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# The Influence of Fine Particulate Matter on Inflammatory Bowel Disease In South Carolina: An Ecological Analysis

Joshua Eric Sellner
*University of South Carolina*

The Influence of Fine Particulate Matter on Inflammatory Bowel Disease
In South Carolina: An Ecological Analysis

by

Joshua Eric Sellner

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Accepted by:

Anwar T. Merchant, Director of Thesis

Bo Cai, Reader

Jan Eberth, Reader

Lacy Ford, Senior Vice Provost and Dean of Graduate Studies

# ABSTRACT

*Background.*   The Inflammatory Bowel Diseases, including both Ulcerative Colitis and Crohn's Disease, are lifelong disorders of the Gastrointestinal tract. In recent years, both conditions have become much more prevalent and recognized as major public health issues. Environmental factors have become the focus of recent research around the cause of these diseases. Although shown to have detrimental effects on diseases similar to that of the Inflammatory Bowel Diseases, fine particulate matter's role in these diseases has not been adequately investigated.

*Aim.*          The purpose of this study was to test the relation of fine particulate matter with hospitalizations attributable to Ulcerative Colitis or Crohn's Disease over a seven-year period in South Carolina.

*Methods.*      Average annual county-level fine particulate matter levels were compared to the annual county-level counts of in-patient hospitalizations attributable to Ulcerative Colitis and Crohn's Disease from the years 2005 through 2011. A generalized linear mixed effects model was developed for both diseases, and incorporated both spatial and temporal components.

*Results.*      Both Ulcerative Colitis and Crohn's Disease hospitalizations significantly increased across the study years, even after adjusting for differences in population sizes; whereas fine particulate matter significantly decreased across the study

years. Overall, fine particulate matter was not found to be a significant predictor
of county-level annual hospitalizations attributable to Ulcerative Colitis or
Crohn's Disease across the study period.

*Conclusions.*   These findings did not support the tested hypothesis that fine particulate
matter would be a significant predictor of Ulcerative Colitis or Crohn's Disease in
South Carolina from the years 2005 through 2011.

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# CHAPTER 1

## INTRODUCTION

Ulcerative Colitis [UC] and Crohn's Disease [CD] are both idiopathic conditions belonging to the Inflammatory Bowel Disease [IBD] family. They are immunologically mediated conditions of the gastrointestinal [GI] tract affecting both males and females of all ages and ethnicities. Most patients are diagnosed within the first three generations of life, and once diagnosed, they experience lifelong intermittently-recurring periods of active symptoms (Loftus & Sandborn, 2002). Although few individuals die from UC or CD, up to 15% of those diagnosed with these conditions die from colorectal cancer (Munkholm, 2012). While the burden of these life-long conditions continues to rise (Molodecky et al., 2012), we still know little as to what causes these diseases.

In 1859 UC became the first recognized disease in the IBD family (Wilks, 1859). Not for over 60 years, in 1932, was CD recognized as a separate condition (Crohn, Ginzburg, & Oppemjeo, 1984). Both conditions are characterized by similar symptoms: reoccurring periods of inflammation, bloody diarrhea and abdominal pain. The distinction between these diseases lies in their locations; while UC is limited to the colon and rectum, CD can be found anywhere along the GI tract (Baumgart, 2008).

Cases of UC and CD, until recently, were largely limited to those living in Europe and North America. For UC, past research has demonstrated a prevalence of 505 and 249

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per 100,000 persons in Europe and the United States [US], respectively. But for CD, the prevalence has been shown to be much more similar with Europe at 322 and the US at 319 per 100,000 persons (Molodecky et al., 2012). More recently, other developed and developing countries in Africa, Asia and Latin America have experienced increasing prevalence and incidence rates of IBD, demonstrating the shift of IBD away from a European and North American disease towards a global disease (Hou, El-Serag, & Thirumurthi, 2009).

The historic homogeneity of individuals diagnosed with UC and CD coupled with a lack of identified dietary culprits misled many prior researchers to conclude that an individual's genetic makeup was the primary causal factor for these diseases. Recent advances in genome wide association studies have demonstrated that only about 25% of IBD cases could be explained by an individual's genetic makeup alone (Abraham & Cho, 2009). These findings have redirected the attention of researchers towards environmental factors and their roles in the etiology of IBD.

Ecological studies, although unable to properly quantify individual risks, have extensively been utilized by IBD researchers due to their cost effectiveness and hypothesis generating properties. Through these studies, a variety of group level environmental factors have been identified. First, a north to south gradient has been shown with consistently more cases being found in northern latitudes than in southern ones (Armitage et al., 2004; Economou & Pappas, 2008; Kappelman et al., 2007; Khalili et al., 2012; Nerich et al., 2006). This finding has led to several etiologic hypotheses including vitamin D deficiencies, dietary factors, and the use of various indoor heating

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devices. None of these hypothesized risk factors have consistently been found to be associated with either CD or UC.

