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Maternal and perinatal factors associated with subsequent meningococcal, *Haemophilus* or enteroviral meningitis in children: database study

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SUMMARY

We used a database of 248 659 births, with follow-up to subsequent disease, in the Oxford record linkage archive (1979–1999) to study the influence of family, maternal, and perinatal factors on subsequent hospital admission for meningococcal, *Haemophilus*, and enteroviral meningitis in the children. In this summary, we report key findings that were significant in multivariate analysis. Meningococcal meningitis was significantly associated with maternal smoking [odds ratio (OR) 2·1, 95% confidence interval (CI) 1·2–3·7]. *Haemophilus* meningitis was associated with having older siblings (e.g. second child compared to first-born, OR 3·3, 95% CI 2·0–5·6). Enteroviral meningitis was associated with low birth weight (OR 2·2, 95% CI 1·3–3·6) and male sex (OR 1·7, 95% CI 1·2–2·3). The mothers of six of the 312 children with enteroviral meningitis had previously had enteroviral meningitis themselves. We concluded that several maternal characteristics influence the risk of these types of meningitis.

Key words: Bacterial meningitis, epidemiology, meningitis, viral meningitis.

INTRODUCTION

There is interest in whether maternal and perinatal factors influence the occurrence of infectious disease later in life [1–4]. A recent study found that low birth weight and pre-term birth are associated with an increased risk of hospitalization for infections during childhood [2]. It has also been reported that maternal smoking and low maternal body mass index pre-pregnancy increased the risk of subsequent hospitalization for infectious disease in children up to age 5 years [1].

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It is well documented that low birth weight predisposes to coliform meningitis in neonates [5], but less is known about whether perinatal and maternal factors influence the risk of meningitis in later infancy and childhood. Suggested risk factors for meningitis in children include smoking in the home, low social class, low birth weight, overcrowding and having older siblings [3, 6–10].

The aims of this study were to investigate associations between maternal and perinatal risk factors and subsequent hospitalization for meningococcal, *Haemophilus* or enteroviral meningitis in the child. These were selected because we were interested in meningitis and they were the three most common causes of meningitis in the dataset used. We used record linkage data from a historical archived dataset in a large geographically defined English population.

METHODS

We used the specialist maternity dataset of the Oxford record linkage study (ORLS). The ORLS included inpatient hospital records, and records of hospital-based day-case care, in an area of South East England. Standard data collection in the ORLS was undertaken in two health districts from 1963 to 1999 (population 0·9 million in 1999) and, from 1975 to 1999, in a further four adjacent districts (total population 1·9 million). The characteristic that distinguished the ORLS from other data collection systems in England was that the data were record-linkable; and they are now in a fully linked archived data file. In other respects, the data are similar to those in routine hospital administration systems in many industrialized countries. In addition, a specialist data collection system for maternity – used as the basis of this study – covered all births in National Health Service (NHS) hospitals in Oxfordshire and West Berkshire from 1970 to 1989.

The maternity data from 1970 to 1989 were abstracted from maternity records by clerical staff who were trained by senior medical staff at the ORLS. The records of each mother and her baby were routinely linked by the use of unique numbers for each mother and each baby that were assigned to both the baby's and the mother's record at the time of birth. Detailed data collection on maternities in the ORLS area ceased in 1989 following government reforms to increase the uniformity of NHS data collection systems. Data collection for general hospital admissions in the ORLS area continued but, with further changes to NHS information systems in 1999, it is not possible to link pre- and post-1999 ORLS data.

We identified cases of meningococcal meningitis from the diagnoses recorded on hospital admission records, using International Classification of Diseases (ICD) codes 036·0 in the eighth and ninth revisions (ICD-8, ICD-9), and A39·0 in ICD-10. We identified cases of *Haemophilus* meningitis using ICD codes 320·0 in the 8th and 9th revisions and G00·0 in the 10th revision. We identified cases of enteroviral meningitis using ICD codes 045 in the eighth revision, 047 in the ninth revision and A87·0 and A87·9 codes in the tenth revision.

