Perinatal and early life risk factors for inflammatory bowel disease

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Abstract

AIM: To investigate associations between perinatal risk factors and subsequent inflammatory bowel disease (IBD) in children and young adults.

METHODS: Record linked abstracts of birth registrations, maternity, day case and inpatient admissions in a defined population of southern England. Investigation of 20 perinatal factors relating to the maternity or the birth: maternal age, Crohn's disease (CD) or ulcerative colitis (UC) in the mother, maternal social class, marital status, smoking in pregnancy, ABO blood group and rhesus status, pre-eclampsia, parity, the infant's presentation at birth, caesarean delivery, forceps delivery, sex, number of babies delivered, gestational age, birthweight, head circumference, breastfeeding and Apgar scores at one and five minutes.

RESULTS: Maternity records were present for 180 children who subsequently developed IBD. Univariate analysis showed increased risks of CD among children of mothers with CD ($P = 0.011$, based on two cases of CD in both mother and child) and children of mothers who smoked during pregnancy. Multivariate analysis confirmed increased risks of CD among children of mothers who smoked (odds ratio = 2.04, 95% CI = 1.06-3.92) and for older mothers aged 35+ years (4.81, 2.32-9.98). Multivariate analysis showed that there were no significant associations between CD and 17 other perinatal risk factors investigated. It also showed that, for UC, there were no significant associations with the perinatal factors studied.

CONCLUSION: This study shows an association between CD in mother and child; and elevated risks of CD in children of older mothers and of mothers who smoked.

INTRODUCTION

Both Crohn's disease (CD) and ulcerative colitis (UC) are considered to be immune-mediated disorders, although the exact pathogenetic mechanisms are not yet clear. It is thought that a combination of environmental factors in genetically susceptible people lead to disordered im-
munity and chronic inflammation. Over the last 50 years, there have been large increases in the incidence of CD and UC in the UK, in other western countries\(^{1-3}\), and more recent increases in Asia\(^{4}\), which indicate changes over time in the environmental factors that can lead to inflammatory bowel disease (IBD).

In recent decades, there have been changes in the management of births, including large increases in caesarean deliveries, advances in neonatal medicine and substantial reductions in neonatal mortality. As perinatal risk factors have been associated with some immune-mediated diseases including asthma\(^{5,7}\) and type 1 diabetes\(^{8,10}\), perinatal risk factors and early life events may be relevant to other immune-mediated diseases, including IBD. One case-control study identified that infectious and non-infectious perinatal health events were linked with 40% of all cases of IBD in the study group\(^{11}\). A systematic review and meta-analysis of 17 (mainly case-control) studies found a small but significant protective effect of breastfeeding against both CD and UC\(^{12}\). However, its authors commented that this finding was far from conclusive, and advocated the need for larger studies. There have been relatively few studies of other perinatal risk factors and IBD.

The aim of this study was to investigate associations between 20 perinatal risk factors and the subsequent development of IBD in children and young adults in a large geographically defined population of South East England. These perinatal risk factors include nine maternal characteristics, such as maternal age, parity, smoking during pregnancy, ABO blood group and social class, and 11 neonatal characteristics, including birthweight, gestational age, head circumference, breastfeeding and Apgar scores.

**MATERIALS AND METHODS**

Ethical approval for analysis of the linkage study data was obtained from the Central and South Bristol Multi-Centre Research Ethics Committee (04/Q2006/176).

We used the Oxford record linkage study (ORLS). The ORLS comprises abstracts of records of birth registrations, maternities, day cases and inpatient admissions in a defined geographical region of South East England around Oxford. The maternity data covered all National Health Service (NHS) hospitals in two health districts of the ORLS up to 1999, in two health districts because of the different periods of follow-up after different years of birth.

The ORLS comprises abstracts of records of birth registrations, maternities, day cases and inpatient admissions in a defined geographical region of South East England around Oxford. The maternity data covered all National Health Service (NHS) hospitals in two health districts of the ORLS up to 1999, in two health districts because of the different periods of follow-up after different years of birth.

For the 114 and 66 children identified with CD and UC respectively, the age at first admission (mean ± SD) was 17.5 ± 5.1 years and 17.7 ± 6.0 years. Approximately half of the cases of both CD and UC had a first recorded admission in early adulthood (when aged 18 to 30 years) rather than in childhood (Table 1). A majority of cases were female; 59 (52%) for CD and 37 (56%) for UC.

