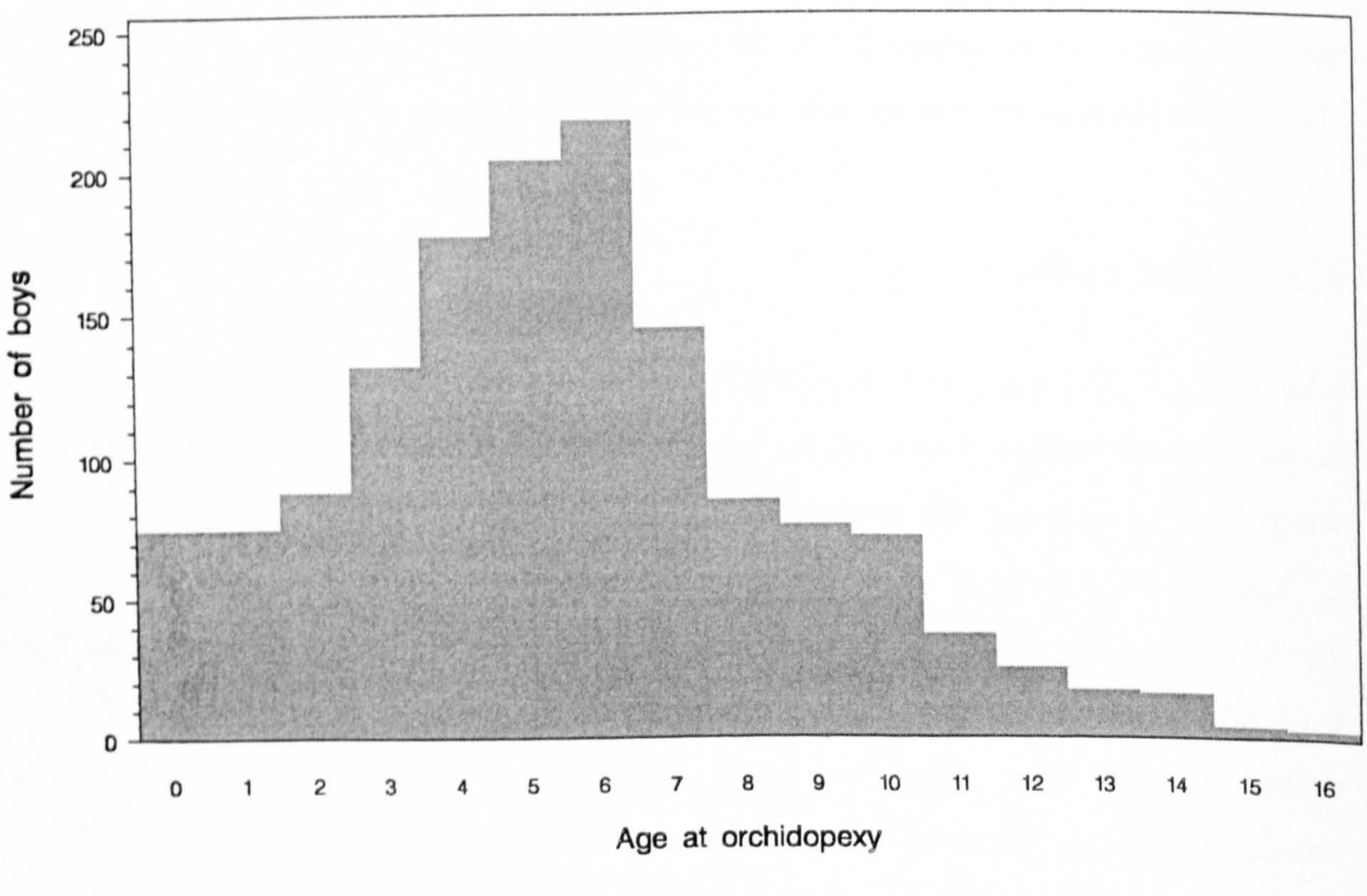

Figure I.3: Age at operation for the 1449 orchidopexy cases

been fully processed and added onto the existing database.

When the date of operation was not recorded on the general hospital file (5 boys) the date of admission was used in its place. Among the 1444 boys with a valid date of operation the median time between admission and operation was one day (interquartile range 0–1 day).

Table I.2: Districts and hospitals where the 1449 cases with undescended testis diagnosed at orchidopexy were born, 1970–86

District Hospital		Number of cases
Oxfordshire		*622*
John Radcliffe		350
Radcliffe Infirmary		39
John Radcliffe	GP unit	17
Churchill		29
Horton Maternity		133
Wantage		9
Abingdon		18
Bicester Cottage		7
Chipping Norton		20
West Berkshire		*827*
Royal Berkshire		647
Dellwood Maternity		63
Wokingham		41
Sandleford		25
St. George's		9
Townlands		23
Wallingford		18
Not known		1
Total		1449

Six-hundred and sixty seven boys (46.2%) were operated upon on the day of admission. The longest time between admission and operation was 31 days, followed by four boys at four days. The median age at operation for the sample of boys in this study was five years (interquartile range: 3–7 years). Of the 75 (5.2%) boys operated on in the first year of life, 48 (64.0%) had their orchidopexy at less than 180 days of age.

Tables I.2 and I.3 list the hospitals where the cases were born and where they were later operated on. Fifty-seven (3.9%) of the cases were operated on in hospitals outside of Oxfordshire or West Berkshire.

I.2.2 Associated operations and diagnoses

The median time on the waiting list, only available for 879 (66.7%) boys, was 41 days (interquartile range, 25–75 days). The median length of stay, available for all the cases, was 2 days (interquartile range, 1–3 days), with 250 (17.3%) boys discharged on the same day as admission.

Table I.3: Districts and hospitals in which the 1449 orchidopexy cases were ascertained

District Hospital	Number of cases
Oxfordshire	*607*
John Radcliffe	397
Radcliffe Infirmary	67
Churchill	14
Horton General	128
Nuffield Orthopaedic	1
West Berkshire	*785*
Royal Berkshire	360
Battle	308
Newbury District	116
Henley District	1
East Berkshire	*24*
Wexham Park	3
Heatherwood	21
Northampton	*4*
Northampton General	1
High Wycombe	*19*
Wycombe General	10
Amersham General	9
Kettering	*2*
Kettering and District General	2
Aylesbury	*9*
Stoke Mandeville	9
Milton Keynes	*2*
Milton Keynes	2
Total	1449

Not including orchidopexy, there were 404 other operations recorded during the hospital visit when the cases had their (first) orchidopexy. These other operations were mainly repair of inguinal hernia (212 boys, 14.6%), circumcision (44 boys, 3.0%), excision, repair or tapping of hydrocele (27 boys, 1.9%), and incision of testis or adnexa (27 boys, 1.9%).

