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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.

Early Life Predictors of Development of IBD

- Neonatal period
  - Maternal diagnosis of IBD (OR=4.53, 95%CI 3.08-6.67)
  - Highest socioeconomic quintile (OR=1.35, 95%CI 1.01-1.79)
- 1st year of life
  - Infections (OR=1.63, 95%CI 1.18-2.24)
  - Infections (OR=3.06, 95%CI 1.07-8.78)
- IBD by age 20
- IBD by age 10
- IBD ever

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 depend 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.

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.

**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 of 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

| Effect                          | Comparison         | OR estimate | 95% Wald confidence limits | P value | Case† (n = 825) | Control‡ (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 NF vs Q1                     | 0.76               | 0.37, 1.56  | .45                       |         | 14.79           | 17.57               | .05     |
| 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           | 86.73               | .2      |
| Apgar 5 min 7+ vs <7            | 1.07               | 0.49, 2.33  | .87                       |         | 99.93           | 98.8                | .55     |
| ICU admission No vs yes         | 1.06               | 0.63, 1.77  | .83                       |         | 97.6            | 97.23               | .57     |
| Gestational age Q1 vs Q5        | 1.004              | 0.95, 1.06  | .88                       |         | 39.4            | 39.4                | .88     |
| Birth weight Q1 vs Q5            | 1.000              | 1.000, 1.000| .79                      |         | 3451            | 3444                | .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                       |         | 2.16            | 2.90                | .24     |

ICU, intensive care unit; NF, not found; Q, quintile.
†Data in case and control columns reflect % in each category unless otherwise specified.
‡Data for % with Apgar of 7+.
§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 = .49).

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 (95% Wald 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     |
| Age at diagnosis                |             |                      |         |
| 7+ yrs vs <7                   | 1.42 (1.02, 1.96) | .04             |
| Apgar 5 min                     | 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)        | .96     |
| Readmitted in ICU              | 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            | Yes vs no   | 0.67 (0.30, 1.51)    | .34     |

ICU, intensive care unit; NF, not found; Q, quintile.

Hospitaized 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. 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. 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. 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. 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, 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. 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, especially IBD.

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 (95% Wald 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 (0.99, 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     |
| Age at diagnosis                |             |                      |         |
| 7+ yrs vs <7                   | 0.78 (0.55, 1.11) | .17             |
| Apgar 5 min                     | 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)        | .61     |
| Readmitted in ICU              | 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            | Yes vs no   | 0.87 (0.41, 1.86)    | .73     |

ICU, intensive care unit; NF, not found; Q, quintile.

Hospitalized for GI means hospitalized for any of gastrointestinal infections, gastrointestinal disease or abdominal pain in the first year of life.
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 = 748) Compared to Controls

| Effect                  | Comparison   | OR estimate | 95% Wald 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.

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. 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.

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 genes 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, nor being born to a mother who experienced antenatal or perinatal infections requiring antibiotics predicted later development of IBD. If delivery mode or

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 = 4491) Compared to Controls

| Effect                  | Comparison   | OR estimate | 95% Wald 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.
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, 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 noted 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, 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.

### References

1. Chassaing B, Darfeuille–Michaud A. Commensal microbe and enteropathogens in the pathogenesis of inflammatory bowel diseases. *Gastroenterology* 2011; 140:1720–1728.

2. Palmer C, Bik EM, Digiulio DB, et al. Development of the human infant intestinal microbiota. *PLoS Biol* 2007; 5:e177.

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**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 = 927) 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        | 0.53, 1.87                | .61     |
| Q2                      | Q2 vs Q1   | 1.56        | 1.04, 2.33                | .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        | —          | 1.28        | 1.22, 1.34                | <.001   |
| Geography               | Rural vs urban | 0.53   | 0.24, 1.19                | .13     |
| Apгар 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.*
3. Stark PL, Lee A. The microbial ecology of the large bowel of breast-fed and formula-fed infants during the first year of life. J Med Microbiol 1982;15:189–203.

