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Prenatal and Perinatal Characteristics Associated with Pediatric-Onset Inflammatory Bowel Disease

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Abstract

Background—The majority of studies that report early life risk factors for pediatric-onset inflammatory bowel disease (IBD) do not account for potential confounding, which can lead to spurious associations and incorrect inferences.

Aims—To assess the relationship between prenatal and perinatal characteristics and the risk of pediatric-onset IBD accounting for potential confounding.

Methods—We conducted a nested case–control study of 189 cases aged 18 years and 3,080 age- and membership-matched controls born at a Kaiser Permanente Northern California facility between 1984 and 2006. The cases were diagnosed with IBD between 1996 and 2006 and diagnosis was confirmed by chart review. We obtained prenatal and perinatal characteristics from the electronic clinical records of the mother and child. Conditional logistic regression was used to assess the associations between these factors and risk of incident IBD, Crohn’s disease, and ulcerative colitis.

Results—In analyses accounting for confounding, maternal IBD (odds ratio [OR] 5.1, 95 % confidence interval [CI] 2.0–12.9) and white race (OR 2.3, 95 % CI 1.6–3.2) were the only factors

statistically associated with pediatric-onset IBD. Maternal respiratory infection during pregnancy (OR 2.0, 95 % CI 1.0–4.0), age < 20 years (OR 2.0, 95 % CI 0.8–4.7) and gestational hypertension (OR 1.7, 95 % CI 1.0–2.7) were associated with pediatric-onset IBD, but did not achieve statistical significance.

Conclusions—Maternal history of IBD and race were the only characteristics of those that we examined that were associated with the development of pediatric IBD in this well-documented population of cases and matched controls.

Keywords

Inflammatory bowel disease; Crohn's disease; Ulcerative colitis; Pediatric; Birth characteristics; Prenatal exposures; Fetal origins; Maternal infections; Epidemiology

Introduction

Inflammatory bowel disease (IBD) includes Crohn's disease (CD), characterized by inflammatory processes occurring anywhere in the luminal gastrointestinal tract, and ulcerative colitis (UC), where only the colon is affected. IBD unclassified, also known as indeterminate colitis, is IBD that could not be distinguished between CD and UC [1]. The etiology of IBD is unknown, but environmental and genetic factors affecting immunologic mechanisms are suspected to be involved [2]. Exposures during the prenatal period coincide with the initial development of the immune system [3]. Perinatal characteristics serve as markers for factors that affect initial exposure to antigens, including bacterial antigens that can populate the intestinal microbiome and viruses that may affect the composition of the microbiome.

Previous studies have examined the relationship between prenatal diseases, birth characteristics, and infections with risk of IBD. Overall, these studies have not found a consistent relationship between birth characteristics such as gestational age, birth weight, mode of delivery, Apgar score, or maternal age with risk of IBD [4–26]. Breastfeeding was found to be protective for adult and pediatric-onset IBD in two meta-analyses [27, 28]. Diseases and infections during pregnancy have also been associated with IBD diagnosis in some, but not all, studies [4, 6, 9, 11, 15, 17, 25]. Prior studies generally used self-reported information collected from questionnaires after IBD diagnosis, although some studies used birth records. Many of these studies did not adjust for confounding by other birth characteristics in analyses. The information presented here was collected during the prenatal period and month following birth, when the exposures occur, and therefore are not subject to recall bias. Potential confounding was accounted for in analyses to protect against spurious associations observed in unadjusted analyses.

We aimed to assess the relationship between prenatal and perinatal characteristics in relation to the risk of pediatric-onset IBD. The case–control study included pediatric-onset IBD cases diagnosed at Kaiser Permanente Northern California between 1996 and 2006 and born at a Kaiser Permanente facility between 1984 and 2006. Pediatric cases were studied exclusively for two reasons: (1) prenatal and perinatal characteristics may have a stronger effect on risk of pediatric-onset IBD because they are more temporally related than in adult-

onset cases, and (2) more complete prenatal and perinatal information was available from the health records of children compared to adults.

Materials and Methods

Study Population

Kaiser Permanente Northern California is a prepaid, integrated system providing comprehensive health care to 30 % of its service areas, comprising 3.2 million members. Comprehensive computerized medical information used for quality assurance and to provide clinical care has been available since 1996, with computerized hospitalization information dating from 1984. The membership represents the underlying population with regard to race and socioeconomic status, although it under-represents Hispanic persons [29]. All children (aged 17 and under) who were members for at least one consecutive year between 1996 and 2006 were eligible for the study. To best assess characteristics recorded during the prenatal period or at birth, we limited the study to children born at a Kaiser Permanente facility in 1984 or later.