All but one of the 1449 orchidopexy cases had at least one discharge diagnosis recorded of which there were 1815 in total. One thousand three hundred and thirteen (90.6%) boys had a concurrent diagnosis of undescended testicle. The most common of the remaining diagnoses were inguinal hernia (204 boys, 14.1%), redundant prepuce and phimosis (63 boys, 4.3%), and hydrocele (31 boys, 2.1%). There were three boys with a diagnosis of

Table I.4: Minor congenital anomalies mentioned at birth among 241 boys from the 1449 cases selected for the orchidopexy study

ICD 9* code	Description of congenital anomaly	Number of mentions of an anomaly
744.1	Accessory auricle	5
747.5	Absence or hypoplasia of umbilical artery	4
752.5	Undescended testicle	200
752.6	Hypospadias and epispadias	7
754.3	Congenital dislocation of hip	25
757.0–757.9	Congenital anomalies of the integument	11
778.6	Hydrocele	9
	Any minor congenital anomaly	261

* International Classification of Diseases, 9th revision

a neoplasm, these being Hodgkin's disease, a benign neoplasm of the skin, and a 'benign neoplasm of other endocrine glands and related structures.'

I.2.3 Minor congenital anomalies

Two-hundred and forty-one (16.6%) boys had a mention of a minor congenital anomaly, as shown in table I.4. One-hundred and ninety six (13.5%) boys had undescended testes mentioned at birth; some had it recorded on the delivery file more than once.

I.2.4 Previous and subsequent operations

Prior to the hospital admission for orchidopexy 319 of the boys had a record of 602 operations and subsequent to this admission 308 of the boys were to have 519 operations. Table I.5 lists the previous and subsequent operations. By definition, none of the boys could have had a prior orchidopexy as recorded by the ORLS, but 106 (7.3%) of the boys had a second mention of an orchidopexy.

I.2.5 Previous and subsequent diagnoses

Six hundred and ten boys had 1480 prior diagnoses and 375 of the boys had 618 subsequent diagnoses. Table I.6 lists the previous and subsequent diagnoses. There were 10 boys with a prior diagnosis of a neoplasm. One boy, on two different hospital visits, had a diagnoses of cancer of 'other and unspecified nervous system', while one boy was classified to an invalid ICD code in the neoplasms coding range and the remaining eight boys had diagnoses of

Table I.5: Operations prior to, and subsequent to, the hospital admission for orchidopexy for the 1449 cases

CSO 3* Operation code	Surgical operation	Number of operations Before first admission for orchidopexy	After
001–059	All nervous system	4	1
061–089	All endocrine system	3	0
100–189	All eye	42	25
190–249	All ear, nose and throat	240	191
193	*incision of eardrum*	*110*	*80*
232–235	*tonsillectomy, or adenoidectomy, or both*	*86*	*65*
250–289	All upper alimentary tract	11	13
290–349	All thorax (with heart and lungs)	2	0
380–389	All breast	2	0
400–559	All abdomen	101	52
410–411	*repair of inguinal hernia, n.e.c.*	*57*	*18*
441–443	*appendicectomy*	*8*	*15*
560–629	All urinary system	39	13
624	*repair of uretha*	*29*	*5*
630–669	All male genital organs	77	161
640	*incision of testis*	*8*	*8*
644-645	*excision or repair of hydrocele*	*15*	*6*
648	*orchidopexy*	*—*	*112*
661	*circumcision*	*47*	*21*
780–879	All orthopaedic surgery	22	29
780	*manipulation of closed fracture*	*9*	*12*
880–909	All peripheral vessels	1	0
910–939	All skin and subcutaneous tissue	29	0
940–959	All other surgical procedures	6	1
960–999	All non-operative procedures	23	12
001–999	All operations or procedures	602	519

* OPCS Classification of Surgical Operations, 3rd revision

benign neoplasms. Five other boys had subsequent diagnoses of neoplasms: two were benign neoplasms, two of 'uncertain behaviour', and one, Hodgkin's disease. This latter case was the same boy who had previously had a diagnosis of Hodgkin's disease during the hospital visit when the orchidopexy was carried out.

Table I.6: General hospital diagnoses prior to, and subsequent to, the index hospital admission for orchidopexy for 1449 cases

ICD 9* code	Discharge diagnosis	Number of diagnoses Before first admission for orchidopexy	After
001–139	Infectious and parasitic diseases	55	14
140–239	Neoplasms	11	5
240–279	Endocrine, nutritional and metabolic diseases and immunity disorders	22	8
280–289	Diseases of blood and blood forming organs	16	5
290–319	Mental disorders	3	1
320–389	Diseases of nervous system and sense organs	180	103
360-379	*disorders of eye and adnexa*	*51*	*22*
380–389	*disorders of the ear and mastoid process*	*115*	*70*
390–459	Diseases of the circulatory system	8	3
460–519	Diseases of the respiratory system	272	118
460–466	*acute respiratory infections*	*109*	*18*
474	*chronic disease of tonsils and adenoids*	*10*	*0*
493	*asthma*	*40*	*18*
520–579	Diseases of the digestive system	153	60
540–543	*appendicitis*	*7*	*16*
550	*inguinal hernia*	*85*	*20*
580–629	Diseases of the genitourinary system	114	56
600–608	*diseases of male genital organs*	*95*	*46*
603	*hydrocele*	*19*	*9*
605	*redundant prepuce and phimosis*	*51*	*22*
680–709	Diseases of the skin and subcutaneous tissue	26	8
710–739	Diseases of the musculoskeletal system and connective tissue	10	26
740–759	Congenital anomalies	205	149
752	*congenital anomalies of genital organs*	*139*	*137*
752.5	*undescended testicle*	*95*	*128*
753	*congenital anomalies of urinary system*	*3*	*2*
760–779	Certain conditions originating in the perinatal period	212	2
780–799	Signs, symptoms and ill-defined conditions	109	51
N800–N999	Injury and poisoning	84	9
001–N999	All causes	1480	618

