I. Introduction

A. Nature of the research problem. Pediatric inflammatory bowel disease (IBD) is a chronic illness that affects as many as 100,000 children and adolescents in the United States. IBD includes Crohn’s disease (CD), characterized by inflammatory processes occurring anywhere in the luminal gastrointestinal tract, and ulcerative colitis (UC), where the colon alone is affected. Environmental factors acting upon the luminal bacteria including infectious agents, breast milk, and cigarette smoke exposure are of particular interest. The strongest predictor of IBD is a positive family history. However, the concordance rate for monozygotic twins is only 37% for CD and 10% for UC suggesting an environmental etiology combined with a familial predisposition.

B. Purpose, scope, and methods of the investigation. The purpose of the study was to identify prenatal and early life risk factors for pediatric onset IBD, with an emphasis on birth characteristics, infections and cigarette smoke exposure.

We conducted a population-based, matched, case control study within the Kaiser Permanente Northern California membership to identify prenatal and early life risk factors for pediatric-onset IBD, with an emphasis on birth characteristics, infections and cigarette smoke exposure. We identified a large, representative cohort of 501 incident pediatric IBD cases receiving care at Kaiser Permanente since 1996. We utilized information from the computerized medical history to identify birth characteristics, infections and active cigarette smoke during the prenatal period and childhood before the onset of IBD. Conditional logistic regression was used.

C. Nature of the findings. Infections and cigarette smoking play roles in the development of pediatric-onset IBD. No specific infection was identified to play a major role. Timing of the infection and initiation of cigarette smoking were important. No birth characteristic was strongly associated with IBD. Children with IBD were more likely to have mothers with IBD.

Future studies of risk factors for pediatric-onset IBD should consider the timing of infection and cigarette smoking initiation in addition to the presence or absence of the exposures. Infections and cigarette smoking initiation may play a role in the development of IBD. These exposures may also serve as markers of symptoms related to undiagnosed IBD.

II. Review of the Literature

IBD includes Crohn’s disease (CD), ulcerative colitis (UC) and indeterminate colitis (IND). CD and UC are considered unique clinical entities. CD is characterized by transmural inflammation occurring anywhere in the luminal gastrointestinal tract although it predominately affects the small and large intestines. In the United States, the majority of patients have UC (60%) and CD (40%), with estimates for IND varying by region, comprising no more than 10% of patients. Complications of CD include fistulae and strictures that frequently lead to surgery. UC’s inflammation is generally limited to the mucosal surface of the large intestine, although backwash ileitis can occur with active disease in the cecum.

The incidence of IBD increased during the last century. The cause of the increased incidence is unknown. Genetic risk factors have been identified for IBD, but it is unlikely that genes alone can explain the rapid increase in incidence. Environmental factors that affect the development and response of the immune system or the intestinal microbial flora have been hypothesized to alter the risk of IBD.
Numerous studies have examined the relationship between environmental factors and risk of IBD, but inconsistent findings were found. The inconsistent findings are possibly due to temporal ambiguity in cross-sectional and retrospective studies. However, several of studies did use prospectively collected information and new findings suggest that environmental factors may play a role in the development of IBD, especially for infections and the medications used to treat them. However, there are also limitations to these studies.

The previous prospective studies cover decades of birth cohorts and disease diagnosis. Overall, 11 prospective studies include births between 1907-2005 (Ekbom 1990; Montgomery 1999; Montgomery 2002; Card 2004; Aspberg 2006; Hildebrand 2008; Klement 2008; Porter 2008; Bengtson 2009; Gradel 2009; Ponsonby 2009). Many changes in prenatal and neonatal care, treatment options for infections and IBD, diagnostics for IBD and smoking patterns have occurred between 1907 and 2005. Studies that limit subjects’ births to time periods when exposure measurements are similar, treatments for infections are similar and IBD diagnostics are similar will help to ensure that the relationship between exposures and outcomes are the result of the exposures themselves and not the changes in exposure measurements or medical improvements with time.

Several prospective studies limited subjects to people born in the 1970s or later (Montgomery 1999; Aspberg 2006; Hildebrand 2008; Klement 2008; Ponsonby 2009). These studies collectively include 2,660 IBD patients during decades with relatively homogenous likelihoods of birth exposures, treatments for infections, diagnostics and treatments for IBD. However, these studies took place in Europe (2 in Sweden, 1 in Britain), Australia and Israel. None took place in North America. Despite all of these regions being considered Westernized, there are differences in prenatal and neonatal care (Thompson 2002), rates of infections (Diekema 2001) and smoking prevalence (Jha 2002) between each of these areas compared to each other and compared to North America.

