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CLINICAL—ALIMENTARY TRACT

Events Within the First Year of Life, but Not the Neonatal Period, Affect Risk for Later Development of Inflammatory Bowel Diseases

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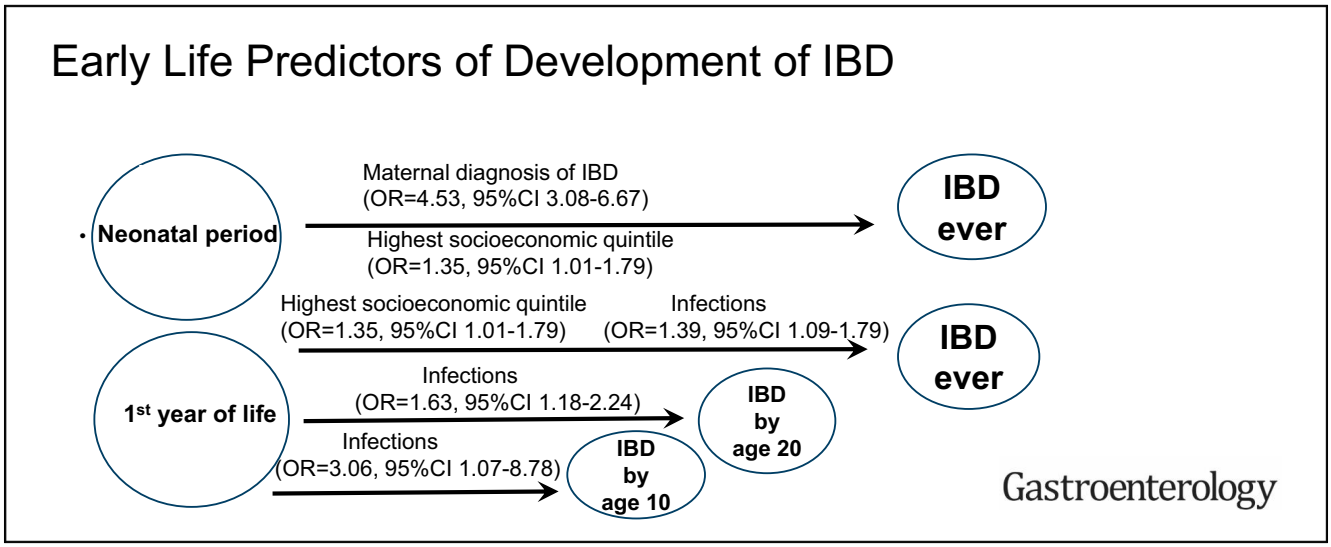
This article has an accompanying continuing medical education activity, also eligible for MOC credit, on page e18 (https://www.gastrojournal.org/cme/home). Learning Objective: Upon completion of this CME activity, successful learners will be able to evaluate a risk paradigm for the development of inflammatory bowel disease (IBD) in children.



See editorial on page 2124. See Covering the Cover synopsis on 2117.

BACKGROUND & AIMS: We performed a population-based study to determine whether there was an increased risk of inflammatory bowel diseases (IBD) in persons with critical events at birth and within 1 year of age. **METHODS:** We collected data from the University of Manitoba IBD Epidemiology Database, which contains records on all Manitobans diagnosed with IBD from 1984 through 2010 and matched controls. From 1970 individuals' records can be linked with those of their mothers, so we were able to identify siblings. All health care visits or hospitalizations during the neonatal and postnatal periods were available from 1970 through 2010. We collected data on infections, gastrointestinal illnesses, failure to thrive, and hospital readmission in the first year of life and sociodemographic factors at birth. From 1979, data were available on gestational age, Apgar score, neonatal admission to the intensive care unit, and birth weight. We compared incident rate of infections, gastrointestinal illnesses, and failure to thrive between IBD cases and matched controls as well as between IBD cases and siblings. **RESULTS:** Data on 825 IBD cases and 5999 matched controls were available from 1979. Maternal diagnosis of IBD was the greatest risk factor for IBD in offspring (odds ratio [OR], 4.53; 95% confidence interval [CI], 3.08–6.67). When we assessed neonatal events, only being in the highest vs lowest socioeconomic quintile increased risk for later development of IBD (OR, 1.35; 95% CI, 1.01–1.79). For events within the first year of life, being in the highest socioeconomic quintile at birth and infections (OR, 1.39; 95% CI, 1.09–1.79) increased risk for developing IBD at any age. Infection in the first year of life was associated with diagnosis of IBD before age 10 years (OR, 3.06; 95% CI, 1.07–8.78) and before age 20 years (OR, 1.63; 95% CI, 1.18–2.24). Risk for IBD was not affected by gastrointestinal infections,

gastrointestinal disease, or abdominal pain in the first year of life. **CONCLUSIONS:** In a population-based study, we found infection within the first year of life to be associated with a diagnosis of IBD. This might be due to use of antibiotics or a physiologic defect at a critical age for gut microbiome development.

Keywords: First Year of Life; Risk Factors; Sibling; Cohort Studies.

It is unknown what triggers the development of inflammatory bowel disease (IBD). However, there is emerging evidence of important dysbiotic changes in the gut microbiome in persons with IBD, such as reduced diversity and alterations in certain species.[1] A variety of factors can change the gut microbiome, such as antibiotic ingestion or dietary changes. However, the permanence of the gut microbiome changes may be dependent on the timing and/or duration of what factor is introduced. The gut microbiome undergoes the most change from birth until 1–2 years of age, when the microbiota composition stabilizes.[2–4] Hence, events that promote alterations in the composition of the gut microbiome in the first year of life may have important effects on its more permanent composition. This, in turn, may impact on the ultimate development of IBD. Infections that impact on the gut microbiome and antibiotic use in the first year of life through their effects on the gut microbiome may, therefore, impact on the ultimate development of IBD.

Therefore, we aimed to determine whether there was an increased risk of IBD among persons who had critical events at birth or within the first year of life, which would be expected to lead to alterations in the gut microbiome. Further, we explored whether these events affected risk for IBD differentially at different ages of IBD onset.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

The first year of life is a critical time for development of the gut microbiome and it is unknown whether neonatal or postnatal events (for up to one year and longer) could impact the risk for developing IBD.

NEW FINDINGS

A maternal diagnosis of IBD was the strongest risk factor for the offspring developing IBD. Other risk factors included infection in the first year of life and being born into a family of higher socioeconomic standard.

LIMITATIONS

This was an administrative database study and it was not clear whether the risk posed by infections were from infections per se or the antibiotics used to treat them, among other variables.

IMPACT

Health providers and parents need to be more circumspect about antibiotic use especially for young children. Further research should be undertaken to study breastfeeding and diet in the first year of life to determine their impact on IBD risk

Methods

The University of Manitoba IBD Epidemiology Database contains records on all Manitobans diagnosed with IBD between 1984 and 2010. Each individual is identified by a unique personal health identification through which all health system contacts can be tracked dating back to 1984. In 1995, we validated an administrative definition of IBD based on frequency of health system contacts.[5] We identified all persons with IBD and created a matched cohort of controls, matching 10 controls without IBD by age, sex, and area of residence to each IBD case. Our administrative definition of IBD allowed updating our database with new cases on an ongoing basis. Starting in 1970, 6-digit family health registration numbers, shared by a mother and all of her offspring, have been used in Manitoba and allow for the accurate linkage of the health care utilization profiles of mothers with their children.[6] Information on diagnoses associated with health care visits or hospitalizations during the neonatal and postnatal periods was available from 1970 to 2010. All hospitalizations and discharge diagnoses (up to 20 by International Classification of Disease, 9th Revision, Clinical Modification codes to 2004 and up to 25 by International Classification of Disease, 10th Revision, Clinical Modification codes after 2004) and outpatient contacts (by International Classification of Disease, 9th Revision, Clinical Modification codes) were tracked. The Medical Records Department of the Children's Hospital of Winnipeg provided all International Classification of Disease, 10th Revision codes identified as the number one discharge abstract diagnosis for the hospitalizations of all children under age 3 years in the years 2013–2016. This allowed the casting of a wide net for possible infections or gastrointestinal illnesses associated with early life hospitalization. We assessed for 26 different categories of infection, 4 categories of gastrointestinal illness, failure to thrive, and for hospital readmission. The types of infections and gastrointestinal illnesses are listed in Supplementary Table 1. The infections included those likely to require antibiotic therapy and also viral infections; it was considered that, if a child was sufficiently ill to be admitted to hospital, even if the discharge diagnosis was that of a viral infection, at some point the child may have received antibiotic therapy. However, we also included a separate analysis excluding what were diagnosed as viral infections. We assessed for the occurrence of those events within the first year of life. We also assessed for those events within the first 3 years of life. Inpatient and outpatient diagnoses were combined in each category to increase the power to determine if any diagnoses with these conditions were associated with a later diagnosis of IBD. We assessed for maternal diagnosis of IBD and we assessed for mode of delivery (cesarean section vs vaginal

Abbreviations used in this paper: **CI, confidence interval; IBD, inflammatory bowel disease; OR, odds ratio.**