4. Dominguez-Bello MG, Blaser MG, Ley RE, et al. Developments of the human intestinal microbiota and insights from high throughput sequencing. Gastroenterology 2011;140:1713–1719.

5. Bernstein CN, Blanchard JF, Rawsthorne P, Wajda A. The epidemiology of Crohn's disease and ulcerative colitis in a central Canadian province: a population-based study. Am J Epidemiol 1999;149:916–924.

6. Jutte DP, Roos LL, Brownell MD. Administrative record linkage as a tool for public health research. Annu Rev Public Health 2011;32:91–108.

7. Chateau D, Metge C, Prior H, et al. Learning from the census: the Socio-economic Factor Index (SEFI) and health outcomes in Manitoba. Can J Public Health 2012;103(Suppl 2):S23–S27.

8. Stiensma LT, Reynolds LA, Turvey SE, Finlay BB. The hygiene hypothesis: current perspectives and future therapies. Immunogens Ther 2015;4:143–157.

9. Alter M, Zhen-xin Z, Davanipour Z, et al. Does delay in acquisition of childhood infection increase risk of multiple sclerosis? Ital Neurol Sci 1987;8:23–28.

10. Gent AE, Hellier MD, Grace RH, et al. Inflammatory bowel disease and domestic hygiene in infancy. Lancet 1994;343:766–767.

11. Forste R, Hoffmann JP. Are US mothers meeting the Healthy People 2010 breastfeeding targets for initiation, duration, and exclusivity? The 2003 and 2004 National Immunization Surveys. J Hum Lact 2008;24:278–288.

12. Palmer C, Bik EM, DiGilio DB, et al. Development of the human infant intestinal microbiota. PLoS Biol 2007;5(7):e177.

13. Bernstein CN, Banerjee A, Targownik LE, et al. Cesarean section delivery is not a risk factor for development of inflammatory bowel disease: a population-based Analysis. Clin Gastroenterol Hepatol 2016;14:50–57.

14. Benchimol EI, Kaplan GG, Otley AR, Nguyen GC, Underwood FE, Guttmann A, et al. Rural and urban residence during early life is associated with risk of inflammatory bowel disease: a population-based inception and birth cohort study. Am J Gastroenterol 2017;112:1412–1422.

15. Shaw S, Blanchard JF, Bernstein CN. Association between the use of antibiotics in the first year of life and pediatric inflammatory bowel disease. Am J Gastroenterol 2010;105:2687–2692.

16. Ungaro R, Bernstein CN, Geary R, et al. Antibiotics associated with increased risk of new-onset Crohn's disease but not ulcerative colitis: a meta-analysis. Am J Gastroenterol 2014;109:1728–1733.

17. Kelsen JR, Sullivan KE. Inflammatory bowel disease in primary immunodeficiencies. Curr Allergy Asthma Resp 2017;17:57.

18. Kalliomaki M, Salminen S, Arvilommi H, et al. Probiotics in primary prevention of atopic disease: a randomized placebo-controlled trial. Lancet 2001;357:1076–1079.

19. Bernstein CN, Burchill C, Targownik LE, et al. Maternal infections that would warrant antibiotic use antepartum or peripartum are not a risk factor for the development of IBD: a population based analysis. Inflamm Bowel Dis 2017;23:635–640.

20. Neu J. Preterm infant nutrition, gut bacteria and necrotizing enterocolitis. Curr Opin Clin Nutr Metab Care 2015;18:285–288.