There were 253 060 pregnancies with a maternity record in the ORLS from 1970 to 1989. Of these, we excluded 985 that were recorded as having ended in abortion, 1560 stillbirths and 1567 neonatal deaths (none of the latter had a diagnostic code in the above list for meningitis). We also excluded 289 maternities in which the birth weight was recorded as <1000 g because many of these records had implausibly low values and/or considerable missing data for some of the other variables. After applying these exclusion criteria there were 248 659 children in the study.

Initial analyses were undertaken on fine groupings of the maternal and perinatal variables and, following scrutiny of whether the fine groups added anything material, broader groupings (as shown in the Tables) were selected for further analysis and presentation herein. Breastfeeding data were recorded in the original ORLS records as mother breastfeeding at discharge. The social class data were based on occupational social class, collected as the occupation of the head of the household (data on education or income was not available). Some of the data items were not collected through the whole period: notably, data on maternal smoking, breastfeeding and social class were only collected after 1975.

The significance of univariate associations was tested using χ^2 tests. When using logistic regression for multivariate modelling, all variables that were significant ($P<0·05$) in the univariate analysis were included in the initial model and the variables that were not significant were removed. In further modelling, each variable that was not significant in univariate analysis was re-introduced, one at a time, into the model. The purpose of this was to test whether any variable, not significant in univariate analysis, became so when modelled with the other significant variables. We did not include maternal meningitis in the model because the number of cases of meningitis in both mother and child was too small to be meaningful to model. Year of the child's birth was included in all models to take account of different lengths of follow-up for children born in different years.

Approval for the research programme of the Unit of Health-Care Epidemiology using the anonymized dataset of the Oxford Record Linkage Study was obtained from the Central and South Bristol Research Ethics Committee (04/Q2006/176).

RESULTS

Of the 248 659 children in the dataset, 127 children had a subsequent admission for meningococcal meningitis, 160 for *Haemophilus* meningitis and 312 children for enteroviral meningitis. Table 1 shows

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the age and sex distribution of cases. There were no neonatal cases. In children with meningococcal meningitis, 33·1% were admitted aged <1 year, 26% were admitted aged 1–4 years and most of the rest were admitted aged ⩾15 years (25·2%). For those with *Haemophilus*, 51·3% were admitted aged <1 year, and 46·9% were admitted aged 1–4 years. For enteroviral meningitis, the spread of cases was much more evenly split between the age groups, with 29·2% admitted aged <1 year, 18·3% aged 1–4 years, 27·2% aged 5–9 years, 12·8% aged 10–14 years and 12·5% aged ⩾15 years. Of those with meningococcal meningitis 53·5% were males, as were 58·1% with *Haemophilus* meningitis and 62·2% with enteroviral meningitis.

Table 1. *Number of children admitted for meningococcal,* Haemophilus *or enteroviral meningitis showing age at admission and sex*

Age at meningitis admission	Male		Female		Total	
	n	%	*n*	%	*N*	%
Meningococcal meningitis						
29–364 days	24	57·1	18	42·9	42	33·1
1–4 years	19	57·6	14	42·4	33	26·0
5–9 years	2	20·0	8	80·0	10	7·9
10–14 years	7	70·0	3	30·0	10	7·9
⩾15 years	16	50·0	16	50·0	32	25·2
Total	68	53·5	59	46·5	127	100·0
Haemophilus meningitis						
29–364 days	47	57·3	35	42·7	82	51·3
1–4 years	44	58·7	31	41·3	75	46·9
5–9 years	1	50·0	1	50·0	2	1·3
10–14 years	0		0		0	0·0
⩾15 years	1	100·0	0	0·0	1	0·6
Total	93	58·1	67	41·9	160	100·0
Enteroviral meningitis						
29–364 days	52	57·1	39	42·9	91	29·2
1–4 years	37	64·9	20	35·1	57	18·3
5–9 years	62	72·9	23	27·1	85	27·2
10–14 years	26	65·0	14	35·0	40	12·8
⩾15 years	17	43·6	22	56·4	39	12·5
Total	194	62·2	118	37·8	312	100·0