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delivery). Considering that some diagnoses of IBD could actually be cases of immunodeficiency syndromes and that persons who are immunodeficient would incur more infections and antibiotic use, we compared the rates for immunodeficiency syndromes among persons with IBD and controls by International Classification of Disease, 9th Revision, Clinical Modification code 279 and by the following International Classification of Disease, 10th Revision, Canada codes including immunodeficiency with predominantly antibody defects (D80), combined immunodeficiencies (D81), immunodeficiency associated with other major defects (D82), common variable immunodeficiency (D83) and other immunodeficiencies (D84). From 1979 onward, data were available on gestational age, Apgar score, neonatal intensive care unit admission, and birth weight. We also assessed rural vs urban residence and family socioeconomic status by quintile at birth. To assess socioeconomic status, we used the median household income quintile for the area of residence at the time of birth identified by the subjects' 6-digit postal code at the time of birth.[7]

Outcomes and Analysis

We compared incident rate of infections, gastrointestinal illnesses, and failure to thrive identified from outpatient visits and on hospitalizations (from the hospital discharge abstracts) between IBD cases and their matched controls, as well as between IBD cases and their siblings. We also analyzed neonatal events. For all of the neonatal events as well as events within the first year of life, we assessed for subsequent development of IBD at any age, development of IBD before age 10 years and development of IBD before age 20 years. We assessed for all diagnoses of IBD and then separately for diagnoses of Crohn's disease and for ulcerative colitis. Comparisons used Fisher's exact test for each category of clinical disease assessed, for socioeconomic status at birth, for rural vs urban residence at birth and for neonatal parameters (mode of delivery, gestational age, birth weight, Apgar score, and neonatal intensive care unit admission). Conditional logistic regression models estimated the odds of developing IBD compared to either matched controls or siblings, and odds ratios (ORs) with 95% confidence intervals (CI) are reported for all individuals available from 1979 so that all variables could be included. We conducted a separate conditional logistic regression model for all individuals available since 1970, excluding the neonatal events available only since 1979 in the model. We repeated these analyses comparing IBD cases with their unaffected siblings.

This study was approved by the University of Manitoba Health Research Ethics Board, the Manitoba Health Information Privacy Committee and the Manitoba Centre for Health Policy Review Committee.

Results

We were able to link the administrative health records of 1671 IBD cases, 1740 siblings, and 10,488 matched controls to their mothers dating back to 1970. The median age of the IBD cohort was 20.0 years (range, 1.0–39.0 years; 25th percentile, 16; 75th percentile, 25). A total of 6824 individuals (n = 825 for IBD cases and n = 5999 for controls) were available to examine all events dating back to 1979. The median age for this cohort was 17.0 years (range 1–30.0; 25th percentile, 13; 75th percentile, 21). This cohort including data dating back to 1979 was used for the following analyses. Among IBD cases, 97 were diagnosed before age 10 years, 499 were diagnosed between ages 10–20 years, and 229 were diagnosed after age 20 years. The strongest predictor for development of IBD in all models was maternal history of IBD (OR, 4.53; 95% CI, 3.08–6.67 in the model including all neonatal and first year of life events). The model assessing all neonatal events and events in the first year of life found that being in the highest or the second highest socioeconomic quintile at birth vs the lowest (OR, 1.35; 95% CI, 1.01–1.79 and OR, 1.37; 95% CI, 1.06–1.77, respectively) and infections within the first year of life were associated with later development of IBD at any age (OR, 1.39; 95% CI, 1.09–1.79) (Table 1). When assessing Crohn's disease (n = 482) separately from ulcerative colitis (n = 343), maternal history of IBD was strongly predictive for both diseases, and having an infection in the first year life trended toward being predictive but did not reach statistical significance in either disease (Tables 2 and 3). Being in a higher socioeconomic status at birth compared to the lowest quintile was predictive of developing ulcerative colitis for all 4 socioeconomic quintiles above the lowest. Assessing neonatal events only, for later development of IBD, the only predictors of later development of IBD were being in the highest vs lowest socioeconomic status by quintile (OR, 1.35; 95% CI, 1.01–1.79) or being in the second highest versus lowest socioeconomic quintile (OR, 1.37; 95% CI, 1.06-1.77).

The predictors of being diagnosed with IBD under age 10 (n = 97 IBD cases and 748 controls) included maternal diagnosis of IBD (OR, 5.92; 95% CI, 1.76–19.98), having an infection in the first year of life (OR, 3.06; 95% CI, 1.07–8.78), and being born rural vs urban (OR, 2.54; 95% CI, 1.24–5.20) (Table 4). The predictors of being diagnosed with IBD under age 20 years (n = 499 IBD cases and 4503 controls) included maternal diagnosis of IBD (OR, 4.95; 95% CI, 3.18–7.71), having an infection in the first year of life (OR, 1.63; 95% CI, 1.18–2.24), and being in the highest socioeconomic quintile compared with the lowest at birth (OR, 1.43; 95% CI, 1.02–2.00) (Table 5). Maternal diagnosis of IBD was a significant predictor of developing Crohn's disease before age 10 years, but no variables significantly predicted development of ulcerative colitis before age 10 years (Supplementary Tables 2 and 3). Maternal diagnosis of IBD was a significant predictor of developing either Crohn's disease or ulcerative colitis before age 20 years and infection in the first year of life was a significant predictor of developing Crohn's disease but not ulcerative colitis before age 20 years (Supplementary Tables 4 and 5).

In a model including data dating back to 1970 from all 1671 persons with IBD and 10,488 controls for mothers IBD status, socioeconomic status at birth, urban vs rural residence, and cesarean section were assessed. For persons with IBD diagnosed at any age, having a maternal IBD diagnosis (OR, 4.54; 95% CI, 3.40–6.06; $P < 0.001$) and being born into the highest socioeconomic quintile vs the lowest (OR, 1.29; 95% CI, 1.05–1.59; $P = 0.01$) were predictive of developing IBD. Being born in rural area was protective against developing IBD (OR, 0.84; 95% CI, 0.72–0.99; $P = 0.04$).

Table 1. Association Between Demographic Variables at Birth and Clinical Events in the First Year of Life (Infections, Gastrointestinal Illnesses, Failure to Thrive, and Hospital Readmission) and the Development of Inflammatory Bowel Disease, at Any Age Among All Persons With Inflammatory Bowel Disease Compared to Controls

					IBD		
Effect	Comparison	OR estimate	95% Wald confidence limits	*P* value	Case[a] (n = 825)	Control[a] (n = 5999)	*P* value
Infection year 1	Yes vs no	1.39	1.09, 1.79	.01	90.3	87.6	.03
Socioeconomic status							
Q1	—	—	—	—	14.79	17.57	.05
NF	NF vs Q1	0.76	0.37, 1.56	.45	1.1	1.8	—
Q2	Q2 vs Q1	1.31	1.02, 1.68	.36	23.52	21.72	—
Q3	Q3 vs Q1	1.09	0.84, 1.42	.52	19.39	21.47	—
Q4	Q4 vs Q1	1.37	1.06, 1.77	.02	24.36	21.94	—
Q5	Q5 vs Q1	1.35	1.01, 1.79	.04	16.85	15.5	—
Geography	Rural vs urban	0.91	0.72, 1.15	.45	38.9	37.3	.18
Apgar 1 min	7+ vs <7	1.09	0.86, 1.39	.46	88.12[b]	86.73	.2
Apgar 5 min	7+ vs <7	1.07	0.49, 2.33	.87	99.03[b]	98.8	.56
ICU admission	No vs yes	1.06	0.63, 1.77	.83	97.6	97.23	.57
Gestational age	—	1.004	0.95, 1.06	.88	39.4	39.4	.88
Birth weight	—	1.000	1.000, 1.000	.79	3451	3444[c]	.76
Readmitted in yr 1	No vs yes	1.21	0.94, .56	.14	88.36	86.23	.09
Cesarean section	Yes vs no	1.06	0.86, 1.32	.57	14.18	14.07	.93
Maternal IBD	Yes vs no	4.53	3.08, 6.67	<.001	5.45	1.25	<.001
Hospitalized for GI	Yes vs no	0.79	0.46, 1.36	.39	2.18	2.90	.24

ICU, intensive care unit; NF, not found; Q, quintile.
[a]Data in case and control columns reflect % in each category unless otherwise specified.
[b]Data for % with Apgar of 7+.
[c]Data reflects grams.

We undertook an analysis assessing only hospitalizations for infections (excluding outpatient contacts for infection). This did not prove to be significantly predictive of developing IBD, although the sample size was likely too small. We also undertook an analysis of predictors of developing IBD excluding viral infections in the first year of life and in this model infections in the first year of life did not prove to be predictive of developing IBD. Only maternal diagnosis of IBD retained its significance as a predictor (Supplementary Table 6). Finally, we undertook an analysis of predictors of IBD, including infections in the first 3 years of life and we found that infections did not predict development of IBD. In this model only maternal diagnosis of IBD and being in the highest or second highest socioeconomic quintile compared to the lowest at birth predicted development of IBD (Supplementary Table 7).