Cases

Cases were initially identified using validated International Classification for Diseases, Clinical Modification 9 (ICD-9-CM) codes for IBD (556 for UC and 555 for CD) [30], which were then confirmed by medical record review in 2007 by the pediatric gastroenterologists of Kaiser Permanente Northern California using a standardized form [31]. Differentiating CD, UC, and IBD unclassified was based on a report from the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition and the Crohn's and Colitis Foundation of America [32]. The number of eligible incident cases was 189.

Controls

Up to 20 controls were matched to each case on membership at two time points: (1) birth date at a Kaiser Permanente facility within 30 days of the case, and (2) the case's IBD diagnosis date. This matching process is called incidence-density sampling [33]. The controls were assigned an index date corresponding to the case's diagnosis date. The median number of controls matched to each case was 17 (minimum 2, maximum 20). The final number of controls was 3,080.

Data Collection

We obtained perinatal characteristics from the electronic records of the child's and mother's hospitalizations at the time of the child's birth. The perinatal characteristics were selected a priori for their potential association with immunologic or intestinal microbial development or because they were associated with IBD in a previous study.

Perinatal characteristics obtained from the child's birth record included length of hospitalization (days), gestational age (<37, 37–42, >42 weeks), birth weight (<2,500, 2,500–4,500, >4,500 g), and Apgar score at 1 and 5 min (0–10). Characteristics obtained from the inpatient birth record as well as encounters occurring through the first month of age in the inpatient or outpatient ICD-9-CM records included breastfeeding (V24.1; exclusive

breast-feeding, formula feeding with or without breast feeding or missing), cigarette smoke exposure (305.1, 649.0, E86.94, V15.82), multiple birth (V31–V37, 651 or 761.5), Cesarean section (V30.01–V39.01, 669.7, 674.1, 763.4), maternal hypertensive disorder (760.0), maternal diabetes (750.0), maternal infection (760.2, 770.0, 770.18, 771), respiratory distress during birth (768–770), and jaundice or hemolytic disorder (773–774).

Ninety-nine percent of cases and 98 % of controls were successfully linked to the electronic maternal records related to the birth hospitalization. Prenatal and perinatal characteristics from the maternal record corresponding to the day of the child's birth included maternal age at the child's birth (<20, 20–34, 35 years), gravidity (number of pregnancies), parity (number of viable pregnancies), and length of hospitalization (days). To obtain information about the prenatal period, the last menstrual period date was calculated from the child's gestational age. If gestation information was missing, the day corresponding to 38 weeks before the child's birth date was used. Information was collected from inpatient and outpatient records from the last menstrual period date to 1 week after the child's birth for the following conditions: breastfeeding (ICD-9-CM V24.1), active cigarette smoking (649.0, 305.1), multiple birth (651 or 761.5), assisted reproductive technology (V26.1, V26.8, V26.9), Cesarean section (procedural code 74), type 1, type 2 or gestational diabetes (250, 648.0), overweight (278.0, 649.1), gestational hypertension, pre-eclampsia or eclampsia (642 or 760.0), known or suspected fetal abnormality affecting management of the mother (655), placental or amniotic problems (656–658) and infections (001–139, 380.1, 381.0–4, 460–466, 480–488, 567, 590, 646.5–6, 647, 659.3, 670, 680–686, 770.0, 770.18, 771). The mother's history of IBD was obtained by linking to the Kaiser Permanente IBD Registry, which requires at least two encounters on separate dates associated with ICD-9-CM codes of 555 or 556 and at least 1 year of continuous membership between 1996 and 2006 [34].

Data Analysis

Proportions and means were first examined by case and control status by year of birth. The year 1997 was chosen as all facilities had complete information on inpatient and outpatient encounters in 1996 creating a complete prenatal and perinatal encounter record for children born 1997 and later (the prenatal period for many of the children born in 1997 contained 1996). Conditional logistic regression, which accounted for the matching factors age and duration of membership, was used for all analyses. Race and sex were differentially distributed between cases and controls. Therefore, we included race (coded non-Hispanic white versus other due to sample size limitations) and sex in all models of analyses. Because each birth characteristic could serve as a confounder of all other birth characteristics, we aimed to provide a fully adjusted model that accounted for all factors in one model. Although the fully adjusted model was expected to be less precise, the OR estimates should be less affected by bias caused by the other factors. To minimize the number of zero cell strata in the fully adjusted model, the fully adjusted model included the factors race and sex as well as all other factors of interest with at least five case and control children in each stratum of exposure. We computed the fully adjusted model separately for CD and UC in addition to IBD. Because only 18 cases had IBD unclassified, they were not analyzed separately.