Meningococcal meningitis

There were 41 patients with meningococcal meningitis born during 1970–1974 (0·06% of all births in the period, $N = 68\,939$), 28 born during 1975–1979 (0·05% of births, $N = 56\,492$), 23 during 1980–1984 (0·04%, $N = 60\,394$), and 35 during 1985–1989 (0·06%, $N = 62\,834$). There was no consistent trend in the incidence of meningococcal meningitis across birth cohorts (χ^2_1 linear association = 0·37, $P = 0·54$). In univariate analysis, meningococcal meningitis was significantly associated with low maternal social class, with mothers who smoked in pregnancy, and with increasing numbers of siblings (Table 2). Only 17·5% of mothers of children who subsequently developed meningococcal meningitis were in social classes 1 or 2 (the most affluent) compared to 35·8% in the whole study population (Table 2). Unmarried motherhood and lack of breastfeeding were significantly, but modestly, associated with meningococcal meningitis (Table 2). Several of the perinatal factors were themselves inter-related (e.g. social class, maternal smoking, parity, birth weight). In the multivariate model, the only factor that remained significantly associated with hospital admission for meningococcal meningitis after taking account of all other factors in the model (which included social class), was maternal smoking [odds ratio (OR) 2·1, 95% confidence interval (CI) 1·2–3·7]. Within each band of social class, children who developed meningococcal meningitis were more likely than other children to have mothers who smoked (Table 3). For example, considering mothers in social classes 1 or 2 (the most affluent classes), 36·4% of mothers whose children developed meningococcal meningitis smoked compared to 12·5% of mothers whose children did not develop meningitis. Considering mothers in social classes 4 and 5 (least affluent), the respective percentages were 44·4% and 32·0%.

Haemophilus meningitis

Considering those who developed *Haemophilus* meningitis, 23 were born during 1970–1974 (0·03% of all births in the period), 31 (0·05%) during 1975–1979, 43 (0·07%) during 1980–1984 and 63 (0·1%) during 1985–1989 respectively. An increasing linear trend in incidence was found across birth cohorts (χ^2_1 linear association = 23·8, $P < 0·001$). Parity was significantly associated with hospital admission for *Haemophilus* meningitis in children: *Haemophilus* meningitis was uncommon in first-born children. Only 18% of children with *Haemophilus* meningitis were first-born, compared to 42% of all children in the study. Low social class was significantly associated with admission for *Haemophilus* meningitis, as was

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Table 2. *Maternal and perinatal characteristics of babies who, in later life, were admitted to hospital with meningococcal,* Haemophilus *or enteroviral meningitis*