Second, areas with higher average socioeconomic statuses [SES], compared to areas with lower SES, have been associated with increased rates of IBD (Aamodt, Jahnsen, et al., 2008; Armitage et al., 2004; Blanchard, Bernstein, Wajda, & Rawsthorne, 2001; Economou & Pappas, 2008; Green, Elliott, Beaudoin, & Bernstein, 2006). This finding has led to investigations in lifestyle factors associated with those of higher SES such as increased physical activity and exercise (Bilski, Brzozowski, Mazur-Bialy, Sliwowski, & Brzozowski, 2014), hospital utilization (Kappelman et al., 2007), type of employment (Sonnenberg, 1990) and dietary factors (Geerling et al., 2000). Findings from these investigations have yielded conflicting results and have further diluted researchers understanding of these diseases.

The third environmental factor found, is an association between those with IBD and urban residency (Aamodt, Jahnsen, et al., 2008; Blanchard et al., 2001; Sonnenberg, 1990; Sonnenberg, McCarty, & Jacobsen, 1991). Even after adjusting for differences in population sizes, many more individuals diagnosed with either UC or CD have been found to live in urban, compared to rural, environments. This finding has led to investigations of water supplies (Aamodt, Bukholm, et al., 2008) and environmental pollutants (Ananthakrishnan, McGinley, Binion, & Saeian, 2011; Beamish, Osornio-Vargas, & Wine, 2011; Kaplan et al., 2010; Salim, Kaplan, & Madsen, 2014; Tornqvist et al., 2007). The research behind the association of IBD with urban residency has not been as extensively studied as those associations with SES or latitude.

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One of the biggest factors separating urban and rural environments is the population density and the resulting high concentrations of traffic related ambient air pollutants. According to the Environmental Protection Agency [EPA], particulate matter [PM] is made up of a wide variety of tiny particles such as dust, acids and metals, which have the ability to be suspended in the air. The density of PM is often measured in micrograms per cubic meter ($\mu m^3$) and is split, by its size, into course particulate matter [$PM_{10}$] or fine particulate matter [$PM_{2.5}$]. The larger of the two, $PM_{10}$, is between 2.5 and 10 microns in size, and often consists of farming and agricultural byproducts. The smaller of the two, $PM_{2.5}$, includes all particulates smaller than 2.5 microns in size and are associated with the combustion of fuels from certain industries and vehicle emissions (Laden, Neas, Dockery, & Schwartz, 2000).

The distinction between $PM_{10}$ and $PM_{2.5}$ is important because of the unique health risks associated with each. Upon inhalation, larger particles are generally captured in the trachea, nasal hairs or the mucous layer of the upper respiratory system. Clearance of $PM_{10}$ containing mucous is generally completed within 24 hours through ciliary beating, where the mucous is transported along the digestive tract and removed. The smaller particles, due to their size, can get deeper into the respiratory system, down into the lungs and even the alveoli, where no mucous transport system exists and the greatest damage is believed to take place (Calderon-Garciduenas et al., 2007). To clear $PM_{2.5}$ from the alveoli, macrophage-mediated clearance is believed to take place, which can take several months for complete clearance to occur (Moller et al., 2004).

Emerging evidence on the wide range of health effects attributable to $PM_{2.5}$ have demonstrated the importance of $PM_{2.5}$ control as a major public health issue. Beyond the

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obvious detrimental effects on the lungs (Fan et al., 2009), increased mortality due to heart and vascular diseases have also been observed following periods of elevated levels of $PM_{2.5}$ (Brook et al., 2010). Both population-based studies and animal models have begun to show links between $PM_{2.5}$ and diseases of the gastrointestinal tract (Kaplan et al., 2009; Kaplan et al., 2012; Orazzo et al., 2009; Salim, Jovel, et al., 2014; Salim, Kaplan, et al., 2014; Tornqvist et al., 2007). Interestingly, even under mounting evidence, population-based studies assessing $PM_{2.5}$ exposure and IBD are sparse.

Only two population-based studies assessing the association between elevated exposure to PM and IBD have been conducted and have yielded discordant conclusions. The aim of this study was to address gaps in the current literature surrounding $PM_{2.5}$ and IBD. Both of the previous studies were comprised of populations residing in northern latitudes; we decided to test the association among a population residing in a latitude closer to the equator, South Carolina [SC]. Although this population lacked an ongoing surveillance system to monitor cases of UC or CD, in-patient hospitalization records were utilized as the source of cases based on their availability and previously validated accuracy in diagnosing UC and CD (Thirumurthi, Chowdhury, Richardson, & Abraham, 2010). Our primary research question was if the average annual levels of $PM_{2.5}$ in SC counties were associated with emergency department in-patient hospitalizations attributable to UC or CD across the years 2005 through 2011. A secondary research question we wished to answer was if there was a statistically significant increase in in-patient emergency department hospitalizations due to UC or CD across the years 2005 through 2011 in SC.