The prospective studies that limited the year of birth for study subjects also limited the age of diagnosis for IBD. Exposures occurring early in life may affect risk of IBD differently for a person diagnosed during childhood versus those diagnosed during adulthood. Environmental exposures during childhood theoretically could have a greater effect on childhood onset disease as the time between exposure and disease onset is shorter than for adult onset disease.

A limitation of previous prospective studies of childhood and early adulthood onset disease was the inability to measure exposures occurring shortly after birth and during childhood. No study reported on infectious or antibiotic exposures occurring during both time periods. No study limited to childhood and early adulthood-onset of disease excluded time periods just before diagnosis in their exposure assessment. Exposures measured just prior to the IBD diagnosis may be influenced by subclinical disease and not reflect risk factors.

III. Study Design and Methods

A. Study design. The overarching goal of the current study was to study environmental exposures related to pediatric-onset IBD while addressing some of the limitations of the previous studies by examining children born during the 1980s or later and diagnosed with IBD through the same health care system. In this nested case-control study, controls also actively received health care through the same system. The collection of birth characteristic exposures, treatments for infections and diagnostics for IBD should be generally homogenous for the study population as all information was captured using the same standardized system. The study included prospectively collected data on children in the modern era. This information was used to look at
birth characteristic differences between children diagnosed with IBD and those not diagnosed with IBD as children.

The specific aims of the study were to examine the relationships between Aim 1) birth characteristics, Aim 2) infections and Aim 3) active cigarette smoking with risk of pediatric onset IBD. Pediatric onset IBD is defined as IBD diagnosed between birth and age 17 while a member of Kaiser Permanente Northern California between 1996 and 2006.

B. Population studied. Kaiser Permanente Northern California is a prepaid, integrated system providing both health insurance and health care to 30% of residents of the San Francisco Bay Area. During 1996-2006 there were three million members per year. Extensive computerized information has been available since 1996, with hospitalization information dating back as far as 1984. The membership broadly represents the underlying population with regard to race and socioeconomic status (Gordon 2006). All children (aged 17 and under) who were members for at least one consecutive year between 1996 and 2006 were eligible for the study.

C. Sample selection. Cases. Cases were initially identified by International Classification of Diseases, Clinical Modifications 9 (ICD-9-CM) codes for IBD (555 for ulcerative colitis [UC] and 556 for Crohn’s disease [CD]) and confirmed by medical record review by the pediatric gastroenterologists of Kaiser Permanente Northern California (Abramson 2010). In addition to confirmed incident IBD, all cases had to have at least one utilization in the two years prior to their diagnosis date to ensure that they were actively using their Kaiser Permanente membership and could be diagnosed at a Kaiser Permanente facility where exposure information could be obtained (one child excluded). We further excluded 21 children who were diagnosed within one year of their first membership, to exclude children who joined the health plan because of symptoms related to IBD.

Controls. Up to 20 controls were matched to each case on age (within 30 days). The matched case’s diagnosis date was defined as the index date for the control. We required the control to be a health plan member at two time points 1) on or before the matched case’s first membership date and 2) on the index date. Control selection used incidence density sampling (Breslow & Day 1980). Similar to cases, controls were required to have at least one utilization within two years prior to the index date and were required to be a member for at least one year prior to the index date.

Aim specific study population requirements. In addition to these broad requirements, each aim had additional requirements. For Aim 1, Birth characteristics and risk of pediatric onset IBD, we restricted the study population to children born at a Kaiser facility. For Aim 2, Infections and risk of pediatric onset IBD, we made no additional requirements. For Aim 3, Active cigarette smoking and risk of pediatric onset IBD, we included only children who were members at Kaiser Permanente at ages 12 or older. Twelve years was chosen because pediatricians first began asking questions about active smoking at age 12. Because we wished to observe at least one year of membership prior to diagnosis in order to collect cigarette smoking information, cases (and their matched controls) were then restricted to those diagnosed ages 13 or older.

D. Exposure assessment. All available information was obtained up to the index date from the outpatient, inpatient or demographic data sources to create the exposure variables of interest according to the aim of the study.