* International Classification of Diseases, 9th revision

I.3 The controls

Initially each case was matched with up to eight livebirths on sex, hospital and year of delivery. This produced a list of 11,529 potential controls. See appendix B for more details about control selection. The list of potential controls was examined and livebirths were successively excluded from entry to the control group if: they had a major congenital anomaly diagnosed at birth (n=380, 3.3%); they were part of a multiple delivery (n=236, 2.0%, including 2 triplets and 1 quadruplet); or they were known to have died *before* the date at which their matched case had its own orchidopexy (n=98, 0.9%). This last condition was to try and ensure that the controls had had the same opportunity for orchidopexy as the cases. Ideally, children should also have been excluded from the control group if they had migrated from the study area before their matched case had its own orchidopexy, but sufficient information about migration was not available to do this. The potential bias caused by migration is discussed in more detail in section 3.

The remaining 10,811 livebirths became the matched control group. One hundred and eighty-two (1.6%) controls were themselves affected and also entered the study as cases. The control group was actually made up of 10,143 individuals, of whom 631 (6.2%) entered into the study more than once, in different matched sets, as controls. Allowing controls to become cases or to be re-selected as controls was valid in the context of this study [321, 330]. The above selection criteria made it possible to estimate prevalence or risk ratios for cryptorchidism. The usual alternative, incidence ratios, were considered inappropriate because boys were deemed to be cryptorchid from birth. Boys who apparently 'acquired' undescended testes [151] after birth were considered to have been affected with an underlying anomaly from birth. Appendix B.3 discusses theoretical issues of control selection in more detail.

Table I.7 shows the number of controls in each matched set. Over ninety-nine percent of the matched sets contained four or more controls.

Table I.7: Number of matched sets by number of controls in each matched set for the 1449 cases and their 10,811 matched controls

Number of controls in matched set	Number of matched sets	Percent
8	853	58.9
7	446	30.8
6	133	9.2
5	7	0.5
4	6	0.4
3	2	0.1
2	0	0.0
1	2	0.1
Total	1449	100.0

Appendix J

Inguinal Hernia in Children

J.1 Children with a record of a repair of inguinal hernia

The Oxford Record Linkage Study (ORLS) identified 2128 boys and 388 girls up to and including five years of age, from general hospital files, who had a record of a repair of an inguinal hernia during 1970-87, and had also been born during 1970–86. By limiting the study to young children the vast majority of the herniae will be indirect [275]. Boys who had a record of an orchidopexy were subsequently removed and boys or girls with major congenital anomalies or who were part of twin or higher order deliveries were also excluded from the analyses, as detailed below.

J.1.1 Orchidopexy

Cryptorchidism and inguinal hernia are often diagnosed together. A study of inguinal hernia, where a proportion of cases have an undescended testis, may simply reflect the risk factors for undescended testis. In this study, therefore, boys with a record of an orchidopexy were excluded from the case and control group. Two-hundred and forty-two (11.4%) boys with a record of an orchidopexy were excluded from the analyses for this reason. Excluding boys with an orchidopexy also makes the male and female groups more comparable because there is no female equivalent to cryptorchidism.

J.1.2 Major congenital anomalies

Table J.1 shows the frequency with which major congenital anomalies were mentioned at birth in the remaining 1886 ORLS delivery records for boys and 388 delivery records for girls with repair of inguinal hernia. Classification of congenital anomalies into major and minor anomalies was described in section F.1.1. Briefly, during 1970–72 only one diagnosis

Table J.1: Major congenital anomalies mentioned at birth among 89 boys and 25 girls with inguinal hernia who had any such anomalies

ICD 9* code	Description of major congenital anomaly	Number of mentions of an anomaly	
		Boys	Girls
740.0–740.9	Anencephalus and similar anomalies	0	0
741.0–741.9	Spina bifida	1	0
742.0–742.9	Other congenital anomalies of nervous system	3	0
743.0–743.9	Congenital anomalies of eye	1	0
744.0, 744.2–744.9	Congenital anomalies of ear, face and neck (*less* accessory auricle)	2	4
745.0–746.9	Bulbus cordis anomalies and anomalies of cardiac septal closure, *and* Other congenital anomalies of heart	3	2
747.0–747.4, 747.6–747.9	Other congenital anomalies of circulatory system (*less* absence or hypoplasia of umbilical artery)	10	5
748.0–748.9	Congenital anomalies of respiratory system	3	0
749.0–749.9	Cleft palate and cleft lip	8	2
750.0–750.9	Other congenital anomalies of upper alimentary tract	7	2
751.0–751.9	Other congenital anomalies of digestive system	5	0
752.0–752.4, 752.7–752.9	Congenital anomalies of genital system, (*less* undescended testicle *and* hypospadias)	7	1
753.0–753.9	Congenital anomalies of urinary system	2	0
754.0–754.2, 754.4–756.9,	Certain congenital anomalies of limbs, *and* Other congenital anomalies of limbs, *and* Other congenital musculoskeletal deformities (*less* congenital dislocation of hip)	47	11
758.0–759.9	Chromosomal anomalies, *and* Other and unspecified anomalies	0	1
	Any major congenital anomaly	99	28

* International Classification of Diseases, 9th revision

was recorded onto the delivery record; from 1973 there was room for up to ten diagnoses. Congenital anomalies coded on the delivery record under ICD 8 were re-coded to their equivalent code under ICD 9.

Eighty-nine (4.7%) boys and 25 girls (6.4%) with at least one mention of a major congenital anomaly were subsequently excluded from the analyses.

J.1.3 Multiple deliveries

Ninety-nine boys (5.2%) and 17 (4.1%) girls, including three boys and one girl with a major congenital anomaly, were part of twin or higher order deliveries. These boys and girls were also excluded from the main analyses because the aetiology of inguinal hernia in twin or higher order births may be different to that in singletons.