Because infections in the first year of life was a strong predictor of developing IBD in several of our analyses, we explored the direct use of antibiotics where we could, and the diagnoses of immunodeficiency syndromes. From 1996 through 2010 (the years in which antibiotic data were available in our administrative data) within our cohort, there were only 33 individuals with IBD and 270 controls who were born after 1996. For this group of 303 individuals, the mean number of antibiotic prescriptions in the first 10 years of life was 8.97 (95% CI, 6.44–11.50) among persons with IBD compared with a mean of 7.59 (95% CI, 6.63–8.55) among controls ($P = .34$ for the difference between IBD cases and controls). We modeled antibiotic users, defined by actual antibiotic prescriptions in the first year of life; socioeconomic status at birth; and rural vs urban residence at birth, and there was a trend for antibiotic prescription in the first year of life predicting later IBD diagnosis; however, it was not statistically significant (OR, 1.66; 95% CI, 0.74–3.74; $P = .21$).

In assessing for immunodeficiency disorders at any time in life, we found them to be diagnosed in 34 of 825 (4.1%) of IBD cases and in 220 of 5999 (3.67%) controls ($P = .49$). Hence, neither overall childhood antibiotic use nor immunodeficiency disorder was associated with a diagnosis of IBD.

Unaffected sibling comparisons showed no predictors of developing IBD at any age (Table 6). Having gastrointestinal infections, gastrointestinal disease, or abdominal pain in the first year of life did not increase the risk for developing IBD.

Discussion

We found that the strongest and most consistent predictor of developing IBD was having a mother with a diagnosis of IBD. This might reflect either an important genetic effect or an important environmental effect or a combination of both. Children share a close environment with their mothers, especially in their developing years, and it has been shown that the gut microbiome of children increasingly mirrors that of their parents' gut microbiome from the

Table 2. Association Between Demographic Variables at Birth and Clinical Events in the First Year of Life (Infections, Gastrointestinal Illnesses, Failure to Thrive, and Hospital Readmission) and the Development of Crohn's Disease, at Any Age Among All Persons With Crohn's Disease Compared to Controls

Effect	Comparison	OR estimate	95% Wald confidence limits	*P* value
Infection year 1	Yes vs no	1.37	0.99, 1.89	.06
Socioeconomic status				
Q1	NF vs Q1	0.41	0.12, 1.39	.15
Q2	Q2 vs Q1	1.11	0.81, 1.53	.51
Q3	Q3 vs Q1	0.86	0.61, 1.20	.37
Q4	Q4 vs Q1	1.21	0.87, 1.69	.25
Q5	Q5 vs Q1	1.12	0.78, 1.62	.54
Geography	Rural vs urban	0.91	0.67, 1.24	.56
Apgar 1 min	7+ vs <7	1.42	1.02, 1.96	.04
Apgar 5 min	7+ vs <7	1.33	0.38, 4.61	.67
ICU admission	No vs yes	0.91	0.49, 1.67	.76
Gestational age	—	1.01	0.94, 1.08	.77
Birth weight	—	1.000	1.000, 1.000	.96
Readmitted in year 1	No vs yes	1.18	0.84, 1.65	.34
Cesarean section	Yes vs no	0.94	0.71, 1.26	.68
Maternal IBD	Yes vs no	5.98	3.72, 9.63	<.001
Hospitalized for GI[a]	Yes vs no	0.67	0.30, 1.51	.34

ICU, intensive care unit; NF, not found; Q, quintile.
[a]Hospitalized for GI means hospitalized for any of gastrointestinal infections, gastrointestinal disease, or abdominal pain in the first year of life.

Table 3. Association Between Demographic Variables at Birth and Clinical Events in the First Year of Life (Infections, Gastrointestinal Illnesses, Failure to Thrive, and Hospital Readmission) and the Development of Ulcerative Colitis, at Any Age Among All Persons With Ulcerative Colitis Compared to Controls

Effect	Comparison	OR estimate	95% Wald confidence limits	*P* value
Infection year 1	Yes vs No	1.41	0.95, 2.08	.09
Socioeconomic status				
Q1	NF vs Q1	1.20	0.48, 3.00	.69
Q2	Q2 vs Q1	1.61	1.07, 2.41	.02
Q3	Q3 vs Q1	1.51	0.996, 2.29	.05
Q4	Q4 vs Q1	1.63	1.08, 2.46	.02
Q5	Q5 vs Q1	1.71	1.09, 2.69	.02
Geography	Rural vs urban	0.91	0.64, 1.29	.6
Apgar 1 min	7+ vs <7	0.78	0.55, 1.11	.17
Apgar 5 min	7+ vs <7	1.04	0.37, 2.89	.95
ICU admission	No vs yes	1.31	0.48, 3.57	.6
Gestational age	—	0.99	0.91, 1.08	.84
Birth weight	—	1.000	1.000, 1.000	.61
Readmitted in year 1	No vs yes	1.25	0.84, 1.84	.27
Cesarean section	Yes vs no	1.22	0.89, 1.69	.22
Maternal IBD	Yes vs no	2.71	1.34, 5.51	.01
Hospitalized for GI[a]	Yes vs no	0.87	0.41, 1.86	.73

ICU, intensive care unit; NF, not found; Q, quintile.
[a]Hospitalized for GI means hospitalized for any of gastrointestinal infections, gastrointestinal disease or abdominal pain in the first year of life.

second through the sixth month of life.[8] We also found that persons with IBD were significantly more likely to be born into higher socioeconomic status families. The association between higher socioeconomic status and IBD may be reflective of the hygiene hypothesis, which posits that a cleaner lifestyle is associated with an increase in chronic immune diseases.[9–11] This lifestyle may involve less risk for childhood infections, cleaner water sources and toilet facilities, and less home crowding. It also may reflect greater attention to health care. Being born into a higher socioeconomic lifestyle may impact on duration of breastfeeding and timing and types of foods that are introduced in the first year of life.[12] Because higher socioeconomic status at birth poses a risk for developing IBD, and prolonged breastfeeding may be protective against developing IBD, then further research will need to tease out which has a greater impact on ultimate development of IBD.[12] We have previously shown that among persons ultimately diagnosed with IBD, compared to controls there was no difference in likelihood of initiating breastfeeding just after delivery,[13] however, studies are needed to ascertain whether the duration of breastfeeding, as well as the exclusivity of breastfeeding (to what extent or at what age formula or table food was introduced) impact on the development of IBD. This will require a prospective study. Being born in rural vs urban settings was predictive of developing IBD (more specifically Crohn's disease) among children under age 10 years, but not for IBD diagnoses at other ages. This contrasts with a Canada-wide report that suggested that rural residence was protective against developing IBD mostly among children who lived rurally under age 5 years, but found a wide variation among provinces.[14] When we assessed a larger sample size excluding neonatal events and assessing maternal and demographic factors with data going back to 1970 (n = 1670 for persons with IBD), being born rural was protective against developing IBD. Further research is required to determine what aspects of a higher family socioeconomic status at birth and family life in general contribute to an increased risk of chronic immune diseases, especially IBD.

Finally, infections in the first year of life were predictive of development of IBD at any age and with the strongest association for infections in the first year of life and development of IBD before age 10 years. We, and others, have previously shown that antibiotics early in life,[15,16] especially in the first year of life,[15] can increase the risk of IBD development in childhood. We did not find that infections in the first 3 years of life were predictive of developing IBD, nor did we find that antibiotic usage in the first 10 years of life were predictive of an IBD diagnosis, although this latter

Table 4. Association Between Demographic Variables at Birth and Clinical Events in the First Year of Life (Infections, Gastrointestinal Illnesses, Failure to Thrive, and Hospital Readmission) and the Development of Inflammatory Bowel Disease, Under Age 10 Years Among All Persons With Inflammatory Bowel Disease (n = 97) Compared to Controls (n = 748)

Effect	Comparison	OR estimate	95% Wald confidence limits	*P* value
Infection year 1	Yes vs no	3.06	1.07, 8.78	.04
Socioeconomic status				
Q2	Q2 vs Q1	1.98	0.93, 4.21	.07
Q3	Q3 vs Q1	1.44	0.64, 3.23	.38
Q4	Q4 vs Q1	1.68	0.75, 3.79	.21
Q5	Q5 vs Q1	1.29	0.53, 3.17	.57
Geography	Rural vs urban	2.54	1.24, 5.20	.01
Apgar 1 min	7+ vs <7	0.81	0.42, 1.54	.51
ICU admission	—			
Gestational age	—	0.94	0.81, 1.09	.44
Birth weight	—	1.000	1.000, 1.001	.22
Readmitted in year 1	No vs yes	0.92	0.49, 1.72	.79
Cesarean section	Yes vs no	0.76	0.39, 1.48	.41
Maternal IBD	Yes vs no	5.92	1.76, 19.98	<.01

ICU, intensive care unit; Q, quintile.