For each aim, exposure information was collected differently. For Aim 1, Birth characteristics and risk of pediatric onset IBD, we obtained birth characteristic information from the inpatient hospitalization associated with birth only. We obtained information from the
child’s and mother’s records. We were able to link the mother and child as each child’s inpatient record at birth includes the mother’s medical record number. For **Aim 2, Infections and risk of pediatric onset IBD**, we obtained infection information from the inpatient records only. Additionally, the infection had to be coded as the principal diagnosis for the hospitalization. To contribute to the analysis in any exposure period, we required the subject to have 1) membership and 2) the index date needed to occur during or later than the exposure period. For **Aim 3, Active cigarette smoking and risk of pediatric onset IBD**, we used inpatient and outpatient diagnostic data to obtain cigarette smoke exposure information. To ensure the provider had an opportunity to assess smoking status during an inpatient or outpatient visit, we restricted the analysis on the basis of membership and utilization during each exposure period. To contribute to the analysis in any exposure period, we required the subject to have 1) membership and 2) utilization during that period as well as 3) the index date needed to occur during or later than the exposure period.

**E. Statistical techniques employed.** Conditional logistic regression accounting for the matching factors age and duration of membership was used for all analyses. Sex and race were differentially distributed between cases and controls. Sex and non-Hispanic white versus not (due to sample size limitations) were also adjusted for in all analyses. The fully adjusted model included these factors as well as the categorical characteristics of interest, as each characteristic may confound the others. CD and UC were examined separately in the multivariable adjusted model. For categorical variables, the group with the largest prevalence of patients was used as the reference group.

**IV. Detailed Findings**

**Aim 1. Birth characteristics and risk of pediatric onset IBD.** For this aim, characteristics of interest included: birth weight, gestational age, Apgar score, length of hospitalization, gravidity, parity, breast and formula feeding, cigarette smoke exposure, multiple birth, cesarean section, jaundice or hemolytic disorder, respiratory distress during birth, maternal hypertensive disorders, maternal diabetes, maternal overweight, assisted reproductive technology use, known or suspected fetal abnormality affecting management of the mother, placental or amniotic problems, maternal infection and maternal IBD.

Only two factors had a relationship with pediatric-onset IBD with a statistically significant confidence interval that did not contain the null value of 1. IBD cases were more likely to be white than controls (fully adjusted IBD OR 2.3, 95% CI 1.6 – 3.2; CD OR 3.1; UC OR 2.6) and more likely to have mothers with IBD than controls (fully adjusted IBD OR 5.1, 95% CI 2.0 – 13.2; CD OR 6.0; UC OR 6.4). Several factors were associated with pediatric-onset IBD in the fully adjusted model (OR≥1.5 or OR≤0.7) but the results were not precise (the CI contained 1): gestational age ≤36 weeks versus ≥37 weeks (OR 0.6, 95% CI 0.3 – 1.5), birth weight <2,500g versus ≥2,500g (OR 1.6, 95% CI 0.7 – 3.8), mother’s age <20 years versus 20 – 34 years (OR 2.0, 95% CI 0.8 – 4.8) and hypertensive disorder during pregnancy (OR 1.7, 95% CI 1.0 – 2.8).

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

**Aim 2. Infections and risk of pediatric onset IBD.** First, we examined the relationship between any hospitalization with a principle diagnosis code (ICD-9-CM) recorded as infection with subsequent risk of IBD. Second, we *a priori* chose to examine the codes used to define any
infection by type of infection. Infections were coded as: 001-139 (infectious and parasitic diseases); 380.1 (infective otitis externa); 381.0, 381.1, 381.2, 381.3, 381.4 and 382 (acute and chronic otitis media); 460-466 (acute respiratory infections); 480-488, 770.0, 770.18 (pneumonia and influenza); 567 (peritonitis and retroperitoneal infections); 590 (infection of kidney); 670 (major puerperal infection); 680-686 (infections of skin and subcutaneous tissue); 771 (infections specific to the perinatal period).

In Analysis 1, we examined the relationship between any infection occurring after birth to the index date. In Analysis 2, because the IBD disease process may be in effect in the intestines before the diagnosis of disease is made and infections occurring after the disease process is in effect cannot alter the risk of disease, i.e., to rule out reverse causation, we conducted analyses after excluding infection information in the one year prior to the index date; effectively reclassifying the date of IBD as one year prior to diagnosis. To test the robustness of this classification, we also looked at the relationship between infections up to two years prior to the index date. In Analysis 3, because infections occurring immediately prior to diagnosis may reflect undiagnosed IBD or a close temporal relationship between infection and disease, we looked at infections occurring in the year prior to the index date and two years prior to the index date.