We also performed a sub-analysis of those born 1997–2006 including cigarette smoke exposure and feeding type, which have previously been associated with IBD. These exposures were more likely to be recorded during this time period and no case born 1984–1996 had codes for cigarette smoke exposure or formula feeding.

Ethical Considerations

This work was done under the approval of the Institutional Review Boards of the Kaiser Foundation Research Institute and Johns Hopkins University.

Results

Demographic Characteristics

The demographic characteristics of the CD and UC cases and controls are presented in Table 1. Cases were more likely to be non-Hispanic white and less likely to have unknown race than controls. Further details on the demographic differences between IBD sub-types have been previously published for this patient population [31].

The prevalence of exposure information is presented separately for children born 1984–1996 (primary data source is inpatient information) and 1997–2006 (when inpatient and outpatient information was fully available during the prenatal period) separated by perinatal characteristics (Table 2) and maternal characteristics (Table 3). Only 13 % of cases were born during 1997–2006. There were more males among cases than controls for the 1984–1996 period (56.1 vs. 51.0 %) but not for 1997–2006 period (44.0 vs. 51.1 %). There were also more encounters for infections in case mothers (40.0 %) versus control mothers (32.9 %) during 1997–2006 compared to very few recorded infections during the earlier period. No case or control mothers had IBD for those born 1997–2006, although more mothers of cases (3.7 %) than controls (0.8 %) had IBD among those born 1984–1996. No other meaningful differences were evident between the time periods.

Two factors had a relationship with pediatric-onset IBD with a statistically significant confidence interval that did not contain the null value of 1. IBD cases were more likely to be white than controls (fully adjusted IBD OR 2.3, 95 % confidence interval (CI) 1.6–3.2; CD OR 3.1; UC OR 2.6) and more likely to have mothers with IBD than controls (fully adjusted IBD OR 5.1, 95 % CI 2.0–13.2; CD OR 6.0; UC OR 6.4; Table 2).

Several factors were associated with pediatric-onset IBD in the fully adjusted model (OR 1.5 or OR 0.7) but the results were not precise (the CI contained 1): gestational age 36 weeks versus 37 weeks (OR 0.6, 95 % CI 0.3–1.5), birth weight <2,500 versus 2,500 g (OR 1.6, 95 % CI 0.7–3.8), mother's age <20 years versus 20–34 years (OR 2.0, 95 % CI 0.8–4.8) and hypertensive disorder during pregnancy (OR 1.7, 95 % CI 1.0–2.8).

Several ORs differed in direction between CD and UC: male sex (CD 0.9; UC 1.4), Cesarean delivery (CD 1.3; UC 0.7), respiratory distress (CD 1.2; UC 0.9), jaundice or hemolytic disorder (CD 1.1; UC 0.6), maternal infection (CD 0.6; UC 1.2), and placental or amniotic problems (CD 0.5; UC 1.9).

The sub-analysis including only children born 1997–2006 found similar, but even more imprecise, results as the main analysis. Feeding and cigarette smoke exposure information were available for these children, although neither exposure was associated with pediatric-onset IBD in the fully adjusted model (formula versus exclusive breast feeding or missing OR 1.1, 95 % CI 0.2–6.1; maternal active cigarette smoke exposure OR 1.1, 95 % CI 0.2–5.3).

Length of stay, Apgar scores, gravidity, and parity are not shown in the tables because these factors did not differ meaningfully between cases and controls. The median length of stay for cases, controls, and their mothers was 2 days. For both cases and controls, the median Apgar score at 1 min was 8 and at 5 min, the score increased to 9. Gravidity (median 3 for case and 2 for control mothers) and parity (median 2 for case and control mothers) did not differ. Maternal overweight is also not shown in the table. No case mothers had codes for overweight. Less than 1 % of control mothers of children born 1984–1996 and 5.7 % of control mothers of children born 1997–2006 had codes for overweight. No case mothers and two control mothers had codes for assisted reproductive technology (one for clomiphene therapy and the other for in vitro fertilization).