Table J.2: Birth order and birth weight of twins with operation for inguinal hernia compared to co-twin

	Twin set			
	Affected male, unaffected male	Affected male, unaffected female	Affected female, unaffected male	Affected female, unaffected female
Birth order of affected case within twin set				
First born	24	9	1	3
Second born	36	9	3	6
Total*	60	18	4	9
Birth weight of affected case within twin set				
Bigger	24	11	3	2
Smaller	34	6	1	5
Equal	1	0	0	1
Unknown	1	1	0	1
Total*	60	18	4	9

* does not include six twin sets where both boys were affected, one twin set where both girls were affected, and one twin set where both the boy and girl were affected

Ninety-two affected boys were part of 86 twin deliveries although the co-twin birth record of one boy was missing; five boys were part of five triplet deliveries and two boys were part of two quadruplet deliveries. Sixteen girls were part of 15 twin deliveries and one girl was part of a triplet delivery.

In 85 complete twin pairs with an affected male there were 66 (77.6%) sets where the co-twin was male and 19 (22.4%) sets where the co-twin was female; in six of the like-sex twin pairs both boys were affected and in one of the unlike-sex twin sets the female co-twin was also affected.

Similarly, among 15 twin pairs with an affected female there were 10 (66.7%) sets where the co-twin was female and five (33.3%) sets where the co-twin was male; in one of the like-sex twin pairs both girls were affected and in one of the unlike-sex twin sets the male co-twin was also affected.

Table J.2 shows the birth order and relative birth weight of the affected twin relative to the unaffected co-twin. In like-sex male twin sets the probability of the affected twin being born second was 0.60 and the probability of being smaller than the unaffected co-twin was 0.59; neither of these were significantly different from a uniform distribution (p=0.156 and p=0.237 respectively).

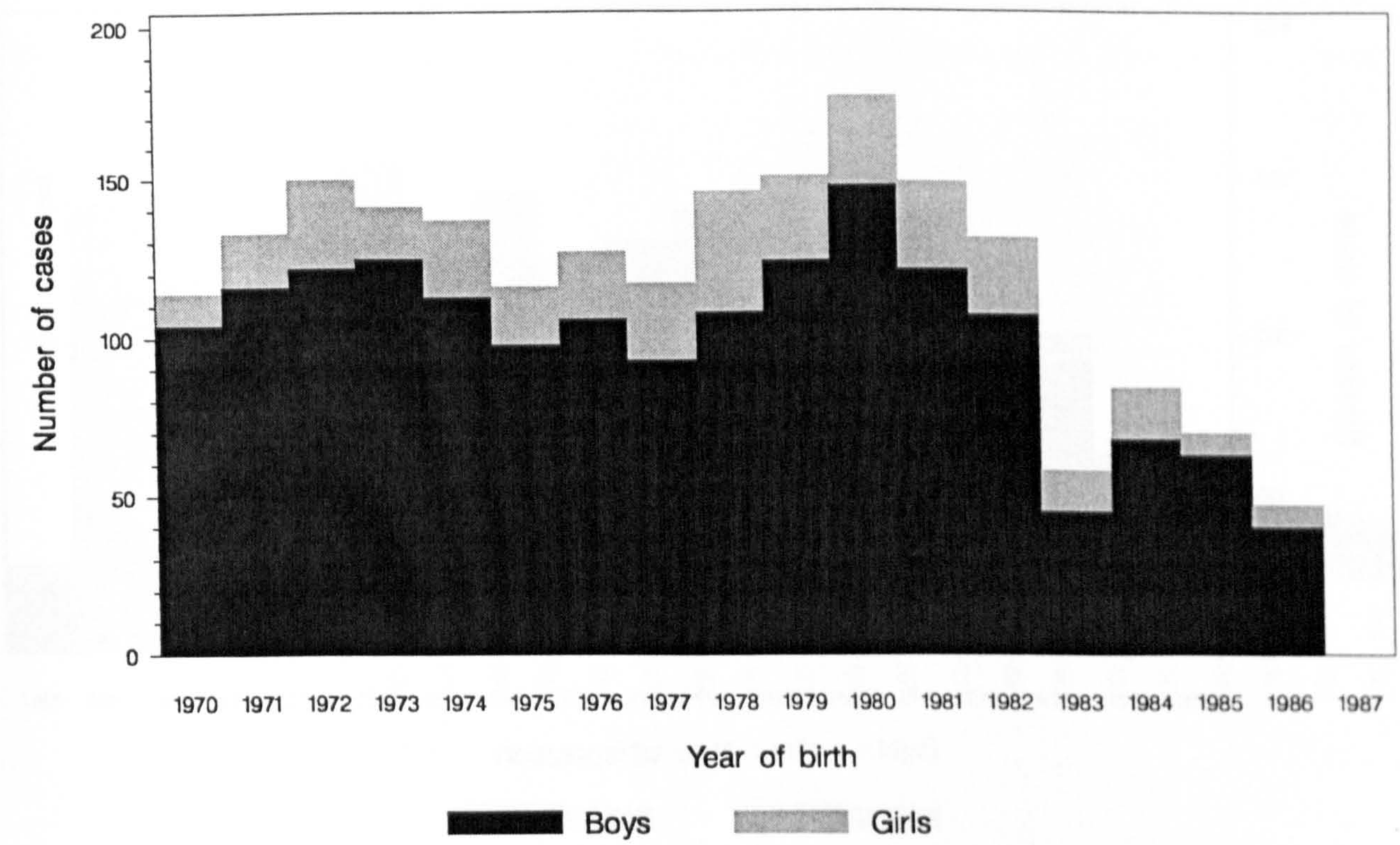

Figure J.1: Year of birth of the 1701 boy and 347 girl cases with inguinal hernia

J.2 The cases

The 1701 (79.9%) boys and 347 (89.4%) girls that remained in the study, after exclusions for orchidopexy, major congenital malformations and multiple deliveries, became the cases. The same exclusion criteria for orchidopexy, congenital anomalies and multiple births were also used when the control group was assembled.

Figures J.1 and J.2 show the distribution of year of birth and year of operation for repair of inguinal hernia for the cases. There was a noticeable drop in the number of cases born after 1982, as seen in figure J.1. Note that since the study period ended in 1987, and cases had to have been born during 1970–86 to enter the study, these distributions do not reflect incidence or prevalence rates.

The ORLS hospital files for 1987 were not complete, with fewer and fewer records of operation from February onwards; the last case was admitted in July of 1987 and the effect of this can been seen in figure J.2.