Table 5. Association Between Demographic Variables at Birth and Clinical Events in the First Year of Life (Infections, Gastrointestinal Illnesses, Failure to Thrive, and Hospital Readmission) and the Development of Inflammatory Bowel Disease, Under Age 20 Years Among All Persons With Inflammatory Bowel Disease (n = 591) Compared to Controls (n = 4491)

Effect	Comparison	OR estimate	95% Wald confidence limits	*P* value
Infection year 1	Yes vs no	1.63	1.18, 2.24	.003
Socioeconomic status				
Q2	Q2 vs Q1	1.46	1.09, 1.96	.01
Q3	Q3 vs Q1	1.11	0.81, 1.51	.52
Q4	Q4 vs Q1	1.37	1.01, 1.86	.04
Q5	Q5 vs Q1	1.43	1.02, 2.00	.03
Geography	Rural vs urban	0.98	0.73, 1.31	.87
Apgar 1 min	7+ vs <7	1.09	0.83, 1.43	.55
ICU admission	No vs yes	1.14	0.63, 2.05	.67
Gestational age	—	1.02	0.96, 1.08	.57
Birth weight	—	1.000	1.000, 1.000	.71
Readmitted in year 1	No vs yes	1.13	0.84, 1.53	.43
Cesarean section	Yes vs no	1.14	0.89, 1.45	.29
Maternal IBD	Yes vs no	4.95	3.18, 7.71	<.001
Hospitalized for GI	Yes vs no	0.60	0.28, 1.27	.18

GI, gastrointestinal; ICU, intensive care unit; Q, quintile.

analysis had a very limited sample size. It is unclear if the risk posed by infections in the first year of life is a manifestation of the infection itself per se or the use of antibiotics to treat the infections. We do not believe the risk posed by infections in the first year of life was secondary to persons with IBD being more likely to have an immunodeficiency disorder; disorders that can often present with an IBD-like picture.[17] We did not find more immunodeficiency disorders diagnosed in our IBD cohort compared with controls. Hence, the first year of life is potentially a critical time for risk for IBD development.

How can these data be used in a practical sense to potentially impact on later IBD diagnosis? Limiting antibiotic usage in the management of routine infections could be desirable; however, it would be difficult to curb antibiotic use for many of the infections as serious as the ones we assessed. If it is increasingly accepted that antibiotics in the first year of life truly pose a risk for later chronic immune disease like IBD, then research is warranted to determine exactly what antibiotic intake does to infant gut microflora or intestinal or systemic immune responses. Interventions such as probiotic or prebiotic use could be considered after a course of antibiotics in children to prevent development of IBD or other chronic immune diseases.[18]

It was particularly noteworthy that there were no differences among possible predictive factors for persons with IBD compared to their unaffected sibling controls. Those ultimately developing IBD compared to their unaffected siblings had similar neonatal events and similar events within the first of life in relation to infections and need for hospitalizations. As infection in the first year of life (and possibly the use of antibiotics to treat infection) is an important risk factor in our comparison of IBD cases with controls, it is uncertain why incidence of infection was not different for cases in comparison with sibling controls. Perhaps this suggests that because cases and siblings share genetics and environment, something unique must be occurring to cases that has not occurred to their unaffected siblings. Perhaps the genes not shared by the unaffected sibling include protective genes, which suggest a closer genetic evaluation of the differences between affected persons and their unaffected siblings may be fruitful. Secondly, while siblings share an environment and likely a similar diet while growing up, our findings suggest that there must be some environmental differences that we have not captured with our analyses. This may warrant a careful scrutiny of the diet and environment of unaffected siblings at the time of index case diagnosis. Some of those unaffected siblings may become affected over time, but many will not. The timing of the assessment of the unaffected siblings' environment and personal health attributes is critical.

No neonatal markers of health were found to be predictive of the eventual development of IBD. We have previously reported that neither undergoing birth by cesarean section[13] nor being born to a mother who experienced antenatal or perinatal infections requiring antibiotics predicted later development of IBD.[19] If delivery mode or

Table 6. Association Between Demographic Variables at Birth and Clinical Events in the First Year of Life (Infections, Gastrointestinal Illnesses, Failure to Thrive, and Hospital Readmission) and the Development of Inflammatory Bowel Disease, Among All Persons With Inflammatory Bowel Disease (n = 827) Compared to Sibling Controls (n = 994)

Effect	Comparison	OR estimate	95% Wald confidence limits	*P* value
Infection year 1	1 vs	1.22	0.90, 1.66	.19
Q1	NF vs Q1	1.83	0.18, 18.73	.61
Q2	Q2 vs Q1	1.56	0.78, 3.13	.21
Q3	Q3 vs Q1	1.37	0.64, 2.95	.42
Q4	Q4 vs Q1	1.76	0.81, 3.81	.15
Q5	Q5 vs Q1	1.06	0.43, 2.61	.89
Sex	Male vs female	0.95	0.74, 1.22	.71
Age at diagnosis[a]	—	1.28	1.22, 1.34	<.001
Geography	Rural vs urban	0.53	0.24, 1.19	.13
Apgar 1 min	7+ vs <7	1.33	0.90, 1.97	.16
Readmission 1 y	No vs Yes	1.27	0.65, 2.45	.48
Cesarean section	Yes vs No	1.21	0.66, 2.24	.53

NF, not found; Q, quintile.
[a]Age at diagnosis of IBD case compared to age of sibling at time of diagnosis.

maternal microbiota do influence the neonate's microbiota at a vulnerable time, or if other markers of neonatal ill health, as we explored in this study, have an impact on neonatal microbiome or immune system development,[20,21] these changes seemingly can all be overcome. However, experiencing an infection in the first year of life was predictive of developing IBD, particularly under age 20 years.

Gastrointestinal illnesses in the first year of life, including abdominal pain, were not found to be associated with later development of IBD. This should be reassuring for parents who worry about whether their young children with infectious or noninfectious gastrointestinal illnesses would be at risk at developing IBD. We did not have enough instances of failure to thrive to fully assess whether it associated with the development of IBD.

Our study has a number of limitations. While we examined the most serious infections experienced by children in our hospital setting, we could not assess definitively which of the conditions were associated with antibiotic prescriptions. It is speculative whether the association of infections in the first year of life with ultimate diagnosis of IBD at all ages is actually related to antibiotic use. It is possible that there are other factors that are as or more important in the first year of life that may increase the risk for IBD, such as diet, or duration of or exclusivity of breastfeeding in the first year of life. Further, other environmental factors in the home, such as smoking, may contribute to the risk for IBD. It is also possible that for onset of IBD into late teenage years and adulthood, there are other factors that overwhelm any risk posed by early life events. However, we did find the strongest association between infection in the first year of life and childhood-onset IBD. In fact, our data support the likelihood that triggers for IBD arising in children may very well be different from triggers that ultimately lead to adult-onset IBD. Risk factors posed from the diet or an environmental factor, such as smoking, may occur well after the first year of life. Because not everyone exposed to infections (or antibiotics) in their first year of life develop IBD, it is also possible that variables such as protective dietary factors experienced later in childhood may protect against the potential risk posed by harmful infections or the antibiotics used to treat them.

However, key strengths of our study include that it is population-based, that we have assessed for all possible diagnoses associated with significant infectious and gastrointestinal illness that lead to early childhood hospitalizations, and that we have included sibling controls. No increased risk was posed by infections in the first year of life in cases of IBD compared to their siblings, yet the risk existed compared to controls. This suggests that other non-communal environmental factors may also be of importance in the pathogenesis of IBD. More research on exploring the childhood household environment in persons who develop IBD compared to those who do not is warranted.

In conclusion, our data suggest that having a mother with a diagnosis of IBD is the strongest predictor of developing IBD. Further, being in the highest socioeconomic quintile at birth, supporting the hygiene hypothesis,[8] and having an infection within the first year of life increase the risk for developing IBD. Gastrointestinal illnesses, including abdominal pain, in the first year of life did not pose a risk for later development of IBD. Neonatal events that reflect infant health at birth did not predict later development of IBD. Together with our past reports that neither cesarean section birth nor antenatal or perinatal maternal use of antibiotics predict ultimate development of IBD, it seems that neonatal changes to the microbiome are subsumed by those occurring in the first year of life. Studies should explore the infant gut microbiome before and for several months after infections and/or antibiotic use to determine what changes occur that might promote the development of IBD later.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2019.02.004.

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Conflicts of interest
These authors disclose the following: Charles Bernstein has been on the advisory boards for AbbVie Canada, Ferring Canada, Janssen Canada, Shire Canada, Takeda Canada, Pfizer Canada, and Napo Pharmaceuticals and consulted to 4D Pharma and Mylan Pharmaceuticals. He has received educational grants from AbbVie Canada, Pfizer Canada, Shire Canada, Takeda Canada, Janssen Canada, and has been on the speaker's panel for Ferring Canada and Shire Canada. Laura Targownik has consulted to or been on the advisory boards of: Takeda Canada, AbbVie Canada, Ferring Canada, Merck Canada, Pfizer Canada, and Janssen Canada. She has received research grant support from Pfizer Canada. She has been on the speakers' bureaus for Janssen Canada, Takeda Canada, and Pfizer Canada. Harminder Singh has consulted to Medial Cancer Screening and has been on advisory board of Pendopharm and Ferring Canada. The remaining authors disclose no conflicts.