Because infections have been associated with IBD in other studies, we chose to look at specific maternal infections by trimester through the first week of birth (“Appendix”). The only infection type that occurred often enough to examine in detail was respiratory infections (ICD-9-CM 460–466, 480–486). Eleven of the 20 (55 %) case mothers who experienced an infection during pregnancy had a respiratory infection compared to 96 of 373 (26 %) infections in control mothers (fully adjusted OR IBD 2.0, 95 % CI 1.0–4.0; CD 2.0, 95 % CI 0.5–7.6; UC 1.9, 95 % CI 0.7–5.5). The most common respiratory infection reported for case and control mothers was acute, unspecified (ICD-9-CM 465.9). The number of infections by trimester in case mothers was too small to discern a trend with only three infections occurring during the first trimester, six infections during the second trimester, two infections occurring during the third trimester, and none at birth to 1 week postnatal. No case of pneumonia was observed in case mothers.

Discussion

We conducted a retrospective case–control study to assess prenatal and perinatal characteristics with risk of pediatric-onset IBD using information recorded prospectively in the hospitalization record. Cases were more likely to have a mother with IBD than controls (3 vs. 1 %) confirming the role of family history of IBD as a risk factor for disease. Cases were more likely to be white compared to controls (75 vs. 56 %). Younger age, maternal hypertension, and maternal respiratory infection during pregnancy showed a non-significant trend for increased odds of incident pediatric IBD. The other common prenatal and perinatal characteristics that we were able to measure do not appear to play a major role in the development of pediatric-onset IBD.

Because the fecal microflora is different in children born vaginally versus those children born by Cesarean section up to 6 months after birth [35, 36], it is plausible that the gastrointestinal microbiome established in the perinatal period could affect IBD risk [36].

Six other studies have reported mode of delivery and risk of IBD. Four studies measured mode of delivery from national birth statistics registries, while two studies used questionnaires. The one birth registry study that accounted for other birth characteristics found no association between Cesarean delivery and CD or UC [25]. The other three birth registry studies found statistically significant relationships between mode of delivery and IBD in their unadjusted analyses, but the directions of the associations were not consistent [17, 19, 26]. Of the two questionnaire-based studies [15, 22], one reported a multivariable model for IBD that showed no statistically significant relationship between Cesarean delivery and CD or UC after adjustment for age, gender, breastfeeding, and postnatal complications (OR CD 1.27, 95 % CI 0.87–1.84; UC 0.89, 95 % CI 0.51–1.54) [22]. The discordant findings in studies to identify mode of birth make it difficult to identify the effect of Cesarean section on risk of IBD and if the effect is different for CD and UC.

A recent study using inpatient records found an increased risk of IBD diagnosis by age 26 with hospitalization for pneumonia in the child before age 5 [16]. Because of this finding, we sought to see if pneumonia in the mother during pregnancy was related to pediatric-onset IBD. However, we did not observe any case with a mother that had been hospitalized or had an outpatient encounter for pneumonia during pregnancy.

The major strengths of the present study are that all information was collected from the electronic hospital record associated with birth and the outpatient records associated with the prenatal and immediately postnatal periods and the adjustment for confounding. Because information was collected in a similar manner for all subjects for the same purpose of documenting the birth incident, the data are not subject to recall bias that can occur in other study designs using retrospectively collected exposure information after the child has been diagnosed with IBD.

Compared to many other studies, we report our results adjusted for the matching factors, sex and race as well as all other potential confounders. Confounding was noted by Molodecky et al. [37] to contribute to the heterogeneity of environmental factors associated with IBD. Accounting for confounding did change some of the effect estimates observed in unadjusted analyses.

The major limitation of the study is the small sample size, which limited our ability to make strong inferences about weak, but potentially important, associations. The study confirmed family history (OR = 5.1, 95 % CI 2.0–13.2) and white race (OR = 2.3, 95 % CI 1.6–3.3) as risk factors for IBD; however, more cases would be required to identify a statistically significant relationship with less common exposures, such as gestational hypertension (OR = 1.7, 95 % CI 1.0–2.8), or weaker associations. Nonetheless, this exploratory study frames the magnitude of these associations for future research. Future directions could also include studying the interaction of pediatric-onset risk alleles with prenatal and perinatal risk factors.