Maternal and perinatal characteristics		Meningococcus		*Haemophilus*		Enteroviral		All offspring	
		n	%	*n*	%	*n*	%	*n*	%
Maternal meningitis	No	127	100	160	100	306	98·1***	247923	99·7
	Yes	0	0	0	0	6†	1·9***	736	0·3
Maternal age	14–24	55	43·7	50	31·3	128	41	86544	34·9
	25–34	62	49·2	100	62·5	160	51·3	142939	57·6
	⩾35	9	7·1	10	6·3	24	7·7	18852	7·6
Social class	1, 2	17	17·5***	30	25·9*	74	29·8	68244	35·8
	3	53	54·6***	55	47·4*	121	48·8	86869	45·6
	4, 5	27	27·8***	31	26·7*	53	21·4	35510	18·6
Marital status	Not married	20	15·7*	19	11·9	27	8·7	23939	9·6
	Married	107	84·3*	141	88·1	285	91·3	224261	90·4
Maternal smoking	No	37	50·7***	79	71·2	102	67·5**	110961	76·4
	Yes	36	49·3***	32	28·8	49	32·5**	34245	23·6
Parity	1st born	59	46·8**	29	18·1***	108	34·6*	104210	42
	2nd born	31	24·6**	74	46·3***	116	37·2*	89081	35·9
	3rd born	16	12·7**	34	21·3***	59	18·9*	36118	14·6
	4th born	14	11·1**	17	10·6***	22	7·1*	12110	4·9
	⩾5th born	6	4·8**	6	3·8***	7	2·2*	6591	2·7
Pre-eclampsia	No	113	89	145	90·6	282	90·4	224360	90·3
	Yes	14	11	15	9·4	30	9·6	24250	9·7
Blood group	A	53	49·5	74	56·9	119	47·2	101010	48·9
	O	54	50·5	56	43·1	133	52·8	105391	51·1
Rhesus	Positive	104	83·2	132	86·8	254	86·4	196650	83·2
	Negative	21	16·8	20	13·2	40	13·6	39805	16·8
No. of babies	1	125	98·4	155	96·9	304	97·4	243269	97·8
	⩾2	2	1·6	5	3·1	8	2·6	5390	2·2
Birth weight	1000–2499	6	4·7	11	6·9	29	9·3**	13775	5·6
	2500–5499	121	95·3	149	93·1	283	90·7**	234078	94·4
Gestational age	24–37 weeks	9	8·7	13	9·6	39	14·4	21912	10·1
	38–41 weeks	81	77·9	106	78·5	210	77·8	173868	80·4
	42–47 weeks	14	13·5	16	11·9	21	7·8	20567	9·5
Breastfeeding	No	33	41·8*	49	37·1	64	34·8	50966	30·3
	Yes	46	58·2*	83	62·9	120	65·2	117364	69·7
Caesarian	No	115	92	149	96·8*	278	90·8	223793	92·5
	Yes	10	8	5	3·2*	28	9·2	18025	7·5
Presentation	Vertex	73	93·6	132	97·8	178	91·3*	158302	95
	Other	5	6·4	3	2·2	17	8·7*	8311	5
Apgar 1	1–5	14	11·9	8	5·6	21	7·6	21356	9·5
	6–8	31	26·3	47	32·6	79	28·4	64469	28·5
	9–10	73	61·9	89	61·8	178	64	140267	62
Sex	Male	68	53·5	93	58·1	194	62·2***	127829	51·4
	Female	59	46·5	67	41·9	118	37·8***	120823	48·6

The numbers for each characteristic do not always add to the total number of children in the study as some records did not contain the corresponding information (notably, because the data items for the characteristic were only collected in certain calendar years).

† All cases were enteroviral.

* P value, for heterogeneity within the risk factor group, between 0·02 and 0·05; ** P value between 0·001 and 0·02; *** $P<0·001$.

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Table 3. *Comparisons within social class groups of whether the child had meningococcal meningitis and whether the mother smoked during pregnancy*

Meningococcal meningitis (yes/no)	Mother smoked during pregnancy	
	%	*n*/*N*
Social classes 1 and 2		
Yes	36·4	4/11
No	12·5	5514/43971
Social class 3		
Yes	35·7	10/28
No	24·3	12297/50501
Social classes 4 and 5		
Yes	44·4	4/9
No	32·0	6365/9898

mode of delivery (Table 2). In the multivariate model, parity was the only factor that remained significant. Compared to first-born (as the reference group), the odds of *Haemophilus* meningitis in second-, third-, fourth- and fifth-born children were, respectively, 3·31 (95% CI 1·97–5·57), 3·25 (95% CI 1·77–5·96), 4·68 (95% CI 2·23–9·86) and 3·12 (95% CI 1·06–9·21).