J.2.1 The repair of inguinal hernia

Where the date of operation was not recorded on the general hospital file (35 cases) the date of admission was used in its place to estimate the date and age at operation. Figure J.3 and J.4 show the age at operation for the cases in this study. Among boys 50.9% were

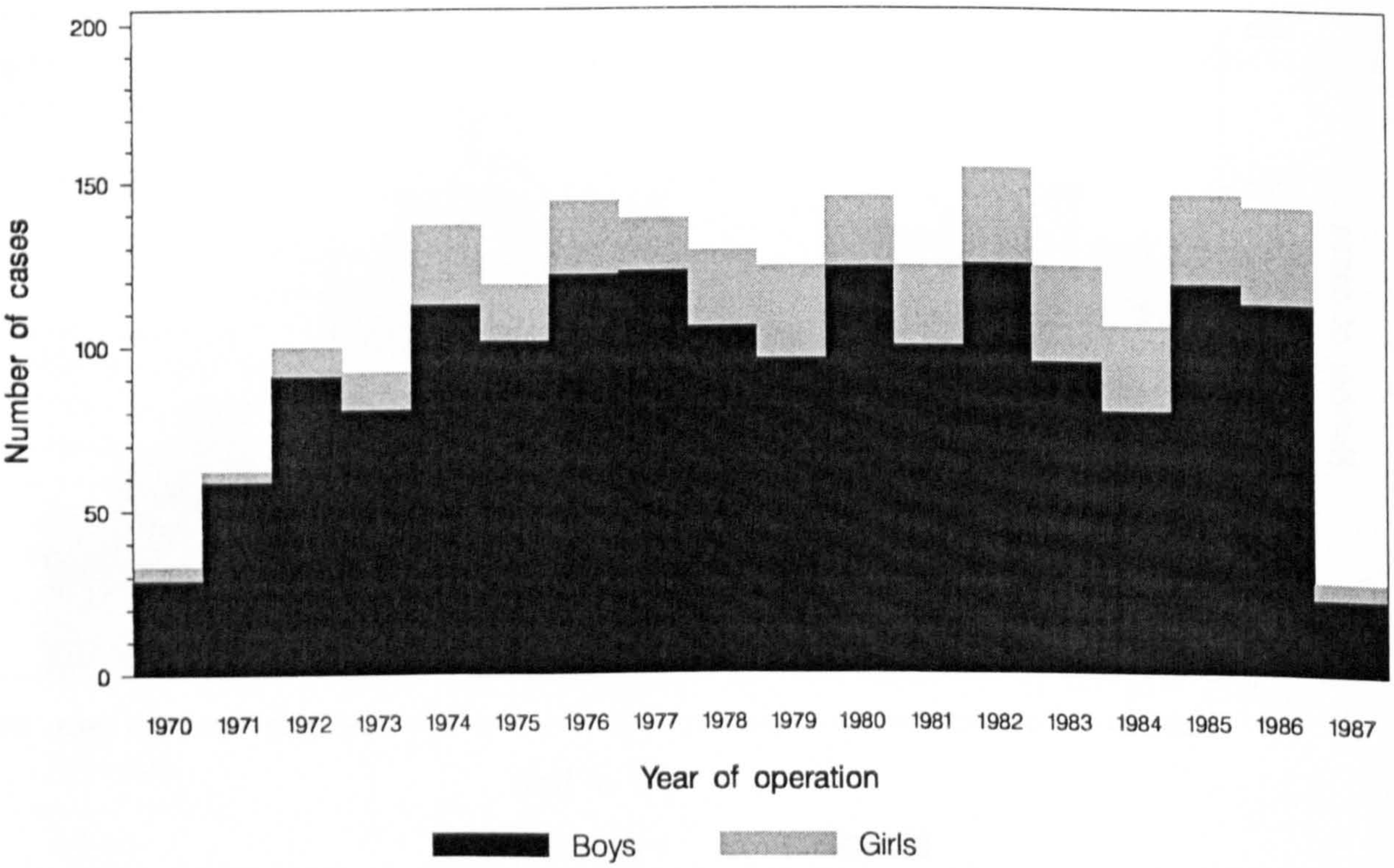

Figure J.2: Year of operation for 1701 boy and 347 girl cases

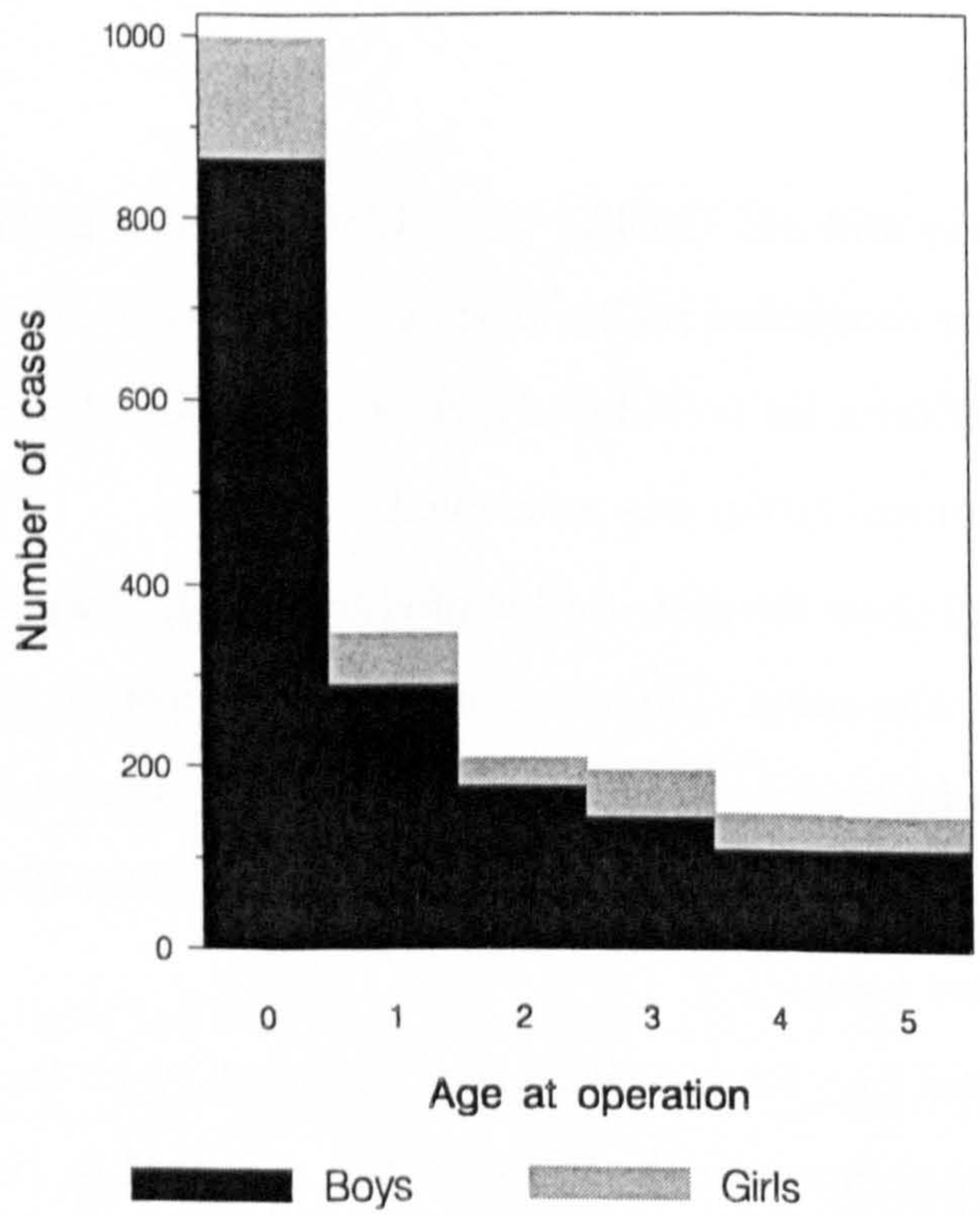

Figure J.3: Age at operation for the 1701 boy and 347 girl cases with inguinal hernia

operated upon within the first year of life, whereas for girls it was 37.8%. The median age at operation for the sample of cases in this study was 346 days (interquartile range: 113–961.5 days) for boys and 649 days for girls (interquartile range: 174–1403 days). Figure J.4 show that there was a peak in operations 50–100 days after birth.