Analysis 1 compared the risk of IBD with any hospitalization for infection after birth. Seventeen percent of controls had ever been hospitalized for an infection listed as the principal diagnosis code compared to 26% of CD, 16% of UC and 16% of IND cases. The odds of hospitalization were significantly elevated for CD (OR 1.6; 95% CI 1.2 – 2.2) compared to controls but there was no elevation for UC (OR 0.8; 95% CI 0.6 – 1.1) or IND (OR 0.9; 95% CI 0.4 – 2.2).

In Analysis 2, when the index date was reclassified as one or two years prior to the diagnosis date and infections were ascertained until that point, there was no difference in hospitalizations between cases and controls although a trend of a decreased risk of IBD with infection was observed for both exclusion periods. When the two years prior to the diagnosis were excluded, the OR for was less than one for CD (OR 0.9; 95% CI 0.6 – 1.3), UC (OR 0.7; 95% CI 0.5 – 1.0) and IND (OR 0.4; 95% CI 0.1 – 1.4) compared to controls.

Analysis 3 aimed to look at risk of IBD with infections occurring only in the period one or two years prior to diagnosis. The odds of IBD were increased in those hospitalized for infection compared to those with no hospitalizations when infections were examined in the one year and two years prior to the index date. The relationship between infection during the year prior to diagnosis and IBD was strongest for CD (OR 11.9; 95% CI 6.9 – 20.8) followed by IND (OR 8.0; 95% CI 2.0 – 31.0) and then UC (OR 3.1; 95% CI 1.5 – 6.1). Infections that occurred during the two years prior to the index date showed an elevated risk, but the relationship was attenuated compared to the infections occurring exclusively in the year prior to diagnosis for CD and UC. For IND, 3 of 37 children were hospitalized in the year prior to diagnosis compared to 4 of 37 hospitalized within two years prior, thus the OR for two years prior was greater than the estimate for one year prior.

When we examined risk of IBD by type of infection, too few children were observed for infective otitis externa (0 children), influenza (1 case and 5 controls), major puerperal infection (0 cases, 20 controls) and infections specific to the perinatal period (1 case and 18 controls) to compute meaningful effect estimates. Cases were more likely to have experienced hospitalization for gastrointestinal infections compared to controls (OR 1.8; 95% CI 1.0 – 3.2), but the relationship was only elevated during the year before diagnosis (OR 15.1; 95% CI 5.0 –
There was no association between gastrointestinal infections and IBD after the year prior to diagnosis was excluded (OR 1.0; 95% CI 0.5 – 2.1). There did not appear to be a relationship between any other infection and IBD diagnosis overall or when the year prior to diagnosis was excluded. Elevated ORs were observed for all examined types of infections during the year prior to diagnosis.

**Aim 3. Active cigarette smoking and risk of pediatric onset IBD.** All available information was obtained up to the index date from the outpatient, inpatient and demographic data sources to create the exposure variable of interest, cigarette smoking by the child. Four different exposure periods were defined: age 12 to the index date (Analysis 1); age 12 to one year before the index date (Analysis 2); and age 12 to 2 years before the index date (Analysis 3). Analyses 2 and 3 were performed to rule out the possibility of reverse causation that could occur if undiagnosed, symptomatic IBD increased the incidence of smoking. Finally, we examined smoking status only in the one year period prior to diagnosis (Analysis 4). Figure 1 depicts the exposure periods for Analyses 1 – 4. To ensure the provider had an opportunity to assess smoking status during an inpatient or outpatient visit, we restricted the analysis on the basis of membership and utilization during each exposure period. To contribute to the analysis in any exposure period, we required the subject to have 1) membership, 2) utilization during that period, and 3) the index date needed to occur during or later than the exposure period.

For each period, if utilization occurred but smoking was not recorded, the subject was considered a non-smoker. In a sensitivity analysis, we restricted the analysis to children with codes for “Active Smoker” or “Never Smoker” from the inpatient or outpatient data sources (181 cases [60%] and 1,943 controls [34%]), excluding those patients with no record indicating their smoking or nonsmoking status.