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Supplementary Table 1. Diagnoses Assessed for Association With Ultimate Development of Inflammatory Bowel Disease

ICD category	ICD-10-CM	Label	ICD-9-CM	Grade
Abdominal pain				
AP	R100	Abdominal and pelvic pain	78907	1
Asthma				
ASTHMA	J450	Asthma	493	U
ASTHMA	J4500	Asthma	49300	1
ASTHMA	J4501	Asthma	49301	1
ASTHMA	J451	Asthma	493	U
ASTHMA	J4510	Asthma	49310	1
ASTHMA	J4511	Asthma	49311	1
ASTHMA	J458	Asthma	493	U
ASTHMA	J4580	Asthma	49300	1
ASTHMA	J4581	Asthma	49301	1
ASTHMA	J459	Asthma	493	U
ASTHMA	J4590	Asthma	49390	1
ASTHMA	J4591	Asthma	49391	1
Bone and muscle inflammation				
BONEI	M6005	Infective myositis, pelvic region and thigh	7280	1
BONEI	M6008	Infective myositis, other	7280	1
BONEI	M8611	Other acute osteomyelitis, shoulder region	73001	1
BONEI	M8612	Other acute osteomyelitis, upper arm	73002	1
BONEI	M8616	Other acute osteomyelitis, lower leg	73006	1
BONEI	M8617	Other acute osteomyelitis, ankle and foot	73007	1
BONEI	M8618	Other acute osteomyelitis, other site	73008	1
BONEI	M8625	Subacute osteomyelitis, pelvic region and thigh	73005	1
BONEI	M8628	Subacute osteomyelitis, other site	73008	1
BONEI	M8666	Other chronic osteomyelitis, lower leg	73016	1
BONEI	M8667	Other chronic osteomyelitis, ankle and foot	73017	1
BONEI	M8686	Other osteomyelitis, lower leg	73026	1
BONEI	M8687	Other osteomyelitis, ankle and foot	73027	1
BONEI	M8690	Osteomyelitis, unspecified, multiple sites	73029	2
BONEI	M8692	Osteomyelitis, unspecified, upper arm	73022	2
BONEI	M8693	Osteomyelitis, unspecified, forearm	73023	2
BONEI	M8694	Osteomyelitis, unspecified, hand	73024	2
BONEI	M8695	Osteomyelitis, unspecified, pelvic region and thigh	73025	2
BONEI	M8696	Osteomyelitis, unspecified, lower leg	73026	2
BONEI	M8697	Osteomyelitis, unspecified, ankle and foot	73027	2
BONEI	M8698	Osteomyelitis, unspecified, other site	73028	2
Cardiac infection				
CARDI	B332	Viral carditis	42989	2
Failure to thrive				
FTT	R628	Failure to thrive	7834	2
Fungal infections				
FUNI	B350	Tinea barbae and tinea capitis	1100	1
FUNI	B354	Tinea corporis	1105	1
FUNI	B369	Superficial mycosis, unspecified	1119	1
FUNI	B370	Candidal stomatitis	1120	1
FUNI	B371	Pulmonary candidiasis	1124	1
FUNI	B372	Candidiasis of skin and nail	1123	1
FUNI	B374	Candidiasis of other urogenital sites	1122	1
FUNI	B377	Candidal sepsis	1125	1
FUNI	B3788	Candidiasis of other sites	11289	1
FUNI	B379	Candidiasis, unspecified	1129	1
FUNI	B402	Pulmonary blastomycosis, unspecified	1160	1
FUNI	B408	Other forms of blastomycosis	1160	1
FUNI	B409	Blastomycosis, unspecified	1160	1
FUNI	B488	Other specified mycoses	1179	1
FUNI	B49	Unspecified mycosis	1179	1
Genitourinary				
GENIT	N10	Acute tubulo-interstitial nephritis	59010	2
GENIT	N309	Cystitis, unspecified	5959	1
GENIT	N4590	Epididymitis	60490	1

Supplementary Table 1. Continued

ICD category	ICD-10-CM	Label	ICD-9-CM	Grade
GENIT	N4591	Orchitis	60490	1
GENIT	N700	Acute salpingitis and oophoritis	6140	1
GENIT	N736	Female pelvic peritoneal adhesions	6146	1
GENIT	N760	Acute vaginitis	61610	1
GENIT	N762	Acute vulvitis	61610	1
GENIT	N764	Abscess of vulva	6164	1
Gastrointestinal infections				
GI	A010	Typhoid fever	020	1
GI	A013	Paratyphoid fever C	023	1
GI	A020	*Salmonella enteritis*	030	1
GI	A029	Salmonella infection, unspecified	039	1
GI	A031	Shigellosis due to *Shigella flexneri*	041	1
GI	A039	Shigellosis, unspecified	049	1
GI	A044	Other intestinal *Escherichia coli* infections	809	2
GI	A045	Campylobacter enteritis	843	1
GI	A047	Enterocolitis due to *Clostridium difficile*	845	1
GI	A048	Other specified bacterial intestinal infections	849	2
GI	A049	Bacterial intestinal infection, unspecified	085	1
GI	A06	Diarrhea (Amebic)	060	U
GI	A060	Diarrhea (Amebic)	060	1
GI	A061	Diarrhea (Amebic)	061	1
GI	A062	Diarrhea (Amebic)	062	1
GI	A063	Diarrhea (Amebic)	068	1
GI	A064	Diarrhea (Amebic)	063	1
GI	A065	Diarrhea (Amebic)	064	1
GI	A066	Diarrhea (Amebic)	065	1
GI	A067	Diarrhea (Amebic)	066	1
GI	A068	Diarrhea (Amebic)	068	1
GI	A069	Diarrhea (Amebic)	069	1
GI	A071	Giardiasis [lambliasis]	071	1
GI	A079	Diarrhea (Protozoal)	079	1
GI	A080	Rotaviral enteritis	861	1
GI	A081	Acute gastroenteropathy due to Norwalk agent	863	2
GI	A082	Adenoviral enteritis	862	1
GI	A083	Other viral enteritis	869	2
GI	A084	Viral intestinal infection, unspecified	088	1
GI	A09	Diarrhea and gastroenteritis of presumed infection	093	2
GI	A090	Other and unspecified gastroenteritis and colitis	5589	U
GI	A099	Gastroenteritis and colitis of unspecified origin	5589	U
GI	P783	Diarrhea neonatal (transient)	7778	2
GI	R11	Vomiting	7870	U
GI	R110	Vomiting	78703	1
GI	R111	Vomiting	78702	1
GI	R112	Vomiting	78703	1
GI	R113	Vomiting	78701	1
Gastrointestinal disease				
GID	K120	Recurrent oral aphthae	5282	1
GID	K121	Other forms of stomatitis	5280	2
GID	K122	Cellulitis and abscess of mouth	5283	2
GID	K123	Oral mucositis (ulcerative)	52801	U
GID	K20	Oesophagitis	53010	2
GID	K210	Gastro-oesophageal reflux disease with esophagitis	53011	1
GID	K219	Gastro-oesophageal reflux disease without esophagitis	53081	1
GID	K222	Oesophageal obstruction	5303	1
GID	K228	Other specified diseases of oesophagus	53089	2
GID	K254	Gastric ulcer, chronic or unspecified with hemorrhage	53140	2
GID	K290	Acute haemorrhagic gastritis	53501	1
GID	K291	Other acute gastritis	53500	1
GID	K295	Chronic gastritis, unspecified	53510	2
GID	K296	Other gastritis	53540	2
GID	K297	Gastritis, unspecified	53550	2

Supplementary Table 1. Continued

ICD category	ICD-10-CM	Label	ICD-9-CM	Grade
GID	K298	Duodenitis	53560	2
GID	K350	Acute appendicitis with generalized peritonitis	5400	1
GID	K351	Acute appendicitis with peritoneal abscess	5401	1
GID	K352	Acute appendicitis with generalized peritonitis	5400	U
GID	K353	Acute appendicitis with localized peritonitis	5401	U
GID	K358	Acute appendicitis, other and unspecified	5409	U
GID	K359	Acute appendicitis, unspecified	5409	1
GID	K650	Acute peritonitis	5672	1
GID	K658	Other peritonitis	5678	2
GID	K659	Peritonitis, unspecified	5679	1
Hepatitis				
HEP	B179	Acute viral hepatitis, unspecified	5733	U
HEP	B181	Chronic viral hepatitis B without delta-agent	7032	1
HEP	B189	Chronic viral hepatitis, unspecified	709	1
HEP	B199	Unspecified viral hepatitis without hepatic coma	709	1
HEP	K754	Autoimmune hepatitis	5733	1
HEP	K758	Other specified inflammatory liver diseases	5733	2
HEP	K759	Inflammatory liver disease, unspecified	5733	1
Herpes virus				
HV	B000	Eczema herpeticum	540	1
HV	B001	Herpes viral vesicular dermatitis	5479	2
HV	B002	Herpes viral gingivitis and pharyngotonsilitis	542	2
HV	B004	Herpes viral encephalitis	543	1
HV	B005	Herpes viral ocular disease	5440	2
HV	B007	Disseminated herpesviral disease	545	1
HV	B008	Other forms of herpesviral infection	546	2
HV	B009	Herpesviral infection, unspecified	549	1
HV	B010	Varicella meningitis	527	2
HV	B011	Varicella encephalitis	520	1
HV	B012	Varicella pneumonia	521	1
HV	B018	Varicella with other complications	527	2
HV	B019	Varicella without complication	529	1
HV	B023	Zoster ocular disease	5320	2
Intracranial infections				
II	A321	Listerial meningitis and meningoencephalitis	270	1
II	A390	Meningococcal meningitis	360	1
II	A858	Other specified viral encephalitis	498	1
II	A86	Unspecified viral encephalitis	499	1
II	A870	Enteroviral meningitis	479	2
II	A871	Adenoviral meningitis	491	1
II	A872	Lymphocytic choriomeningitis	490	1
II	A879	Viral meningitis, unspecified	479	1
II	B941	Sequelae of viral encephalitis	1390	1
II	G000	Haemophilus meningitis	3200	1
II	G001	Pneumococcal meningitis	3201	1
II	G002	Streptococcal meningitis	3202	1
II	G003	Staphylococcal meningitis	3203	1
II	G008	Other bacterial meningitis	32089	2
II	G009	Bacterial meningitis, unspecified	3209	1
II	G01	Meningitis in bacterial diseases classified elsewhere	3207	2
II	G020	Meningitis in viral diseases classified elsewhere	3212	1
II	G030	Nonpyogenic meningitis	3220	1
II	G038	Meningitis due to other specified causes	3229	2
II	G039	Meningitis, unspecified	3229	1
II	G040	Acute disseminated encephalitis	3235	2
II	G042	Bacterial meningoencephalitis and meningomyelitis,	3209	1
II	G048	Other encephalitis, myelitis and encephalomyelitis	3238	1
II	G049	Encephalitis, myelitis and encephalomyelitis, unspecified	3239	1
II	G050	Encephalitis, myelitis and encephalomyelitis in ba	3234	1
II	G051	Encephalitis, myelitis and encephalomyelitis	3230	1
II	G060	Intracranial abscess and granuloma	3240	1