21. Ubeda C, Pamer EG. Antibiotics, microbiota, and immune defense. Trends Immunol 2012;33:459–466.

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Conflicts of interest
These authors disclose the following: Charles Bernstein has been on the advisory boards of 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. Harinder 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 |     |                                    | 7834     | 2     |
| FTT R628     |           | Failure to thrive                   |          |       |
| 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     |
| 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        | N750      | 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) | 063 | 1 |
| GI | A064 | Diarrhea (Amebic) | 064 | 1 |
| GI | A065 | Diarrhea (Amebic) | 065 | 1 |
| GI | A066 | Diarrhea (Amebic) | 066 | 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 oesophagitis | 53011 | 1 |
| GID | K219 | Gastro-oesophageal reflux disease without oesophagitis | 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 |
| ICD category | ICD-10-CM | Label | ICD-9-CM | Grade |
|--------------|-----------|-------|----------|-------|
| GID K298     | Duodenitis |       | 53660    | 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 meningoencephalitis, unspecified | 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         | P39      | 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 |     |       |          |       |
| Opisi        | B084      | Enteroviral vesicular stomatitis with exanthem | 743   | 1        |
| Opisi        | B085      | Enteroviral vesicular pharyngitis | 740   | 1        |
| Opisi        | B250      | Cytomegaloviral pneumonia | 785   | 1        |
| Opisi        | B251      | Cytomegaloviral hepatitis | 785   | 1        |
| Opisi        | B258      | Other cytomegaloviral diseases | 785   | 1        |
| Opisi        | B259      | Cytomegaloviral disease, unspecified | 785   | 1        |
| Opisi        | B270      | Gamma herpes viral mononucleosis | 075   | 1        |
| Opisi        | B279      | Infectious mononucleosis, unspecified | 075   | 1        |
| Opisi        | J00       | Acute nasopharyngitis [common cold] | 460   | 1        |
| Opisi        | J010      | Acute maxillary sinusitis | 4610  | 1        |
| Opisi        | J012      | Acute ethmoidal sinusitis | 4612  | 1        |
| Opisi        | J013      | Acute sphenoidal sinusitis | 4613  | 1        |
| Opisi        | J019      | Acute sinusitis, unspecified | 4619  | 1        |
| Opisi        | J020      | Streptococcal pharyngitis | 340   | 1        |
| Opisi        | J028      | Acute pharyngitis due to other specified organisms | 462   | 1        |
| Opisi        | J029      | Acute pharyngitis, unspecified | 462   | 1        |
| Opisi        | J030      | Streptococcal tonsillitis | 340   | 1        |
| Opisi        | J039      | Acute tonsillitis, unspecified | 463   | 1        |
| Opisi        | J040      | Acute laryngitis | 4640  | 1        |
| Opisi        | J041      | Acute tracheitis | 46410 | 1        |
| Opisi        | J050      | Acute obstructive laryngitis [croup] | 4644  | 1        |
| Opisi        | J051      | Acute epiglottitis | 46430 | 1        |
| Otitis media |          |       |          |       |
| Ttit         | H65       | Nonsuportive otitis media * | unknown | U |
| Ttit         | H650      | Nonsuportive otitis media * | 38101  | 1        |
| Ttit         | H651      | Nonsuportive otitis media * | 38100  | 2        |
| Ttit         | H652      | Nonsuportive otitis media * | 38110  | 2        |
| Ttit         | H653      | Nonsuportive otitis media * | 38120  | 2        |
| Ttit         | H654      | Nonsuportive otitis media * | 3813   | 1        |
| Ttit         | H659      | Nonsuportive otitis media * | 3814   | 1        |
| Ttit         | H66       | Otitis media * | unknown | U |
| Ttit         | H660      | Otitis media * | 38200  | 2        |
| Ttit         | H661      | Otitis media * | 3821   | 1        |
| 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

| PAN C K85 | Acute pancreatitis | 5770 | U |
| PAN C K850 | Idiopathic acute pancreatitis | 5770 | 2 |
| PAN C K851 | Biliary acute pancreatitis | 5770 | 2 |
| PAN C K858 | Other acute pancreatitis | 5770 | 2 |
| PAN C 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, unspecified | 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)