The median age for the first active smoking code occurred at age 15.0 for cases compared to 14.7 years of age for controls. Cases had a higher prevalence of smoking overall compared to controls (Analysis 1: 28% versus 7%; OR 2.1; 95% confidence interval [CI] 1.4 – 3.0) driven by smoking occurring during the year prior the index date (Analysis 4: 25% versus 4%; OR 2.8; 95% CI 1.8 – 4.4). The OR was increased for both CD (3.6; 95% CI 1.9 – 6.8) and UC (2.1; 95% CI 1.0 – 4.2) during the year prior to the index date. When the year prior to the index date was excluded in Analysis 2, the prevalence of smoking was similar (5.4% versus 4.4% [OR 1.1; 95% CI 0.6 – 1.9]) with little difference between CD (OR 1.3; 95% CI 0.6 – 2.7) and UC (OR 1.0; 95% CI 0.4 – 2.5). When the two years prior to the index date were excluded in Analysis 3, CD cases had a greater smoking prevalence (4.3%) than UC cases (1.6%) and controls (2.9%). The Analysis 3 OR was similar for CD compared to controls (1.1; 95% CI 0.4 – 3.0) and lower for UC compared to controls (0.6; 95% CI 0.1 – 2.6) but neither was statistically significant.

In the sensitivity analysis, when the analysis was restricted to those who had a reported smoking status of ever/never during the time period in Analysis 1, we observed that 47.5% of cases were smokers compared to 19.9% of controls (OR 1.4; 95% CI 0.9 – 2.3; Table 3). The OR was similar in direction to the main analysis that imputed non-smoking status for those with no information as in the paragraph above (OR 1.4 versus 2.0), but included only 60% of the case and 34% of the control populations and higher percentages of smokers.

**V. Discussion and Interpretation of Findings**

**A. Conclusions to be drawn from findings.** This study examined the relationships between birth characteristics, infections and active cigarette smoking with risk of pediatric onset IBD in members of Kaiser Permanente Northern California diagnosed between 1996 and 2006.
**Birth characteristics.** We found no birth characteristic strongly associated with IBD. This lack of association is similar to the majority of other studies of birth characteristics and IBD where no single factor was consistently observed to increase IBD risk. We did confirm the strong role of family history of IBD with the observation that a child with IBD was four times more likely to have a mother with IBD compared to controls.

**Infections.** No single infection was associated with IBD. Infections were six times more common in IBD patients compared to controls in the year prior to diagnosis, a finding observed for all types of infections examined. When the year prior to diagnosis was excluded, there was no relationship between any individual infection or infections overall. Children diagnosed before age 5 did have an elevated odds of IBD even when the year prior to diagnosis was excluded, although the relationship was not statistically significant. However, it is unclear if these infections are promoting the IBD disease process or they serve as markers for undiagnosed disease.

**Cigarette Smoking.** Children with CD and UC were more likely to smoke in the years prior to diagnosis compared to controls. When the two years prior to diagnosis were excluded, there was no relationship observed between smoking and CD. Children with UC were 30% less likely to smoke compared to controls when the two years prior to diagnosis were excluded, although this finding was not statistically significant. In adults, UC patients are less likely to smoke compared to the general population. However, CD adults are more likely to smoke. We observed that both CD and UC children were more likely to smoke immediately prior to disease diagnosis.

**B. Explanation of study strengths and limitations.** The strengths of this study include 1) the timing of the data collection prior to disease diagnosis; 2) standardized collection as part of a clinical record; 3) cases and controls representing an identifiable population broadly representative of the source population; 4) large number of cases to perform analyses by time periods of interest. First, all data was collected prior to disease diagnosis. Because birth characteristics, infections and smoking were recorded independent of the future IBD status, any missing or miscoded data will result in the reported effect estimates being artificially closer to the null value than the true value. Second, the electronic record is part of clinical record and not used for physician reimbursement that could increase the prevalence of related disease codes with higher reimbursement. Third, cases and controls are generally representative of the Northern California population served by the health plan (Gordon 2006). Cases thus represent a broad spectrum of severity at diagnosis as experienced in the population at large. The controls also come from the same health plan, thus if they had IBD, they would likely have been diagnosed at a Kaiser Permanente facility. Fourth, a large number of cases were observed allowing us to look at infections and smoking occurring during multiple time periods and a range of ages at IBD diagnosis.