Supplementary Table 1. Continued

ICD category	ICD-10-CM	Label	ICD-9-CM	Grade
II	G061	Intraspinal abscess and granuloma	3241	1
II	G062	Extradural and subdural abscess, unspecified	3249	1
II	G08	Intracranial and intraspinal phlebitis and thrombosis	325	1
Lymphadenitis				
LYMPH	L040	Acute lymphadenitis of face, head and neck	683	1
LYMPH	L041	Acute lymphadenitis of trunk	683	1
LYMPH	L042	Acute lymphadenitis of upper limb	683	1
LYMPH	L043	Acute lymphadenitis of lower limb	683	1
LYMPH	L048	Acute lymphadenitis of other sites	683	1
Newborn infections				
NEWI	P027	Fetus and newborn affected by chorioamnionitis	7627	1
NEWI	P360	Sepsis of newborn due to streptococcus, group B	7718	1
NEWI	P361	Sepsis of newborn due to other and unspecified streptococcus	7718	1
NEWI	P362	Sepsis of newborn due to Staphylococcus aureus	7718	1
NEWI	P363	Sepsis of newborn due to other and unspecified staphylococcus	7718	1
NEWI	P364	Sepsis of newborn due to Escherichia coli	7718	1
NEWI	P368	Other bacterial sepsis of newborn	7718	1
NEWI	P369	Bacterial sepsis of newborn, unspecified	7718	1
NEWI	P38	Omphalitis of newborn with or without mild hemorrhage	7714	1
NEWI	P390	Neonatal infective mastitis	7715	1
NEWI	P391	Neonatal conjunctivitis and dacryocystitis	7716	1
NEWI	P393	Neonatal urinary tract infection	7718	1
NEWI	P394	Neonatal skin infection	7718	2
NEWI	P398	Other specified infections specific to the perinatal period	7718	1
NEWI	P77	Necrotizing enterocolitis of fetus and newborn	7775	1
Ocular infections				
OI	B303	Acute epidemic haemorrhagic conjunctivitis	774	1
OI	B309	Viral conjunctivitis, unspecified	7799	1
Oral, pharyngeal sinus infections				
OPSI	B084	Enteroviral vesicular stomatitis with exanthem	743	1
OPSI	B085	Enteroviral vesicular pharyngitis	740	1
OPSI	B250	Cytomegaloviral pneumonitis	785	1
OPSI	B251	Cytomegaloviral hepatitis	785	1
OPSI	B258	Other cytomegaloviral diseases	785	1
OPSI	B259	Cytomegaloviral disease, unspecified	785	1
OPSI	B270	Gammaherpesviral mononucleosis	075	1
OPSI	B279	Infectious mononucleosis, unspecified	075	1
OPSI	J00	Acute nasopharyngitis [common cold]	460	1
OPSI	J010	Acute maxillary sinusitis	4610	1
OPSI	J012	Acute ethmoidal sinusitis	4612	1
OPSI	J013	Acute sphenoidal sinusitis	4613	1
OPSI	J019	Acute sinusitis, unspecified	4619	1
OPSI	J020	Streptococcal pharyngitis	340	1
OPSI	J028	Acute pharyngitis due to other specified organisms	462	1
OPSI	J029	Acute pharyngitis, unspecified	462	1
OPSI	J030	Streptococcal tonsillitis	340	1
OPSI	J039	Acute tonsillitis, unspecified	463	1
OPSI	J040	Acute laryngitis	4640	1
OPSI	J041	Acute tracheitis	46410	1
OPSI	J050	Acute obstructive laryngitis [croup]	4644	1
OPSI	J051	Acute epiglottitis	46430	1
Otitis media				
OTIT	H65	Nonsuportive otitis media*	unknown	U
OTIT	H650	Nonsuportive otitis media*	38101	1
OTIT	H651	Nonsuportive otitis media*	38100	2
OTIT	H652	Nonsuportive otitis media*	38110	2
OTIT	H653	Nonsuportive otitis media*	38120	2
OTIT	H654	Nonsuportive otitis media*	3813	1
OTIT	H659	Nonsuportive otitis media*	3814	1
OTIT	H66	Otitis media*	unknown	U
OTIT	H660	Otitis media*	38200	2
OTIT	H661	Otitis media*	3821	1

Supplementary Table 1. Continued

ICD category	ICD-10-CM	Label	ICD-9-CM	Grade
OTIT	H662	Otitis media*	3822	1
OTIT	H663	Otitis media*	3823	1
OTIT	H664	Otitis media*	3824	1
OTIT	H669	Otitis media*	3829	1
OTIT	H67	Otitis media class elsewhere*	UNK	U
OTIT	H670	Otitis media class elsewhere*	38202	3
OTIT	H671	Otitis media class elsewhere*	38202	1
OTIT	H678	Otitis media class elsewhere*	38202	3
Pancreatitis				
PANC	K85	Acute pancreatitis	5770	U
PANC	K850	Idiopathic acute pancreatitis	5770	2
PANC	K851	Biliary acute pancreatitis	5770	2
PANC	K858	Other acute pancreatitis	5770	2
PANC	K859	Acute pancreatitis, unspecified	5770	2
Parasitic infections				
PARI	B508	Other severe and complicated *Plasmodium falciparum*	840	1
PARI	B509	Plasmodium falciparum malaria, unspecified	840	1
PARI	B519	Plasmodium vivax malaria without complication	841	1
PARI	B54	Unspecified malaria	846	1
PARI	B588	Toxoplasmosis with other organ involvement	1307	2
PARI	B589	Toxoplasmosis, unspecified	1309	1
PARI	B829	Intestinal parasitism, unspecified	129	1
PARI	B830	Visceral larva migrans	1280	1
PARI	B850	Pediculosis due to *Pediculus humanus capitis*	1320	1
PARI	B851	Pediculosis due to *Pediculus humanus corporis*	1321	1
PARI	B852	Pediculosis, unspecified	1329	1
PARI	B86	Scabies	1330	1
PARI	B878	Myiasis of other sites	1340	1
PARI	B89	Unspecified parasitic disease	1369	1
Pulmonary infections (bacterial)				
PI	A1501	Tuberculosis of lung, confirmed by sputum microscopy	1193	2
PI	A151	Tuberculosis of lung, confirmed by culture only	1194	2
PI	A1531	Tuberculosis of lung, confirmed by unspecified measures	1190	1
PI	A157	Primary respiratory tuberculosis, confirmed bacteriology	1090	2
PI	A1611	Tuberculosis of lung, bacteriological and histological confirmation	1191	1
PI	A162	Tuberculosis of lung, without mention of bacteriological and histological confirmation	119	U
PI	A1621	Tuberculosis of lung, without mention of bacteriol	1196	2
PI	A167	Primary respiratory tuberculosis	1196	2
PI	A169	Respiratory tuberculosis unspecified	119	U
PI	A1690	Respiratory tuberculosis unspecified	1196	2
PI	A170	Tuberculous meningitis	1300	2
PI	A178	Other tuberculosis of nervous system	1380	2
PI	A182	Tuberculous peripheral lymphadenopathy	1720	2
PI	A370	Whooping cough due to Bordetella pertussis	330	1
PI	A371	Whooping cough due to Bordetella parapertussis	331	1
PI	A379	Whooping cough, unspecified	339	1
PI	J068	Other acute upper respiratory infections	4658	1
PI	J069	Acute upper respiratory infection, unspecified	4659	1
PI	J13	Pneumonia due to *Streptococcus pneumoniae*	481	2
PI	J14	Pneumonia due to *Haemophilus influenzae*	4822	1
PI	J150	Pneumonia due to *Klebsiella pneumoniae*	4820	1
PI	J151	Pneumonia due to Pseudomonas	4821	1
PI	J152	Pneumonia due to Staphylococcus	48240	1
PI	J153	Pneumonia due to Streptococcus, group B	48232	1
PI	J154	Pneumonia due to other streptococci	48239	2
PI	J156	Pneumonia due to other Gram-negative bacteria	48283	1
PI	J157	Pneumonia due to *Mycoplasma pneumoniae*	4830	1
PI	J158	Other bacterial pneumonia	48289	1
PI	J159	Bacterial pneumonia, unspecified	4829	1
PI	J170	Pneumonia in bacterial diseases classified elsewhere	4848	2
PI	J171	Pneumonia in viral diseases classified elsewhere	4848	2