**CD**

Considering risk factors relating to the maternity, in univariate analysis there was a significant association (\(P = \)}
between CD in the mother and CD in the child (OR = 8.36, 95% CI = 2.06-33.9), based on two cases of CD in both (Table 2). There was a borderline significant association (P = 0.05) for maternal smoking and CD in the child (OR = 1.92, 95% CI = 1.03-3.56). There was no significant association between CD and mother’s age in the age groupings that we originally selected (< 25, 25-34 and 35+ years; Table 2), but there was a non-significantly increased risk among children of older mothers aged 35+ years, when compared with mothers aged under 35 years (OR = 1.70; 0.97-2.08). Accordingly, we recategorised mothers’ age as < 35 years vs 35+ years in the multivariate analysis (see below).

We found no significant associations between CD and birth order or with any of the other six maternal risk factors considered, including marital status, ABO blood group, rhesus status and presentation at delivery (Table 2). We found no significant associations between CD and any of the perinatal risk factors relating to the birth, including birthweight, gestational age, caesarean delivery, forceps, Apgar scores and breastfeeding (Table 3).

Using multivariate analysis to assess the independent

### Table 1: Age at first hospitalisation (yr) with inflammatory bowel disease

|                | Total | < 1 | 5-9 | 10-14 | 15-19 | 20-29 |
|----------------|-------|-----|-----|-------|-------|-------|
| **Crohn’s disease** |       |     |     |       |       |       |
| Male           | 1 (2) | 1 (2) | 4 (7) | 11 (20) | 18 (33) | 20 (36) |
| Female         | 0     | 0    | 0    | 11 (19) | 19 (32) | 29 (49) |
| Total          | 1 (1) | 1 (1) | 4 (4) | 22 (19) | 37 (32) | 49 (43) |
| **Ulcerative colitis** |       |     |     |       |       |       |
| Male           | 0     | 1 (3) | 2 (7) | 2 (7) | 7 (24) | 17 (59) |
| Female         | 0     | 1 (3) | 3 (8) | 6 (16) | 11 (30) | 16 (43) |
| Total          | 0     | 2 (3) | 5 (8) | 8 (12) | 18 (27) | 33 (50) |

### Table 2: Associations between maternal characteristics and inflammatory bowel disease in the child

| Maternal characteristics | No. of births | Crohn’s disease | Ulcerative colitis |
|--------------------------|---------------|-----------------|--------------------|
|                          | No. of cases  | Percent         | P-value            | No. of cases  | Percent         | P-value            |
| Maternal age (yr)        |               |                 |                    |               |                 |                    |
| 14-24                    | 86,544        | 41              | 0.047%             | 21             | 0.024%          |                    |
| 25-34                    | 142,939       | 59              | 0.041%             | 40             | 0.028%          |                    |
| 35-49                    | 18,852        | 14              | 0.074%             | 5              | 0.027%          |                    |
| Maternal Crohn’s disease or ulcerative colitis | | | | | | |
| No                       | 248,132       | 112             | 0.045%             | 66             | 0.027%          | 1.00               |
| Yes                      | 530           | 2               | 0.380%             | 0              |                 | 0.12               |
| Maternal social class    |               |                 |                    |               |                 |                    |
| I & II                   | 68,244        | 21              | 0.031%             | 12             | 0.018%          |                    |
| III                      | 86,869        | 54              | 0.062%             | 32             | 0.037%          |                    |
| IV & V                   | 35,510        | 22              | 0.062%             | 11             | 0.031%          |                    |
| Marital status           |               |                 |                    |               |                 |                    |
| Married                  | 224,261       | 109             | 0.049%             | 65             | 0.029%          | 0.042              |
| Not married              | 23,939        | 5               | 0.021%             | 1              | 0.004%          |                    |
| Maternal smoking during pregnancy | | | | | | |
| No                       | 110,961       | 27              | 0.024%             | 18             | 0.016%          |                    |
| Yes                      | 34,245        | 16              | 0.047%             | 4              | 0.012%          |                    |
| Maternal ABO blood group |               |                 |                    |               |                 |                    |
| A                        | 101,010       | 44              | 0.044%             | 26             | 0.026%          | 0.81               |
| O                        | 105,391       | 49              | 0.046%             | 30             | 0.028%          |                    |
| Maternal rhesus Status   |               |                 |                    |               |                 |                    |
| Negative                 | 39,805        | 18              | 0.045%             | 10             | 0.025%          | 0.97               |
| Positive                 | 196,652       | 87              | 0.044%             | 53             | 0.027%          |                    |
| Pre-eclampsia            |               |                 |                    |               |                 |                    |
| No                       | 224,360       | 99              | 0.044%             | 60             | 0.027%          | 1.00               |
| Yes                      | 24,250        | 15              | 0.062%             | 6              | 0.025%          |                    |
| Parity                   |               |                 |                    |               |                 |                    |
| O                        | 104,210       | 41              | 0.039%             | 25             | 0.024%          | 0.59               |
| 1+                       | 144,214       | 73              | 0.051%             | 41             | 0.028%          |                    |