| PL A1501 | Tuberculosis of lung, confirmed by sputum microscopy | 1193 | 2 |
| PL A151 | Tuberculosis of lung, confirmed by culture only | 1194 | 2 |
| PL A1531 | Tuberculosis of lung, confirmed by unspecified measures | 1190 | 1 |
| PL A157 | Primary respiratory tuberculosis, confirmed bacteriology | 1090 | 2 |
| PL A1611 | Tuberculosis of lung, bacteriological and histological confirmation | 1191 | 1 |
| PL A162 | Tuberculosis of lung, without mention of bacteriological and histological confirmation | 119 | U |
| PL A1621 | Tuberculosis of lung, without mention of bacteriology | 1196 | 2 |
| PL A167 | Primary respiratory tuberculosis | 1196 | 2 |
| PL A169 | Respiratory tuberculosis unspecified | 119 | U |
| PL A1690 | Respiratory tuberculosis unspecified | 1196 | 2 |
| PL A170 | Tuberculous meningitis | 1300 | 2 |
| PL A178 | Other tuberculosis of nervous system | 1380 | 2 |
| PL A182 | Tuberculous peripheral lymphadenopathy | 1720 | 2 |
| PL A370 | Whooping cough due to *Bordetella pertussis* | 330 | 1 |
| PL A371 | Whooping cough due to *Bordetella parapertussis* | 331 | 1 |
| PL A379 | Whooping cough, unspecified | 339 | 1 |
| PL J068 | Other acute upper respiratory infections | 4658 | 1 |
| PL J069 | Acute upper respiratory infection, unspecified | 4659 | 1 |
| PL J13 | Pneumonia due to *Streptococcus pneumoniae* | 481 | 2 |
| PL J14 | Pneumonia due to *Haemophilus influenzae* | 4822 | 1 |
| PL J150 | Pneumonia due to *Klebsiella pneumoniae* | 4820 | 1 |
| PL J151 | Pneumonia due to *Pseudomonas* | 4821 | 1 |
| PL J152 | Pneumonia due to *Staphylococcus* | 48240 | 1 |
| PL J153 | Pneumonia due to *Streptococcus, group B* | 48232 | 1 |
| PL J154 | Pneumonia due to other *streptococci* | 48239 | 1 |
| PL J156 | Pneumonia due to other Gram-negative bacteria | 48283 | 1 |
| PL J157 | Pneumonia due to *Mycoplasma pneumoniae* | 4830 | 1 |
| PL J158 | Other bacterial pneumonia | 48289 | 1 |
| PL J159 | Bacterial pneumonia, unspecified | 4829 | 1 |
| PL J170 | Pneumonia in bacterial diseases classified elsewhere | 4848 | 2 |
| PL 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       | J18       | Bronchopneumonia                        | 481 | U     |
| PI J180      | J180      | Bronchopneumonia, unspecified           | 485 | 1     |
| PI J181      | J181      | Lobar pneumonia, unspecified            | 481 | 1     |
| PI J182      | J182      | Bronchopneumonia                        | 514 | 1     |
| PI J188      | J188      | Bronchopneumonia                        | 486 | 1     |
| PI J189      | J189      | Pneumonia, unspecified                  | 486 | 1     |
| PI J200      | J200      | Acute bronchitis                        | 4660| U     |
| PI J201      | J201      | Acute bronchitis                        | 4660| 1     |
| PI J202      | J202      | Acute bronchitis                        | 4660| 1     |
| PI J203      | J203      | Acute bronchitis                        | 4660| 1     |
| PI J204      | J204      | Acute bronchitis                        | 4660| 1     |
| PI J205      | J205      | Acute bronchitis                        | 4660| 1     |
| PI J206      | J206      | Acute bronchitis                        | 4660| 1     |
| PI J207      | J207      | Acute bronchitis                        | 4660| 1     |
| PI J310      | J310      | Chronic rhinitis                        | 4720| 1     |
| PI J312      | J312      | Chronic pharyngitis                      | 4721| 1     |
| PI J320      | J320      | Chronic maxillary sinusitis             | 4730| 1     |