Supplementary Table 1. Continued

ICD category	ICD-10-CM	Label	ICD-9-CM	Grade
PI	J18	Bronchopneumonia	481	U
PI	J180	Bronchopneumonia, unspecified	485	1
PI	J181	Lobar pneumonia, unspecified	481	1
PI	J182	Bronchopneumonia	514	1
PI	J188	Bronchopneumonia	486	1
PI	J189	Pneumonia, unspecified	486	1
PI	J20	Acute bronchitis	4660	U
PI	J200	Acute bronchitis	4660	1
PI	J201	Acute bronchitis	4660	1
PI	J202	Acute bronchitis	4660	1
PI	J203	Acute bronchitis	4660	1
PI	J204	Acute bronchitis	4660	1
PI	J205	Acute bronchitis	4660	1
PI	J206	Acute bronchitis	4660	1
PI	J207	Acute bronchitis	4660	1
PI	J310	Chronic rhinitis	4720	1
PI	J312	Chronic pharyngitis	4721	1
PI	J320	Chronic maxillary sinusitis	4730	1
PI	J322	Chronic ethmoidal sinusitis	4732	1
PI	J329	Chronic sinusitis, unspecified	4739	1
PI	J47	Bronchiectasis	494	1
PI	R05	Cough	7862	1
Systemic bacterial infections, primary site not specified				
SBNOS	A191	Acute miliary tuberculosis of multiple sites	1800	2
SBNOS	A199	Miliary tuberculosis, unspecified	1890	2
SBNOS	A400	Sepsis due to streptococcus, group A	380	1
SBNOS	A401	Sepsis due to streptococcus, group B	380	1
SBNOS	A403	Sepsis due to *Streptococcus pneumoniae*	382	1
SBNOS	A408	Other streptococcal sepsis	380	1
SBNOS	A409	Streptococcal sepsis, unspecified	380	1
SBNOS	A410	Sepsis due to *Staphylococcus aureus*	3810	1
SBNOS	A411	Sepsis due to other specified staphylococcus	3819	1
SBNOS	A412	Sepsis due to unspecified staphylococcus	3810	1
SBNOS	A413	Sepsis due to *Haemophilus influenzae*	3841	1
SBNOS	A4150	Sepsis due to *Escherichia coli* [*E coli*]	3842	1
SBNOS	A4151	Sepsis due to *Pseudomonas*	3843	1
SBNOS	A4158	Sepsis due to other Gram-negative organisms	3849	1
SBNOS	A4180	Sepsis due to *Enterococcus*	388	1
SBNOS	A4188	Other specified sepsis	388	1
SBNOS	A419	Sepsis, unspecified	389	1
SBNOS	A490	Staphylococcal infection, unspecified site	4111	1
SBNOS	A491	Streptococcal infection, unspecified site	4109	1
SBNOS	A492	*Haemophilus influenzae* infection, unspecified site	415	1
SBNOS	A498	Other bacterial infections of unspecified site	4189	1
SBNOS	A499	Bacterial infection, unspecified	419	1
SBNOS	A689	Relapsing fever, unspecified	879	1
SBNOS	B948	Sequelae of other specified infectious and parasites	1398	1
SBNOS	B950	Streptococcus, group A, as the cause of diseases	4101	1
SBNOS	B956	*Staphylococcus aureus* as the cause of diseases	4111	1
SBNOS	B961	*Klebsiella pneumoniae* [*K pneumoniae*] as the cause	413	1
SBNOS	B962	*Escherichia coli* [E coli] as the cause of disease	414	1
SBNOS	B963	*Haemophilus influenzae* [*H influenzae*] as the cause	415	1
SBNOS	B9680	*Helicobacter pylori* [*H pylori*] as the cause of disease	4186	1
SBNOS	B9681	Enterococcus as the cause of diseases classified	4104	1
SBNOS	B9688	Other specified bacterial agents as the cause of disease	4189	1
Respiratory infections (viral)				
RI	J09	Influenza due to certain identified influenza virus	4878	1
RI	J100	Influenza with pneumonia, other influenza virus identified	4870	1
RI	J101	Influenza with other respiratory manifestations	4871	1
RI	J108	Influenza with other manifestations	4878	1

Supplementary Table 1. Continued

ICD category	ICD-10-CM	Label	ICD-9-CM	Grade
RI	J110	Influenza with pneumonia, virus not identified	4870	1
RI	J111	Influenza with other respiratory manifestations	4871	1
RI	J118	Influenza with other manifestations, virus not identified	4878	1
RI	J120	Adenoviral pneumonia	4800	1
RI	J121	Respiratory syncytial virus pneumonia	4801	1
RI	J122	Parainfluenza virus pneumonia	4802	1
RI	J123	Human metapneumovirus pneumonia	4808	U
RI	J128	Other viral pneumonia	4808	1
RI	J129	Viral pneumonia, unspecified	4809	1
RI	J40	Bronchitis, not specified	490	1
RI	J41	Simple and mucopurulent chronic bronchitis	4911	U
RI	J410	Simple and mucopurulent chronic bronchitis	4910	1
RI	J411	Simple and mucopurulent chronic bronchitis	4911	1
RI	J418	Simple and mucopurulent chronic bronchitis	4918	2
RI	J42	Unspecified chronic bronchitis	4919	1
Skin infection				
SI	A281	Cat-scratch disease	783	1
SI	A46	Erysipelas	35	1
SI	B081	Molluscum contagiosum	780	1
SI	L00	Staphylococcal scalded skin syndrome	69581	2
SI	L010	Impetigo [any organism] [any site]	684	1
SI	L011	Impetiginization of other dermatoses	684	1
SI	L020	Cutaneous abscess, furuncle and carbuncle of face	6800	1
SI	L021	Cutaneous abscess, furuncle and carbuncle of neck	6801	1
SI	L022	Cutaneous abscess, furuncle and carbuncle of trunk	6802	1
SI	L023	Cutaneous abscess, furuncle and carbuncle of buttock	6805	1
SI	L024	Cutaneous abscess, furuncle and carbuncle of limb	6803	1
SI	L028	Cutaneous abscess, furuncle and carbuncle of other	6808	1
SI	L0300	Cellulitis of finger	68100	1
SI	L0301	Cellulitis of toe	68110	1
SI	L0310	Cellulitis of upper limb	6823	1
SI	L0311	Cellulitis of lower limb	6826	1
SI	L032	Cellulitis of face	6820	1
SI	L0330	Cellulitis of chest wall	6822	1
SI	L0331	Cellulitis of abdominal wall	6822	1
SI	L0332	Cellulitis of umbilicus	6822	1
SI	L0333	Cellulitis of groin	6822	1
SI	L0334	Cellulitis of back [any part except buttock]	6822	1
SI	L0335	Cellulitis of buttock	6825	1
SI	L0336	Cellulitis of perineum	6822	1
SI	L0339	Cellulitis of trunk, unspecified	6822	1
SI	L038	Cellulitis of other sites	6828	2
SI	L039	Cellulitis, unspecified	6829	1
SI	L050	Pilonidal cyst with abscess	6850	1
SI	L059	Pilonidal cyst without abscess	6851	1
SI	L080	Pyoderma	68609	1
SI	L088	Other specified local infections of skin and subcutaneous tissue	6868	1
SI	L089	Local infection of skin and subcutaneous tissue	6869	1
Congenital infection				
STI-related infection				
STI	A630	Anogenital (venereal) warts	7819	1
STI	A749	Chlamydial infection, unspecified	7888	2
STI	A500	Early congenital syphilis, symptomatic	900	2
CONI	A509	Congenital syphilis, unspecified	909	1

Supplementary Table 1. Continued

ICD category	ICD-10-CM	Label	ICD-9-CM	Grade
Systemic viral infection primary site not specified				
SVNOS	B088	Other specified viral infections characterized by	7889	2
SVNOS	B09	Unspecified viral infection characterized by skin	579	2
SVNOS	B340	Adenovirus infection, unspecified site	790	1
SVNOS	B341	Enterovirus infection, unspecified site	7889	2
SVNOS	B348	Other viral infections of unspecified site	7989	1
SVNOS	B349	Viral infection, unspecified	7999	2
SVNOS	B970	Adenovirus as the cause of diseases	790	1
SVNOS	B971	Enterovirus as the cause of diseases	7989	2
SVNOS	B972	Coronavirus as the cause of diseases	7989	2
SVNOS	B974	Respiratory syncytial virus as the cause of disease	796	1
SVNOS	B9780	Parainfluenza virus as the cause of diseases	7989	2
SVNOS	B9788	Other viral agents as the cause of diseases classified	7989	1
Miscellaneous				
MIS	A227	Anthrax sepsis	223	1
MIS	A312	Disseminated mycobacterium avium-intracellulare	312	1
MIS	A319	Mycobacterial infection, unspecified	319	1
Meningococcus	A398	Other meningococcal infections	3689	2
MIS	A829	Rabies, unspecified	071	1

BONEI, bone inflammation; CARDI, cardiac inflammation; FUNI, fungal infection; GENIT, genitourinary; GI, Gastrointestinal infections; GID, gastrointestinal disease.