In summary, after adjusting for confounding, other than increased risk for children of mothers with IBD or for children who are white compared with non-white, no differences were observed in the prenatal or perinatal characteristics that we examined between IBD cases and their age and membership matched controls for children born 1984–2006 and

diagnosed with IBD between 1996 and 2006 in the insured pediatric population of Kaiser Permanente Northern California.

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Appendix

See Table 4.

Table 4

Specific infections of mothers during the prenatal period to 1 week after birth

Infection	Cases (n = 189)	Controls (n = 3,080)
ICD-9-CM	n (%)	n (%)
At least 1 infection	20 (10.6)	373 (12.1)
Intestinal	0	2 (<0.1)
001–009		
<i>Staphylococcus</i>	0	2(<0.1)
041.1		
<i>Streptococcus</i>	1 (0.5)	16 (0.5)
041.1		
<i>E. coli</i>	1 (0.5)	8 (0.3)
041.4		
<i>Candida</i>	0	29 (0.9)
112		
Herpes simplex	1 (0.5)	33 (1.1)
054		
Herpes zoster	2 (1.1)	1 (<0.1)
054		
Syphilis and other venereal diseases	1 (0.5)	41 (1.3)
090–099, 647.0–2		
Respiratory	11 (5.8)	96 (3.1)
460–466, 480–488		
Acute, unspecified	7 (3.7)	49 (1.6)
465.9		
Pneumonia	0	9 (0.3)
480–486		
Major puerperal infection	1 (0.5)	28 (0.9)
670		

Infection	Cases (n = 189)	Controls (n = 3,080)
ICD-9-CM	n (%)	n (%)
Kidney infection	0	7 (0.2)
590		

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Table 1

Demographics and disease characteristics of childhood IBD cases and matched controls born within 30 days of the case at a Kaiser Permanente facility, 1984–2006

	Crohn's disease (n = 79)	Ulcerative colitis (n = 92)	All IBD (n = 189)	Controls (n = 3,080)
Gender (%)				
Male	50.6	55.4	54.0	53.5
Age at index date, median (minimum–maximum)	12.7 (2.6–17.7)	11.7 (2.2–17.7)	12.1 (2.0–17.9)	11.9 (1.9–17.9)
Race (%)				
Non-Hispanic white	81.0	75.0	74.6	56.1
Non-Hispanic African American	8.9	3.3	6.9	7.8
Hispanic	1.3	12.0	7.4	8.9
Asian/Pacific Islander	2.5	7.6	6.9	17.5
Native American	1.3	0	0.5	0.4
Other/unknown	5.1	2.2	3.7	9.3

Table 2

Distributions and adjusted odds ratio and 95 % CI for the relationship of prenatal and perinatal characteristics with risk of pediatric-onset IBD

Characteristics (%)	Born 1984–1996 ^a		Born 1997–2006 ^b		Odds ratio (95 % CI) Born 1984–2006			
	Cases (<i>n</i> = 164)	Controls (<i>n</i> = 2,661)	Cases (<i>n</i> = 25)	Controls (<i>n</i> = 419)	Race- and sex- adjusted IBD ^c	Fully adjusted IBD ^d	Fully adjusted CD ^d	Fully adjusted UC ^d
White	77.4	57.2	56.0	48.9	2.3 (1.6–3.2)	2.3 (1.6–3.3)	3.1 (1.7–5.5)	2.6 (1.6–4.3)
Male	56.1	51.0	44.0	51.1	1.2 (0.9–1.6)	1.2 (0.9–1.6)	0.9 (0.6–1.5)	1.4 (0.9–2.2)
Gestation								
36 weeks	4.3	5.8	8.0	8.1	0.8 (0.4–1.6)	0.6 (0.3–1.5)	0.4 (0.1–1.6)	0.6 (0.2–2.2)
>37 weeks	95.7	94.2	92.0	91.9	Reference			
Birth weight								
2,499 g	5.5	4.7	4.0	5.3	1.2 (0.6–2.4)	1.6 (0.7–3.8)	2.7 (0.7–10.4)	1.6 (0.5–5.1)
>2,500	88.4	90.6	92.0	94.5	Reference			
Missing	6.1	4.7	4.0	0.2	<i>e</i>			
Child from multiple birth	2.4	2.1	0	4.3	NA			
Feeding, birth to 1 month								
Exclusive breast feeding	NA	NA	56.0	54.7	NA			
Formula with or without breast feeding	NA	NA	12.0	11.0				
Missing	NA	NA	32.0	34.4				
Cesarean delivery	18.9	18.6	20.0	18.4	1.1 (0.7–1.6)	1.1 (0.7–1.6)	1.3 (0.7–2.4)	0.7 (0.4–1.4)
Respiratory distress	9.2	11.1	12.0	7.2	0.9 (0.6–1.5)	0.9 (0.5–1.5)	1.2 (0.5–2.8)	0.9 (0.4–2.0)
Jaundice	12.2	13.9	20.0	22.7	0.9 (0.6–1.4)	0.9 (0.5–1.4)	1.1 (0.6–2.2)	0.6 (0.3–1.3)