With respect to limitations for **Aim 1**, we were unable to ensure our model adjusted for all potential confounders because of missing information. Because we saw a potentially important association between hypertensive disorders during pregnancy and pediatric-onset IBD, we would have liked to have adjusted for maternal overweight or obesity. However, BMI information was not routinely collected during the study period and we observed fewer codes for overweight and obesity than expected. Less than 1% of control mothers of children born 1984 – 1996 and 5.7% of control mothers of children born 1997 – 2006 had codes for overweight.

The major limitation of **Aim 2** was the restriction to severe infections requiring hospitalization, excluding infections treated in an outpatient setting or managed without medical
advice. We cannot know what factors may encourage or prevent parents from seeking outpatient care for a child with an infection even when they have health care. However, hospitalization for infection represents a severe infection that should, hypothetically, be less affected by care-seeking behavior. Also, more severe infections could affect the immune system and bacterial flora more than an infection treated as an outpatient and thus could affect the risk of disease more strongly than a less severe infection. Alternatively, if less severe infections that were treated in the outpatient setting or not treated at all affected the risk of IBD, we have under-reported the true effect of infection independent of future IBD status and our results are closer to the null value than in reality.

The major limitation of Aim 3 was the lack of information on passive cigarette smoke exposure. Although passive smoke exposure during childhood has not been associated with IBD diagnosis at any age (Jones 2008), we had hoped to examine the relationship between passive smoke exposure and teenage-onset IBD and adjust for passive smoke exposure when examining active smoking as a risk factor. Unfortunately, passive smoking was not estimable because only 2% of children had a recorded diagnostic code for passive smoking exposure compared to 41% reported among American teenagers in the Global Youth Tobacco Surveillance study (Warren 2008).

C. Comparison with findings of other studies. For Aim 1, birth characteristics, previous studies found no consistent differences in birth characteristics and IBD, similar to the present study. The most prevalent infections observed in Aim 2 of this study have also been associated with IBD risk in other studies. A Swedish cohort found that children with hospitalizations for pneumonia or otitis media under age 5 were more likely to later develop CD during childhood or young adulthood (Hildebrand 2008). In an attempt to confirm the Swedish cohort’s result, we computed the OR for all ages at diagnosis for pneumonia or otitis media under age 5 (Pneumonia OR 0.9, 0.5 – 1.4; Otitis media OR 0.9; 0.4 – 2.0). One plausible explanation is a difference in treatment strategies between the providers in Sweden and at Kaiser Permanente Northern California. Hildebrand was using infections as a marker of antibiotic use; antibiotic use differences between the regions could explain the disparate findings. Although we did not find the same trend as the Swedish group, we did find that there was something different about infections in very young children. We observed that children diagnosed under age 5 were more likely to have had any infection prior to diagnosis, even when the year prior to diagnosis was excluded.

Similar to our study, a Danish study found that IBD was more likely after infection. Danish citizens with laboratory confirmed Salmonella or Campylobacter gastroenteritis were more likely to later develop IBD, especially in the year after infection, although when the year prior to diagnosis was excluded the increased risk of IBD remained two times greater than matched controls (OR 1.9; 95% CI 1.4 – 2.6; Gradel 2009). A study within the United States Department of Defense Medical Surveillance System also found an association between infectious gastroenteritis as measured by ICD-9 codes during military service even when the six months prior to diagnosis were excluded (OR 1.4; 95% CI 1.2 – 1.7; Porter 2008). The present study and these studies of infectious gastroenteritis differ in that the increased risk of IBD persisted in the Danish study even when the year prior to diagnosis was excluded as well as in the United States military study when 6 months prior to diagnosis were excluded, whereas we saw no association between infections and IBD after excluding the year prior to diagnosis. Looking specifically at these pathogens, we saw only 6 Campylobacter and 19 Salmonella infections, all of which occurred in controls. This study was of pediatric onset cases, whereas
the Danish and United States military studies included adult-onset disease. It is possible that infectious gastroenteritis could play a different role in childhood versus adult onset disease.

A meta-analysis has been performed to examine the relationship between active smoking and adult-onset IBD, but not pediatric-onset IBD, \textit{Aim 3}. The meta-analysis found a protective association of smoking with UC (OR 0.58) and harmful association with CD (OR 1.75; Mahid 2006).

This paper expanded upon the previous findings by reporting active smoking by teenagers prior to their diagnosis of disease. In addition, rather than looking at smoking status at diagnosis or at any point prior to diagnosis, time periods were examined within the one year before diagnosis (when the disease may have been present) and excluding one to two years before diagnosis (when the disease may not have been present and when smoking may have played a role in initiating, or dampening, disease activity).