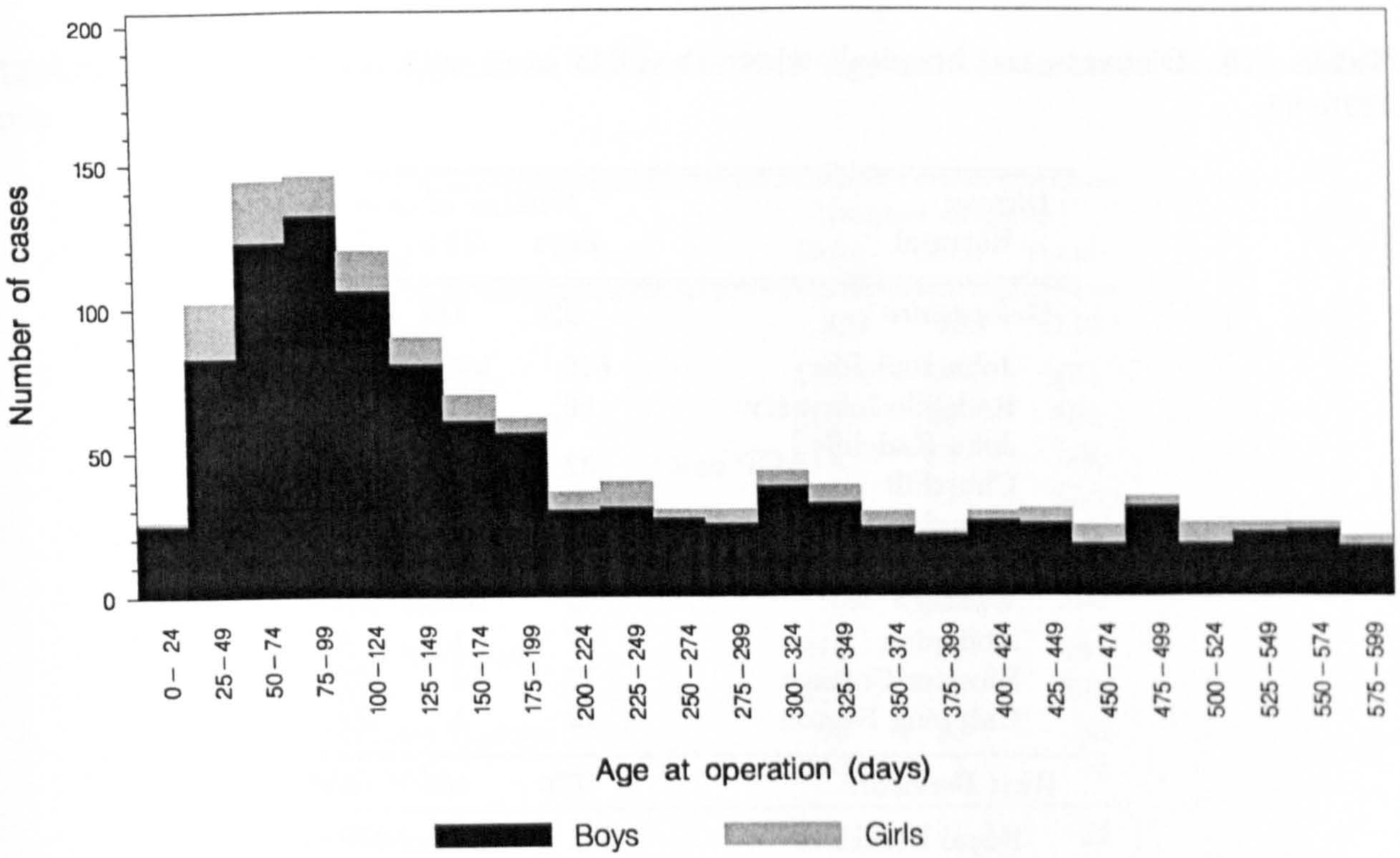

Figure J.4: Age at operation for the cases with inguinal hernia: birth–600 days of age

Among the cases with a valid date of operation the median time between admission and operation was zero days (interquartile range 0–1 day). One thousand one hundred and forty two cases (56.7%) were operated upon on the day of admission and 734 (36.5%) on the second day. The longest time between admission and operation was 373 days, followed by cases at 30, 23 and 16 days.

Tables J.3 and J.4 list the hospitals where the cases were born and where they were later operated upon. Thirty-seven (2.1%) of the cases were operated on in hospitals outside of Oxfordshire or West Berkshire.