NA not available or fewer than five case and control children in each exposure stratum

^aComplete information available in inpatient record during pregnancy; some information for outpatient information for those born during 1995–1996

^bComplete information available from the inpatient and outpatient records during pregnancy

^cConditional logistic OR accounting for matching, sex and race (non-Hispanic white versus other). The OR included children born during both time periods in the model

^dPlus adjustment for all other factors in the table and Table 3 with sufficient sample size

^eThose with missing information for gestational age were assigned to the 37 weeks category and birth weight were assigned to the 2,500-g category

Table 3

Distributions and adjusted odds ratio and 95 % CI for the relationship of maternal characteristics with risk of pediatric-onset IBD

Characteristics (%)	Born 1984–1996 ^a		Born 1997–2006 ^b		Odds ratio (95 % CI) Born 1984–2006			
	Cases (n = 164)	Controls (n = 2,661)	Cases (n = 25)	Controls (n = 419)	Race- and sex-adjusted IBD ^c	Fully adjusted IBD ^d	Fully adjusted CD ^d	Fully adjusted UC ^d
Mother's age at child's birth								
19 years old	3.1	1.4	4.0	4.5	2.0 (0.8–4.7)	2.0 (0.8–4.8)	2.1 (0.4–9.5)	2.7 (0.9–8.3)
20–34 years old	75.0	78.9	76.0	74.2	Reference	Reference	Reference	Reference
35 years old	22.0	19.3	16.0	20.8	1.1 (0.8–1.6)	1.1 (0.8–1.6)	1.5 (0.8–2.6)	1.0 (0.5–1.6)
Missing	0	0.5	4.0	0.5 ^e				
Smoker, prenatal to 1 month	NA	NA	8.0	7.4	NA			
Maternal diabetes (gestational, type 1 or type 2)	1.8	1.8	4.0	5.7	NA			
Gestational hypertension, pre-eclampsia, or eclampsia	7.3	5.2	20.0	10.7	1.6 (0.9–2.7)	1.7 (1.0–2.8)	1.7 (0.7–4.2)	1.7 (0.8–3.5)
Pre-eclampsia	3.7	2.7	12.0	5.3	NA			
Eclampsia	0	0.2	0	0				
Placental or amniotic problems	18.3	20.1	28.0	19.8	1.0 (0.7–1.4)	1.0 (0.7–1.5)	0.5 (0.2–1.0)	1.9 (1.2–3.2)
PPROM	1.8	3.8	4.0	3.1	NA			
Known or suspected fetal abnormality affecting management of mother	0	0.2	16.0	4.8	NA			
Maternal infection, inpatient or outpatient visit	6.7	8.9	40.0	32.9	0.9 (0.5–1.5)	0.9 (0.5–1.5)	0.6 (0.2–1.7)	1.2 (0.6–2.4)
Infection requiring hospitalization	3.7	5.4	4.0	4.3	NA			
Infection recorded during outpatient visit	3.1	3.6	36.0	28.6				
Maternal IBD	3.7	0.8	0	0	5.1 (2.0–12.9)	5.1 (2.0–13.2)	6.0 (1.5–24.7)	6.4 (1.5–26.4)

NA not available or fewer than five case and control children in each exposure stratum

^aComplete information available in inpatient record during pregnancy; some information for outpatient information for those born during 1995–1996^bComplete information available from the inpatient and outpatient records during pregnancy^cConditional logistic OR accounting for matching, sex and race (non-Hispanic white versus other). The OR included children born during both time periods in the model^dPlus adjustment for all other factors in the table and Table 3 with sufficient sample size^eMissing mother's age assigned to 20–34 years