Enteroviral meningitis

There were 108 people born during 1970–1974 diagnosed with enteroviral meningitis (0·16% of all births), 91 (0·16%) during 1975–1979, 71 (0·12%) during 1980–1984, and 42 (0·07%) during 1985–1989. A decreasing linear trend was found across birth cohorts, (χ^2_1 linear association = 24·5, $P < 0·001$). Enteroviral meningitis in the child was significantly associated with maternal parity, maternal smoking during pregnancy, babies' low birth weight, non-vertex presentation at birth, and a maternal history of enteroviral meningitis (Table 2). It was also considerably more common in male than female offspring (Table 2). The majority of children with enteroviral meningitis were first or second born. In the multivariate model, male sex (OR 1·7, 95% CI 1·2–2·3), low birth weight (OR 2·2, 95% CI 1·3–3·6; <2500 g *vs.* ⩾2500 g) and presentation other than vertex (OR 1·9, 95% CI 1·1–3·3) remained the only significant risk factors for enteroviral meningitis. There were six families in which the mother and her child both had hospital admissions for enteroviral meningitis. In all six families, the mother's admission occurred before that of the child. The time intervals between admission of mother and child were 4 days, 61 days, 1½ years, 2½ years, 5 years, and 20 years.

DISCUSSION

A strength of this analysis is that it was undertaken in a large, defined population that covered over 30 years of data collection and almost 250 000 births. Another strength is that information about perinatal risk factors and the main outcome measures – meningococcal, *Haemophilus* and enteroviral meningitis in the child –were originally recorded independently of each another. They were subsequently brought together by record linkage. This means that data about each risk factor could not have been influenced by the presence or absence of the outcome measure, as could be the case in interview-based studies of people with meningitis. The study is therefore not subject to potential biases, such as interviewer and recall bias, that can affect interview-based case-control studies.

We acknowledge the limitations of our study design. We were not able to identify data from resident children who may have been admitted to hospital outside the ORLS area or about children who were admitted with meningitis after moving outside the ORLS area. We do not have information on the diagnostic criteria or methods used in making a clinical diagnosis or laboratory confirmation of the diagnosis. The sensitivity of the diagnostic method used for enteroviral meningitis during most of the study period, most likely viral culture of cerebrospinal fluid (CSF), is less accurate than more recent CSF polymerase chain reaction (PCR) methods [11, 12]. In addition, we do not have follow-up information on breastfeeding after discharge and as a result have no information on the duration or exclusivity of breastfeeding. We have no way of testing the validity of the data on breastfeeding.

To test the likely validity of the data on maternal smoking, we undertook a separate analysis of the smoking status of mothers in the dataset with inflammatory bowel disease. We did this because it is well recognized that smoking is associated with an increased risk of Crohn's disease and that it protects against ulcerative colitis [13]. In the whole ORLS perinatal dataset from 1975 to 1989 (during which times hospitals were asked to record maternal smoking) there was a smoking history for 146 811 pregnancies. In these, 23·7% (34 728) of mothers smoked

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(34 728/146 811). Considering pregnancies of mothers with Crohn's disease, 37·3% (62/166) of the mothers smoked; considering pregnancies of mothers with ulcerative colitis, only 7% (9/129) smoked. We conclude that the smoking data in our dataset are likely to be valid and that the ORLS data on maternal smoking in pregnancy are good proxies for longer-term smoking by the woman.

The data are, of course, archival and old. Nonetheless they include data items that are not available in routinely collected hospital maternity statistics even now in England – notably, the mother's smoking history, whether the baby was breastfed, the family's occupational social class, as well as such items as ABO blood group and rhesus. The principal findings – smoking and meningococcal disease, family size and *Haemophilus*, familial occurrence of enteroviral meningitis – are unlikely to be affected by whether the data are recent or old. It is possible, however, that recent introduction of immunization against some meningococcal strains and against *Haemophilus* may have modified the impact of such factors in the modern era. The programme of MenC vaccination was initiated in 1999, and its effects were therefore outside the scope of our analysis. Widespread use of immunization against *Haemophilus influenzae* was largely introduced in 1992 and largely post-dates our study period [14].