1. P-values obtained through χ² tests, with Yates continuity corrections; 2. Comparing those with Crohn’s disease with those without known inflammatory bowel disease (IBD); 3. Comparing those with ulcerative colitis with those without known IBD. *P < 0.05.
significance of perinatal risk factors, there was a significantly increased risk of CD among the offspring of mothers who were aged 35+ years, compared with those aged under 35 years (OR = 4.81, 95% CI = 2.32-9.98), and an increased risk of CD among children of mothers who smoked during pregnancy compared with those who did not (2.04, 1.06-3.92). Numbers were too small to warrant inclusion of maternal CD in the multivariate analysis (Table 4).

**UC**

For UC, in univariate analysis there was only a (marginal) significantly reduced risk for mothers who were not married ($P = 0.042$), although this was based on only one case of an unmarried mother with a child with UC (Tables 2 and 3). Numbers were too small to warrant inclusion of marital status, i.e. a stratum with just one case, in the multivariate analysis. Using multivariate analysis, there were no other significant associations between UC and any of the other 19 perinatal risk factors relating to either the mother or the birth (Table 4).

**DISCUSSION**

A strength of our study is that we have investigated 20 perinatal risk factors for IBD, unlike other studies that have mostly investigated one, two or only a few factors. The study is based on a geographically defined population, covering prospective data collected over 30 years. Another important strength is that information about the perinatal risk factors and the main outcome measure - IBD in offspring - were collected independently of each other. They were subsequently brought together independently through systematic record linkage, such that information collected for each risk factor was not influenced by knowledge of

Table 3  Associations between characteristics of the births and inflammatory bowel disease in the child

| Characteristics of the births | No. of births | No. of cases | Percent | $P$-value$^1$ | No. of cases | Percent | $P$-value$^2$ |
|------------------------------|---------------|-------------|---------|--------------|-------------|---------|--------------|
| Presentation at delivery     |               |             |         |              |             |         |              |
| Vertex                       | 158302        | 52          | 0.033%  | 0.47         | 26          | 0.016%  |              |
| Other                        | 8311          | 1           | 0.012%  |              | 1           | 0.012%  |              |
| Cesarean birth               |               |             |         | 0.72         |             |         |              |
| No                           | 223793        | 104         | 0.046%  |              | 63          | 0.028%  |              |
| Yes                          | 181025        | 10          | 0.055%  |              | 3           | 0.017%  |              |
| Forceps delivery             |               |             |         | 1.00         |             |         |              |
| No                           | 210100        | 99          | 0.047%  |              | 58          | 0.028%  |              |
| Yes                          | 31718         | 15          | 0.047%  |              | 8           | 0.025%  |              |
| Sex                          |               |             |         | 0.56         |             |         |              |
| Male                         | 127829        | 55          | 0.043%  |              | 29          | 0.023%  |              |
| Female                       | 120823        | 59          | 0.049%  |              | 37          | 0.031%  |              |
| No. of babies                |               |             |         | 0.53         |             |         |              |
| 1                            | 243269        | 113         | 0.046%  |              | 63          | 0.026%  |              |
| 2+                           | 5390          | 1           | 0.019%  |              | 3           | 0.056%  |              |
| Gestational age (wk)         |               |             |         | 0.72         |             |         |              |
| 24-37                        | 21912         | 8           | 0.037%  |              | 5           | 0.023%  |              |
| 38-41                        | 173868        | 82          | 0.047%  |              | 51          | 0.029%  |              |
| 42-47                        | 20567         | 12          | 0.058%  |              | 3           | 0.014%  |              |
| Birth weight (g)             |               |             |         | 0.72         |             |         |              |
| 1000-2999                    | 58553         | 31          | 0.053%  |              | 14          | 0.024%  |              |
| 3000-3499                    | 169149        | 73          | 0.043%  |              | 43          | 0.026%  |              |
| 3500+                        | 21151         | 10          | 0.047%  |              | 9           | 0.043%  |              |
| Head circumference (cm)      |               |             |         | 0.34         |             |         |              |
| < 34                         | 34681         | 13          | 0.037%  |              | 6           | 0.017%  |              |
| 34-35                        | 39128         | 15          | 0.038%  |              | 6           | 0.015%  |              |
| 35-36                        | 38528         | 6           | 0.016%  |              | 7           | 0.018%  |              |
| 36+                         | 51035         | 14          | 0.027%  |              | 7           | 0.014%  |              |
| Breastfeeding                |               |             |         | 0.89         |             |         |              |
| Artificial                   | 50966         | 17          | 0.033%  |              | 10          | 0.020%  |              |
| Breastfed                    | 117364        | 36          | 0.031%  |              | 18          | 0.015%  |              |
| Apgar 1 score                |               |             |         | 0.34         |             |         |              |
| 1-5                          | 21356         | 14          | 0.066%  |              | 6           | 0.028%  |              |
| 6-8                          | 64469         | 27          | 0.042%  |              | 16          | 0.025%  |              |
| 9-10                         | 140267        | 57          | 0.041%  |              | 37          | 0.026%  |              |
| Apgar 5 score                |               |             |         | 0.87         |             |         |              |
| 1-5                          | 884           | 0           | 0.001%  |              | 1           | 0.11%   |              |
| 6-8                          | 4229          | 2           | 0.047%  |              | 0           |         |              |
| 9-10                         | 148835        | 43          | 0.029%  |              | 23          | 0.015%  |              |