Supplementary Table 2. Association Between Demographic Variables at Birth and Clinical Events in the First Year of Life (Infections, Gastrointestinal Illnesses, Failure to Thrive, and Hospital Readmission) and the Development of Crohn's Disease, Under Age 10 Years Among All Persons With Crohn's Disease Compared to Controls

Effect	Comparison	OR estimate	95% Wald confidence limits	*P* value
Infection year 1	Yes vs no	3.15	0.70, 14.14	.13
Socioeconomic status				
Q1	Q2 vs Q1	2.21	0.79, 6.17	.13
Q2	Q3 vs Q1	1.16	0.38, 3.54	.79
Q3	Q4 vs Q1	1.64	0.53, 5.08	.39
Q4	Q5 vs Q1	1.69	0.49, 5.83	.40
Geography	rural vs urban	3.03	1.17, 7.84	.02
Apgar 1 min	7+ vs <7	1.22	0.50, 2.97	.66
Gestational age	—	0.91	0.75, 1.11	.35
Birth weight	—	1.000	1.000, 1.001	.46
Readmitted in year 1	No vs yes	1.12	0.46, 2.75	.80
Cesarean section	Yes vs no	0.48	0.19, 1.21	.12
Maternal IBD	Yes vs no	9.22	1.80, 47.32	.01

Q, quintile.

Supplementary Table 3. Association Between Demographic Variables at Birth and Clinical Events in the First Year of Life (Infections, Gastrointestinal Illnesses, Failure to Thrive, and Hospital Readmission) and the Development of Ulcerative Colitis, Under Age 10 Years Among All Persons With Ulcerative Colitis Compared to Controls

Effect	Comparison	OR estimate	95% Wald confidence limits	*P* value
Infection year 1	Yes vs no	2.71	0.60, 12.20	.19
Q2	Q2 vs Q1	1.63	0.49, 5.41	.42
Q3	Q3 vs Q1	1.97	0.58, 6.66	.28
Q4	Q4 vs Q1	1.97	0.58, 6.62	.28
Q5	Q5 vs Q1	1.10	0.30, 4.07	.89
Geography	Rural vs urban	1.83	0.58, 5.77	.30
Apgar 1 min	7+ vs <7	0.44	0.16, 1.21	.11
Gestational age	—	0.98	0.76, 1.26	.88
Birth weight	—	1.000	1.000, 1.001	.28
Readmitted in year 1	No vs yes	0.75	0.30, 1.83	.52
Cesarean section	Yes vs no	1.45	0.52, 4.06	.48
Maternal IBD	Yes vs no	3.13	0.31, 31.89	.34

Q, quintile.

Supplementary Table 4. Association Between Demographic Variables at Birth and Clinical Events in the First Year of Life (Infections, Gastrointestinal Illnesses, Failure to Thrive, and Hospital Readmission) and the Development of Crohn's Disease, Under Age 20 Years Among All Persons With Crohn's Disease Compared to Controls

Effect	Comparison	OR estimate	95% Wald confidence limits	*P* value
Infection year 1	Yes vs no	1.70	1.12, 2.59	.01
Socioeconomic status				
Q2	Q2 vs Q1	1.26	0.87, 1.84	.22
Q3	Q3 vs Q1	0.89	0.59, 1.35	.59
Q4	Q4 vs Q1	1.36	0.92, 2.01	.12
Q5	Q5 vs Q1	1.33	0.86, 2.06	.19
Geography	rural vs urban	0.90	0.62, 1.32	.59
Apgar 1 min	7+ vs <7	1.38	0.95, 2.01	.09
ICU admission	No vs yes	1.07	0.53, 2.17	.85
Gestational age	—	1.04	0.96, 1.13	.35
Birth weight	—	1.000	1.000, 1.000	.38
Readmitted in year 1	No vs yes	1.14	0.77, 1.71	.50
Cesarean section	Yes vs no	1.05	0.76, 1.47	.76
Maternal IBD	Yes vs no	7.07	4.10, 12.22	<.001
Hospitalization for GI	Yes vs no	0.63	0.21, 1.91	.42

GI, gastrointestinal; ICU, intensive care unit; Q, quintile.

Supplementary Table 5. Association Between Demographic Variables at Birth and Clinical Events in the First Year of Life (Infections, Gastrointestinal Illnesses, Failure to Thrive, and Hospital Readmission) and the Development of Ulcerative Colitis, Under Age 20 Years Among All Persons With Ulcerative Colitis Compared to Controls

Effect	Comparison	OR estimate	95% Wald confidence limits	*P* value
Infection year 1	Yes vs no	1.48	0.90, 2.44	.12
Socioeconomic status				
Q2	Q2 vs Q1	1.77	1.11, 2.82	.02
Q3	Q3 vs Q1	1.47	0.90, 2.38	.12
Q4	Q4 vs Q1	1.38	0.84, 2.27	.19
Q5	Q5 vs Q1	1.53	0.90, 2.61	.12
Geography	Rural vs urban	1.05	0.67, 1.64	.84
Apgar 1 min	7+ vs <7	0.77	0.51, 1.16	.21
ICU admission	No vs yes	1.20	0.39, 3.68	.75
Gestational age	—	0.99	0.89, 1.09	.75
Birth weight	—	1.000	1.000, 1.000	.56
Readmitted in year 1	No vs yes	1.09	0.68, 1.72	.73
Cesarean section	Yes vs no	1.24	0.86, 1.78	.25
Maternal IBD	Yes vs no	2.45	1.07, 5.61	.03
Hospitalization for GI	Yes vs no	0.57	0.20, 1.59	.28

GI, gastrointestinal; ICU, intensive care unit; Q, quintile.

Supplementary Table 6. Association Between Demographic Variables at Birth and Clinical Events in the First Year of Life (Infections Excluding Viral Infections, Gastrointestinal Illnesses, Failure to Thrive, and Hospital Readmission) and the Development of Inflammatory Bowel Disease, at Any Age Among All Persons With Inflammatory Bowel Disease Compared With Controls

Effect	Comparison	OR estimate	95% Wald confidence limits	*P* value
Bacterial infect only	Yes vs no	1.10	0.94, 1.30	.24
Q1	NF vs Q1	0.75	0.36, 1.54	.43
Q2	Q2 vs Q1	1.31	1.02, 1.68	.04
Q3	Q3 vs Q1	1.09	0.84, 1.42	.51
Q4	Q4 vs Q1	1.37	1.06, 1.77	.02
Q5	Q5 vs Q1	1.35	1.01, 1.79	.04
Geography	Rural vs urban	0.91	0.72, 1.15	.43
Apgar 1 min	7+ vs <7	1.10	0.87, 1.39	.44
Apgar 5 min	7+ vs <7	1.06	0.49, 2.31	.88
ICU admission	No vs yes	1.07	0.64, 1.79	.79
Gestational age	—	1.002	0.95, 1.06	.93
Birth weight	—	1.000	1.000, 1.000	.82
Readmitted in year 1	No vs yes	1.20	0.93, 1.54	.16
Cesarean section	Yes vs no	1.06	0.86, 1.32	.58
Maternal IBD	Yes vs no	4.57	3.11, 6.73	<.001
Hospitalization for GI	Yes vs no	0.78	0.45, 1.35	.38

GI, gastrointestinal; ICU, intensive care unit; Q, quintile.

Supplementary Table 7. Association Between Demographic Variables at Birth and Clinical Events in the First 3 Years of Life (Infections, Gastrointestinal Illnesses, Failure to Thrive, and Hospital Readmission) and the Development of Inflammatory Bowel Disease, at Any Age Among All Persons With Inflammatory Bowel Disease Compared to Controls

Effect	Comparison	OR estimate	95% Wald confidence limits	*P* value
Infection in first 3 y	Yes vs no	1.26	0.77, 2.06	.35
Socioeconomic status				
Q1	NF vs Q1	0.76	0.37, 1.56	.45
Q2	Q2 vs Q1	1.31	1.02, 1.68	.04
Q3	Q3 vs Q1	1.09	0.84, 1.42	.51
Q4	Q4 vs Q1	1.36	1.05, 1.76	.02
Q5	Q5 vs Q1	1.35	1.01, 1.79	.04
Geography	Rural vs urban	0.91	0.72, 1.15	.44
Apgar 1 min	7+ vs <7	1.11	0.88, 1.40	.39
Apgar 5 min	7+ vs <7	1.09	0.50, 2.36	.83
ICU admission	No vs yes	0.89	0.55, 1.46	.65
Gestational age	—	1.01	0.96, 1.06	.82
Birth weight	—	1.000	1.000, 1.000	.8
Readmitted in year 1	No vs yes	1.18	0.92, 1.51	.20
Cesarean section	Yes vs no	1.06	0.86, 1.32	.58
Maternal IBD	Yes vs no	4.60	3.13, 6.77	<.001
Hospitalization for GI	Yes vs no	0.77	0.50, 1.17	.22

GI, gastrointestinal; ICU, intensive care unit; Q, quintile.