Meningococcal meningitis

Low social class and maternal smoking were the strongest predictors of meningococcal meningitis in children. Previous studies have shown socioeconomic factors to be associated with meningococcal risk [10, 15–17]. A study by Yusuf *et al.* [6] found an association between factors such as unmarried motherhood and low maternal education (<12 years schooling) with meningococcal disease [6]. In our study, a parity of three or more and unmarried motherhood were also risk factors for meningococcal meningitis, but, when social class was taken into account, they were not independent predictors of risk. We add further evidence that maternal smoking is an independent predictor of meningococcal meningitis in children [3, 6, 15, 18]. Our adjusted odds ratio for this, at 2·1, is very similar to that found in a Danish record-linkage study (OR 1·8) [3]. The Danish study also found low birth weight and premature birth to be risk factors for meningococcal disease [3].

Haemophilus meningitis

An important determinant of admission of a child to hospital for *Haemophilus* meningitis was having older children in the family. First-born children were significantly less likely to have *Haemophilus* meningitis than children with older siblings. It has been previously reported that the occurrence of *Haemophilus* meningitis in single-child families is very low, suggesting that older siblings introduce it into the home [19]. Siblings [20] and household overcrowding [7, 8, 21, 22] have been attributed as risk factors for *Haemophilus* infection, with a dose-response effect reported for increasing risk with increasing numbers of children sharing a bedroom [22]. We found an increasing linear trend in *H. influenzae* over the time period studied. An increase over time was also reported in Sweden prior to the introduction of Hib vaccine [23, 24]. While research in the USA found that an increased risk of contracting *H. influenzae* was associated with the use of daycare centers [25], the Swedish research suggested that the increase in the incidence of *H. influenzae* could not be explained by the use of child daycare services themselves [23]. The Swedish researchers suggested changes in bacterial virulence or host susceptibility might have contributed to the observed increase [24], or it may be due to a low breastfeeding rate in the population as the incidence was correlated with breastfeeding rates over time in a negative way [23]. Although our results do not show a significant relationship between breastfeeding and *Haemophilus* meningitis, previous studies have found breastfeeding to be a strong protective factor against *H. influenzae* [7, 21, 23, 24, 26].

Enteroviral meningitis

Data on perinatal risk factors for enteroviral meningitis are sparse. We confirm the findings of a record-linkage study performed in Denmark that reported that male sex and low birth weight were associated with non-polio enteroviral meningitis [9]. Other studies have noted a strong association with male sex [27, 28]. The Danish study also reported several other risk factors for enteroviral meningitis including a large number of younger children in the household, gestational age, Apgar score, Caesarean section, season, age, calendar period, number of adults in the household, and urbanization [9]. We cannot offer an explanation for our finding of an association with non-vertex presentation. It is possible that, although significant, it is nonetheless a chance

finding. A study in the USA found that meningitis in enterovirus-infected infants was more frequent in those with a certain enteroviral serotype (echoviruses 30, 11, and type B coxsackie viruses) [29]. Transmission of enterovirus may occur nosocomially or through vertical transmission from mother to child (either transplacentally or at the time of delivery) [30]. Most mother-and-child pairs in our study were remote in time suggesting either familial susceptibility or longstanding carriage, or both.

CONCLUSIONS

In summary, this study used record-linkage analysis to examine maternal and perinatal risk factors for subsequent hospitalization for meningococcal, *Haemophilus*, and enteroviral meningitis in Oxfordshire over a 30-year period. We confirm the findings of previous studies that low social class and maternal smoking are risk factors for meningococcal meningitis. This study also shows that *Haemophilus* meningitis tends to be associated with having older siblings in the household. Finally, hospitalization for enteroviral meningitis was associated with a number of factors including enteroviral meningitis in the mother.

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DECLARATION OF INTEREST

None.

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