$^1P$-values obtained through $\chi^2$ tests, with Yates continuity corrections; $^2$Comparing those with Crohn's disease with those without known inflammatory bowel disease (IBD); $^3$Comparing those with ulcerative colitis with those without known IBD.
the outcome measure. Our study is therefore not subject to potential interviewer and recall bias, e.g. about whether the mother smoked during pregnancy, which can affect studies based on interviews or self-reporting, and which provide much of the evidence about IBD and perinatal risk factors. The Oxford record linkage study has also been used as the basis of previous studies of perinatal risk factors [19,20,21].

The study has several limitations. There was variable follow-up after birth, with shorter durations of follow-up for those born in the more recent years of the study period. However, there was at least 10 years follow-up for all IBD cases among offspring. Maternities during the early years of the study period, and among younger mothers, had fewer years of pre-pregnancy inclusion to ascertain maternal IBD, while data for three of the 20 risk factors (social class, smoking and breastfeeding), were not available for the first four years of the study period. The study would not have identified offspring who were diagnosed with IBD after migrating out of the ORLS region, which would reduce the number of observed cases of IBD.

The identification of cases of IBD in the offspring was restricted to those who were admitted as inpatients or day cases. We will have missed some cases of IBD where the only inpatient or day case admission was for a diagnostic endoscopy and biopsy in patients with suspected IBD, and where the pathology results were not available to create a record of the diagnosis at the time of discharge. We will also have missed people without any day case or inpatient care. Migration over time in the Oxford region population would also have lowered our observed incidence of IBD, particularly among adults. Our age-specific cumulative incidence rates of 1.6 and 0.9 per 100,000 for CD and UC among 0-29 year olds, and 1.0 and 0.5 respectively among 0-19 year olds, are lower than those in some UK studies, particularly among adults. Our study investigated 20 perinatal factors. It is possible that children born to older mothers may be more exposed, or more susceptible, to factors associated with the aetiology of subsequent CD, but not UC, in their children. It is also possible that our finding on maternal age, though significant, was a chance one, and is not a true association. Overall, this indicates that any possible association between social-economic background and subsequent IBD in children is probably quite weak. We did not find a significant association between social class and either CD or UC.

A systematic review and meta analysis of (mainly case-control) studies reported a small but significant protective effect of breastfeeding against subsequent IBD in offspring [22], although it concluded that new larger studies were required. More recent studies have shown little association between breastfeeding and IBD [19] or even increased risks of CD [20,21]. We found no association between breastfeeding at the time of discharge from hospital and IBD, although this includes those who subsequently discontinued breastfeeding after discharge, and is therefore an incomplete marker of breastfeeding.