When the year prior to diagnosis was considered, smoking was increased in CD and UC patients compared to controls. This finding could reflect the role smoking plays in initiating or prompting disease in the time period leading up to clinical diagnosis or smoking could be a response to the already existent, though undiagnosed disease. The current study cannot separate the effect of smoking as an initiator versus a response to disease during the time period immediately prior to disease diagnosis.

However, when the two years prior to diagnosis were excluded, the active smoking results for children in this study were similar in trend (though not statistical significance) to active smoking in the adult literature for UC where smoking was recorded at or prior to diagnosis. Excluding the two years prior to diagnosis eliminated the assessment of smoking exposure during a time period when the IBD disease process may have been present. In our population, symptoms were identified in the medical record a median of 44 days prior to diagnosis (range 0 days – 3.5 years). Excluding two years is thus more than sufficient to exclude the period when symptoms were already present for the majority of cases.

It is plausible that active smoking could play no role in disease initiation in pediatric CD cases and protect against disease in UC cases. However, the current results are also consistent with both a protective and harmful association between smoking and CD and UC development as observed by the wide confidence intervals.

\textit{D.Possible application of findings to actual MCH health care delivery situations.} Cigarette smoking is prevalent in teenagers with IBD prior to diagnosis. IBD may be another smoking-related disease, providing yet further impetus to minimize smoking among young people.

\textit{E. Policy implications.} There are no policy implications of this report.

\textit{F. Suggestions for further research.} These findings have implications for research surrounding each of the factors studied. Future studies in infections and cigarette smoking have relevance to the epidemiologist, clinical researcher and bench scientist.

\textit{Birth characteristics.} The future study of birth characteristics and IBD does not seem warranted for most birth characteristics. Over 30 studies have examined the relationship between birth characteristics and IBD and no factor previously studied seems to play a role. We did find an association between IBD and a novel factor. We found that hypertensive disorders during pregnancy were associated with a 70\% increased odds of IBD, although the finding was of borderline statistical significance (OR 1.7, 95\% CI 1.0 – 2.8). Because we studied hypertensive disorders during pregnancy and risk of IBD for the first time, we recommend that future studies of birth characteristics and IBD risk study this factor. We also recommend
accounting for maternal weight, which we were not able to study, in addition to gestational diabetes and other maternal factors in future analyses.

Infections. Determining if infections that occur immediately prior to disease diagnosis are due to undiagnosed IBD or have a causal effect is vital. If infection plays a causal role in disease development by affecting the immune system, microbiome or virome and the mechanism can be identified, this finding could serve as a target for interventions to prevent disease as well as to create novel pharmacologic agents. If the infections affect the gut microbiome, it is possible that bacteria could be consumed to fix alterations in the gut microbiome after infection to decrease the risk of IBD. Novel therapeutic agents could be developed to target bacteria in the gut after infection or to alter the activation or response of key immunologic players identified as treatments for disease. Studying the treatments of infections prior to diagnosis and their relationship to IBD is also warranted.

Cigarette smoking. The novel finding that cigarette smoking was more prevalent in cases compared to controls prior to disease onset should be confirmed in larger pediatric populations. The potentially protective effect of smoking on UC when the period prior to diagnosis was excluded should also be examined critically to help elucidate the mechanism by which smoking protects against UC onset. If cigarette smoking is prevalent in IBD children prior to diagnosis, this could be useful for physicians. For example, a child who smokes could be asked about gastrointestinal symptoms. Although most children who smoke are unlikely to develop IBD, such a question could be a cost-effective measure to decrease the time to IBD diagnosis. If cigarette smoking is a response to undiagnosed IBD, it is possible that children may be suffering from psychological distress as well. Psychological effects of IBD should be examined in children.

VI. List of products

A. In preparation.  

Infections and Risk of Pediatric Onset Inflammatory Bowel Disease. Anticipated submission, winter 2010 or spring 2011.

Cigarette Smoking and Teenage Onset Inflammatory Bowel Disease. Anticipated submission to Pediatrics, winter 2010.

B. Published dissertation.  
Environmental factors and risk of pediatric onset inflammatory bowel disease

C. Grants. Future grant in preparation to study medications to treat infections and risk of IBD in children.