| PI J322      | J322      | Chronic ethmoidal sinusitis             | 4732| 1     |
| PI J329      | J329      | Chronic sinusitis, unspecified           | 4739| 1     |
| PI J47       | J47       | Bronchiectasis                          | 494 | 1     |
| PI R05       | 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       | J09       | Influenza due to certain identified influenza virus | 4878 | 1   |
| RI J100      | J100      | Influenza with pneumonia, other influenza virus identified | 4870 | 1   |
| RI J101      | J101      | Influenza with other respiratory manifestations | 4871 | 1   |
| RI J108      | 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 | 789 1 |
| SI L00    | Staphylococcal scalded skin syndrome | 69381 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 specific 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 | Other specified viral infections characterized by | 7889 | 2 |
| SVNOS | B088 | Unspecified viral infection characterized by skin | 579 | 2 |
| SVNOS | B09 | Adenovirus infection, unspecified site | 790 | 1 |
| SVNOS | B340 | Enterovirus infection, unspecified site | 7889 | 2 |
| SVNOS | B341 | Non-viral infections of unspecified site | 7989 | 1 |
| SVNOS | B348 | Viral infection, unspecified | 7999 | 2 |
| SVNOS | B970 | Adenovirus as the cause of disease | 790 | 1 |
| SVNOS | B971 | Enterovirus as the cause of disease | 7989 | 2 |
| SVNOS | B972 | Coronavirus as the cause of disease | 7989 | 2 |
| SVNOS | B974 | Respiratory syncytial virus as the cause of disease | 796 | 1 |
| SVNOS | B9780 | Parainfluenza virus as the cause of disease | 7989 | 2 |
| SVNOS | B9788 | Other viral agents as the cause of disease classified | 7989 | 1 |
| Miscellaneous | MIS | Anthrax sepsis | 223 | 1 |
| MIS | A227 | Disseminated mycobacterium avium-intracellulare | 312 | 1 |
| MIS | A312 | Mycobacterial infection, unspecified | 319 | 1 |
| MIS | A319 | Mycobacterial infection, unspecified | 319 | 1 |
| MIS | A319 | Mycobacterial infection, unspecified | 319 | 1 |
| MIS | A398 | Parvovirus B19 infection | 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 vs Q1 | 2.21 | 0.79, 6.17 | .13 |
| | Q2 vs Q1 | 1.16 | 0.38, 3.54 | .79 |
| | Q3 vs Q1 | 1.64 | 0.53, 5.08 | .39 |
| | Q4 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 — | 1.00 | 1.00, 1.00 | .46 |
| Readmitted in year 1 No vs yes | 1.12 | 0.46, 2.75 | .60 |
| Cesarean section Yes vs no | 0.48 | 0.19, 1.21 | .12 |
| Maternal IBD Yes vs no | 9.22 | 1.80, 47.32 | .01 |

### 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 vs Q1 | 1.63 | 0.49, 5.41 | .42 |
| Q3 vs Q1 | 1.97 | 0.58, 6.66 | .28 |
| Q4 vs Q1 | 1.97 | 0.58, 6.62 | .28 |
| 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 — | 1.00 | 1.00, 1.00 | .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 vs Q1   | 1.26        | 0.87, 1.84                | .22     |
|                                 | Q3 vs Q1   | 0.89        | 0.59, 1.35                | .59     |
|                                 | Q4 vs Q1   | 1.36        | 0.92, 2.01                | .12     |
|                                 | 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 vs Q1   | 1.77        | 1.11, 2.82                | .02     |
|                                 | Q3 vs Q1   | 1.47        | 0.90, 2.38                | .12     |
|                                 | Q4 vs Q1   | 1.38        | 0.84, 2.27                | .19     |
|                                 | 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 infection 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.