The use of multivariate analysis, we found higher risks of CD, but not UC, among children of older mothers (aged 35+ years). This is consistent with a Swedish study that reported an increased risk of paediatric CD among female offspring born to older mothers [23], although other studies have identified no link between mother’s age and IBD in children [24,25]. Births among older mothers are sometimes associated with increased risks of prenatal medical and obstetric complications, intrapartum complications, perinatal and neonatal morbidity and mortality, as well as increased subsequent risks of various disorders. It is possible that children born to older mothers may be more exposed, or more susceptible, to factors associated with the aetiology of subsequent CD, but not UC, in their children. It is also possible that our finding on maternal age, though significant, was a chance one, especially as our study investigated 20 perinatal factors. It is worth noting, however, that the finding was highly significant (P < 0.01 in multivariate analysis).

We found an indication of reduced risks of IBD, particularly UC, among children of mothers who were unmarried at the time of birth, which is consistent with findings from Sweden [21] and Australia [20].

It has been suggested that caesarean section might increase the risk of subsequent IBD in children, because there is less exposure to paternal bacteria than in vaginal delivery [26]. The reasoning behind this is that, according to the hygiene hypothesis, inadequate exposure to microorganisms in early life might result in higher levels of immune-mediated pathology in later life. Although one study found an increased risk of CD for elective caesarean

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Table 4 Perinatal factors with significant, independent effect on Crohn’s disease in the child

| Perinatal risk factor                      | Odds ratio | 95% CI      |
|-------------------------------------------|------------|-------------|
| Maternal age (yr)                         |            |             |
| 14-34                                     | 1.00       | Ref.        |
| 35-49                                     | 4.81       | 2.32-9.98   |
| Maternal smoking during pregnancy         |            |             |
| No                                        | 1.00       | Ref.        |
| Yes                                       | 2.04       | 1.06-3.92   |
sections\(^{28}\), another found no association for either CD or UC\(^{9}\). We also found no association for either CD or UC.

We found no association between maternal parity and IBD. Although increased risks of IBD have been reported occasionally for first born\(^{41,42}\), or subsequent siblings\(^{43}\), most studies have found no association between birth order and IBD\(^{11,20,25,30,39}\). We also found no association between IBD and any of the other perinatal factors studied, including pre-eclampsia, birthweight, gestational age and Apgar score. These perinatal factors have not usually been associated with IBD in previous studies\(^{11,19,25,28,30}\).

To summarise, of the 20 perinatal risk factors investigated in this study, we found that maternal CD, smoking during pregnancy and advanced maternal age were associated with increased risks of CD in offspring. For UC, there were no factors associated with increased risks after multivariate adjustment. This, and the fact that the few factors that were associated with CD had quite small effect sizes, suggests that perinatal risk factors have only a minor role in the aetiology of IBD.

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COMMENTS

Background
Both Crohn's disease (CD) and ulcerative colitis (UC) are considered to be immune-mediated disorders, although the exact pathogenetic mechanisms are not yet clear. Perinatal risk factors have been linked with other immune-mediated diseases, including asthma and type 1 diabetes. Other than a suggested, small protective effect of breastfeeding, little has been reported on the role of perinatal factors for either CD or UC.

Research frontiers
This study investigated associations between 20 perinatal risk factors relating to the maternity or the birth and subsequent inflammatory bowel disease (IBD) in offspring in the Oxford region, UK. Risk factors investigated included maternal characteristics such as maternal age, IBD, social class, marital status, smoking in pregnancy, ABO blood group, rhesus status and parity, and characteristics of the birth such as caesarean delivery, number of babies delivered, gestational age, birthweight, breastfeeding and Apgar scores.

Innovations and breakthroughs
The study found increased risks of CD among children of mothers with CD, among children of mothers who smoked during pregnancy, and of older mothers aged 35+ years. There were no significant associations between CD and the 17 other perinatal risk factors investigated, and no associations for UC.

Applications
The findings indicate that these three perinatal risk factors might have some influence on subsequent IBD in children. Overall, however, perinatal factors appear to have a limited role in the aetiology of IBD. This study will help stimulate further research into the influence of perinatal risk factors on IBD. The findings should also provide an important source of information for future systematic reviews and meta analyses of perinatal factors and IBD.

Terminology
Odds ratios were used to assess any increased risks of developing IBD. These denote the chance or odds of developing IBD for a child exposed to a given perinatal risk factor (e.g. caesarean delivery) as a ratio of the chance or odds for a child not exposed to caesarean delivery. The study used record linkage of maternity exposure data and IBD outcome data, which were collected independently of each other.

Peer review
This is a very well written original article. I would like to congratulate the authors on such a nicely done original paper that contributes a lot of new information about perinatal and early risk factors for IBD.

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