J.2.2 Associated operations and diagnoses

The median time on the waiting list, only available for 1126 (55.0%) cases, was 32 days (interquartile range, 18–55 days). The median length of stay, available for all the cases, was one day (interquartile range, 0–3 days), with 741 (36.2%) of cases discharged on the same day as admission.

Not including the hernia operation, there were 209 other operations or procedures recorded for the male cases during the hospital visit when they had their (first) hernia operation. These other operations were mainly repair or tapping of hydrocele (98 boys, 5.8%), circumcision (27 boys, 1.6%) and operation on abdominal hernia (17 boys, 1.0%). The female cases had 11 other operations recorded during the index admission, mainly

Table J.3: Districts and hospitals where the 2048 cases with inguinal hernia were born, 1970–86

District Hospital		Number of cases Boys	Girls	Total
Oxfordshire		*924*	*184*	*1108*
John Radcliffe		619	135	754
Radcliffe Infirmary		50	7	57
John Radcliffe	GP unit	32	11	43
Churchill	GP unit			
Churchill		48	4	52
Horton Maternity		128	23	151
Wantage		9	0	9
Abingdon		7	1	8
Bicester Cottage		12	0	12
Chipping Norton		19	3	22
West Berkshire		*776*	*163*	*939*
Royal Berkshire		642	137	779
Dellwood Maternity		48	14	62
Wokingham		29	3	32
Sandleford		23	2	25
St. George's		6	0	6
Townlands		9	4	13
Wallingford		19	3	22
Not known		1	0	1
Total		1701	347	2048

operation on abdominal hernia (6 girls, 1.7%).

All but two of the 1701 boys had at least one discharge diagnosis (ICD 9: 001–999N) recorded, of which there were 1990 in total. One thousand six hundred and eighty one boys (99.8%) had at least one diagnosis of inguinal hernia, leaving 276 other diagnoses. Mostly the remaining diagnoses were hydrocele (109 boys, 6.4%) and redundant prepuce and phimosis (35 boys, 2.1%). Although boys with a mention of an orchidopexy were excluded from the case group, six boys had a diagnosis of undescended testis.

All 347 girls had at least one discharge diagnosis, of which there were 370 in total. Each girl had one or more diagnosis of inguinal hernia leaving, 17 other miscellaneous diagnoses.

There were five boys and no girls with a concurrent diagnosis of a neoplasm. There were two lipomas, and one each of: haemangioma and lymphangioma; malignant neoplasm of lip; and malignant neoplasm of liver and intrahepatic ducts.

Table J.4: Districts and hospitals in which the 2048 inguinal hernia cases were operated upon

District Hospital	Number of cases Boys	Girls	Total
Oxfordshire	*930*	*186*	*1116*
John Radcliffe	372	99	471
Radcliffe Infirmary	315	46	361
Churchill	114	30	144
Horton General	127	11	138
Victoria Cottage	2	0	2
West Berkshire	*735*	*155*	*890*
Royal Berkshire	415	82	497
Battle	253	52	305
Newbury District	63	20	83
Peppard	4	1	5
East Berkshire	*18*	*3*	*21*
Wexham Park	5	1	6
Heatherwood	13	2	15
Northampton	*1*	*0*	*1*
Northampton General	1	0	1
High Wycombe	*8*	*2*	*10*
Wycombe General	6	1	7
Amersham General	2	1	3
Kettering	*4*	*1*	*5*
Kettering and District General	4	1	5
Aylesbury	*4*	*0*	*4*
Stoke Mandeville	4	0	4
Milton Keynes	*1*	*0*	*1*
Milton Keynes	1	0	1
Total	1701	347	2048

J.2.3 Minor congenital anomalies

Two-hundred and two (9.5%) boys and 21 girls (5.0%) had at least one mention of a minor congenital anomaly, as shown in table J.5. Although boys with a mention of an orchidopexy were excluded from the case group, there were 45 mentions of undescended testis at birth; a considerable proportion of these would be expected to descend naturally within the first few months after birth [144].

Table J.5: Minor congenital anomalies mentioned at birth among 152 cases from the 2048 cases selected for the inguinal hernia study

ICD 9* code	Description of congenital anomaly	Number of mentions: among boys	among girls	Total
744.1	Accessory auricle	4	1	5
747.5	Absence or hypoplasia of umbilical artery	0	1	1
752.5	Undescended testicle	45	—	45
752.6	Hypospadias and epispadias	11	—	11
754.3	Congenital dislocation of hip	33	15	48
757.0–757.9	Congenital anomalies of the integument	23	3	26
778.6	Hydrocele	21	0	21
	Any minor congenital anomaly	137	20	157

* International Classification of Diseases, 9th revision

J.2.4 Previous and subsequent operations

Prior to the admission for the hernia operation 91 boys and 14 girls had a record of 143 and 20 operations or procedures respectively, and subsequent to this admission 532 boys and 86 girls were to have 1033 and 194 operations or procedures respectively. Table J.6 lists the previous and subsequent operations. By definition, none of the cases could have had an orchidopexy or a prior hernia operation, as recorded by the ORLS, but 150 boys (8.8%) and 31 girls (8.9%) were to have a subsequent inguinal hernia operation.

J.2.5 Previous and subsequent diagnoses

Four hundred and eighty seven boys and 88 girls had 1551 and 260 prior diagnoses respectively, and 680 boys and 110 girls had 1895 and 282 subsequent diagnoses. Table J.7 lists the previous and subsequent diagnoses.

There were four boys with a prior diagnosis of a neoplasm: three with polycythaemia vera and one with haemangioma or lymphangioma. Among the girls there was one prior diagnosis of a neoplasm: a benign neoplasm of the face.

Eleven boys had subsequent diagnoses of a neoplasm: three benign neoplasms; two haemangiomas or lymphangiomas, and one each of lipoma, a neoplasm of uncertain behaviour (major salivary gland), brain, colon, other endocrine gland, and lymphatic leukaemia. One of the haemangioma and lymphangioma cases had a similar diagnosis prior to the index admission. Four girls had subsequent diagnoses of a neoplasm, these being: benign neoplasm

Table J.6: Operations prior and subsequent to the hospital admission for the hernia operation in the 2048 cases

CSO 3 Operation code*	Surgical operation	Number of operations Before 1st admission for hernia operation		After	
		Boys	Girls	Boys	Girls
001–059	All nervous system	2	1	6	2
061–089	All endocrine system	0	0	2	1
100–189	All eye	16	5	43	10
190–249	All ear, nose and throat	43	7	446	112
193	*incision of eardrum*	*16*	*1*	*212*	*61*
232–235	*tonsillectomy, or adenoidectomy, or both*	*16*	*3*	*149*	*34*
250–289	All upper alimentary tract	0	1	19	4
290–349	All thorax (with heart and lungs)	1	0	7	1
380–389	All breast	0	0	0	0
400–559	All abdomen	22	0	219	41
410–411	*repair of inguinal hernia, n.e.c.*	—	—	*159*	*32*
441–443	*appendicectomy*	*2*	*0*	*8*	*2*
560–629	All urinary system	10	0	22	0
624	*repair of uretha*	*4*	*0*	*12*	*0*
630–669	All male genital organs	27	—	120	—
640	*incision of testis*	*0*	—	*4*	—
644–645	*excision or repair of hydrocele*	*8*	—	*21*	—
648	*orchidopexy*	—	—	—	—
661	*circumcision*	*16*	—	*77*	—
671–739	All female genital organs	—	0	—	1
740–779	All obstetric	—	0	—	0
780–879	All orthopaedic surgery	1	2	61	9
780	*manipulation of closed fracture*	*1*	*0*	*20*	*2*
880–909	All peripheral vessels	0	0	3	0
910–939	All skin and subcutaneous tissue	5	2	43	7
940–959	All other surgical procedures	5	0	11	1
960–999	All non-operative procedures	11	2	31	5
001–999	All operations or procedures	143	20	1033	194

* Classification of Surgical Operations, 3rd revision

of skin; haemangioma or lymphangioma; lipoma and myeloid leukaemia.

Table J.7: General hospital diagnoses prior to, and subsequent to, the index hospital admission for the hernia operation for 2048 cases

ICD 9* code	Discharge diagnosis	Number of diagnoses			
		Before		After	
		first admission for hernia operation			
		Boys	Girls	Boys	Girls
001–139	Infectious and parasitic diseases	26	6	60	10
140–239	Neoplasms	4	1	22	13
240–279	Endocrine, nutritional and metabolic diseases and immunity disorders	11	7	14	6
280–289	Diseases of blood and blood forming organs	5	2	24	2
290–319	Mental disorders	6	0	5	4
320–389	Diseases of nervous system and sense organs	56	12	281	65
360-379	*disorders of eye and adnexa*	*22*	*8*	*39*	*9*
380–389	*disorders of the ear and mastoid process*	*31*	*4*	*216*	*53*
390–459	Diseases of the circulatory system	7	0	5	1
460–519	Diseases of the respiratory system	133	19	386	57
460–466	*acute respiratory infections*	*65*	*11*	*108*	*6*
474	*chronic disease of tonsils and adenoids*	*14*	*2*	*112*	*29*
463	*asthma*	*12*	*2*	*78*	*2*
520–579	Diseases of the digestive system	209	37	277	54
540–543	*appendicitis*	*0*	*0*	*6*	*3*
550	*inguinal hernia*	*173*	*29*	*199*	*36*
580–629	Diseases of the genitourinary system	53	2	155	4
600–608	*diseases of male genital organs*	*43*	—	*128*	—
603	*hydrocele*	*20*	—	*23*	—
605	*redundant prepuce and phimosis*	*15*	—	*77*	—
614–629	*diseases of female genital organs*	—	*1*	—	*1*
680–709	Diseases of the skin and subcutaneous tissue	31	3	21	2
710–739	Diseases of the musculoskeletal system and connective tissue	2	1	33	5
740–759	Congenital anomalies	75	17	66	10
752	*congenital anomalies of genital organs*	*21*	*2*	*21*	*0*
752.5	*undescended testicle*	*10*	—	*3*	—
753	*congenital anomalies of urinary system*	*8*	*0*	*7*	*0*
760–779	Certain conditions originating in the perinatal period	414	58	2	0
780–799	Signs, symptoms and ill-defined conditions	72	20	128	18
N800–N999	Injury and poisoning	32	8	76	8
001–N999	All causes	1125	193	1555	259

* International Classification of Diseases, 9th revision

J.3 The controls

Initially each case was matched with up to eight livebirths on sex, hospital and year of delivery. This produced a list of 16,289 potential controls. See appendix B for details about control selection. It was not possible to match all cases with eight controls because in some instances there were not enough livebirths who satisfied the matching criteria. One male case born in 1986 did not match to any potential controls. There was, however, one control male livebirth from the study of undescended testis diagnosed by orchidopexy, born in the same hospital in 1985 as this case, and this boy was used as a potential control, giving 16,290 potential controls in total. After removing boys with a record of an orchidopexy there remained 16,063 potential controls. The list of potential controls was examined and livebirths were successively excluded from entry to the control group if: they had a major congenital anomaly diagnosed at birth (n=617, 3.8%); they were part of a multiple delivery (n=335, 2.1%, including nine triplets and four quads) or they were known to have died (n=107, 0.7%) *before* the date at which their matched case had its own operation.

The remaining 15,013 livebirth records became the matched control group. Two hundred and twenty-two (1.5%) controls were themselves affected and so also enter the study as cases. The control group was actually made up of 14,111 individuals, of whom 513 (3.6%) enter into the study again, in different matched sets, as controls. This sampling scheme enabled prevalence ratios (or risk ratios) to be estimated using conditional logistic regression (see appendix G for more details). In nested case-control studies an individual can serve as a control for more than one case [321, 330]. Table J.8 shows the number of controls in each matched set. Over ninety-nine percent of the matched sets contained four or more controls.

Table J.8: Number of matched sets by number of controls in each matched set for the 2048 cases (11701 boys; 347 girls) and their 15013 matched controls (12436 boys; 2577 girls)

Number of controls in matched set	Boys		Girls	
	Number of matched sets	Percent	Number of matched sets	Percent
8	850	50.0	196	56.5
7	614	36.1	114	32.9
6	179	10.5	32	9.2
5	43	2.5	2	0.6
4	10	0.6	2	0.6
3	1	<0.1	0	0.0
2	2	0.1	0	0.0
1	2	0.1	1	0.3
Total	1701	100.0	347	100.0

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