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CHAPTER 2

LITERATURE REVIEW

Although, only two known epidemiologic studies have been conducted assessing human exposure to elevated PM as a potential risk factor for the development of IBD, there is strong evidence for the association through other scientific research studies. Other studies include mouse models assessing direct PM exposure and IBD related symptoms, and human studies assessing PM exposure with inflammatory biomarkers and nonspecific abdominal pain.

A mouse-model was conducted in Alberta, Canada assessing exposure to PM during the neonatal period of life and altered colitis later in life among genetically susceptible mice (Salim, Jovel, et al., 2014). Pregnant Interleukin $10^{-/-}$ mice were first randomized into a control or study group. The mice in the study group were fed a diet mixed with $PM_{10}$ whereas the mice in the control group were fed a normal diet. The pups of the pregnant mice were then studied at 10, 14, and 20 weeks of age. Each study point consisted of approximately six control and six study mice whose intestines were removed and studied. Although the two groups experienced similar disease outcomes, it was demonstrated that the $PM_{10}$ fed mice experienced an earlier onset of colitis than the mice fed a normal diet. Additionally, those mice fed a $PM_{10}$ diet were shown to have decreased abilities to cope with intestinal injuries later in life compared to the mice fed a normal

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diet. Systemic inflammatory effects of PM exposure among humans was demonstrated in a study published in 2007 (Tornqvist et al., 2007). Researchers utilized a randomized, double-blind, crossover trial with 15 healthy males between the ages of 18 and 38 years. At two study separate study cycles, participants were exposed to either filtered air or diesel exhaust in a monitored chamber for a duration of one hour. During both cycles, participants were asked to perform bouts of moderate exercise followed by bouts of rest. Inflammatory markers were assessed 24 hours after each study cycle. To control for the possibility of a carryover of effects, the researchers included a washout period of at least two weeks between study cycles. The researchers found statistically significant increases in plasma cytokine levels, including both tumor necrosis factor alpha and interleukin-6, when participants were exposed to diesel exhaust compared to the filtered air. This robust study on a human population successfully demonstrated a significant link between an exposure to diesel particles, a significant contributor to PM, and markers of systemic inflammation.

A study published in the October, 2012 issue of the journal PLOS ONE demonstrated a statistically significantly positive association between $PM_{2.5}$ and non-specific abdominal pain hospitalizations (Kaplan et al., 2012). In order to control for potential across-individual confounders, the authors utilized a case crossover study design, where each cases served as their own control. Participants included all individuals who were diagnosed with non-specific abdominal pain in emergency departments across two Canadian cities, Edmonton and Montreal, during the years 1992-2002. These hospitalizations were compared to daily mean concentrations of six pollutants, including both $PM_{10}$ and $PM_{2.5}$, which were gathered from fixed monitoring stations within each of

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the study areas. Through the use of a conditional logistic regression statistical model, and after adjusting for temperature, relative humidity, and day of the week of hospitalization, individuals between the ages of 15 and 24 years were significantly more likely to be hospitalized for non-specific abdominal pain on days of elevated $PM_{2.5}$ in both cities. This study provides credible evidence for environmental pollutants, such as $PM_{2.5}$, having negative effects on the gastrointestinal tracts of susceptible individuals.

The first, of two, population-based studies assessing the association of PM exposure and IBD was conducted in the United Kingdom [UK] using a nested case control study design (Kaplan et al., 2010). The authors examined the annual mean concentration of three air pollutants: $PM_{10}$, sulfur dioxide, and nitrogen dioxide within wards of approximately 2,000 residents. After stratifying the wards into either high or low exposure groups (based on quintiles), a conditional logistic regression model was used to assess the relationship of the air pollutants and the incidence of UC and CD. Overall, none of the air pollutants were associated with the incidence of IBD; but among those 23 years of age or younger, those who lived in areas with higher nitrogen dioxide levels were associated with CD but not UC. Also, for UC, but not CD, those 25 years of age and younger were more likely to live in areas of high sulfur dioxide levels. No association between $PM_{10}$ and either UC or CD incidence were observed, even in the sub-analyses.

The second study, was conducted in the northern U.S., Wisconsin, used an ecological analysis at the county level to examine the association of ambient air pollutants and IBD hospitalizations (Ananthakrishnan et al., 2011). This study included five air pollutants: volatile organic compounds, carbon monoxide, nitrous oxide, sulfur

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dioxide, and $PM_{2.5}$. Using a Poisson regression model, the authors found statistically significant positive associations between each of the five air pollutants and both UC and CD hospitalizations.

Strong evidence for elevated PM exposure as a risk factor for IBD exists through a variety of studies. But, the only two known population-based studies assessing the relationship between PM exposure with IBD differed substantially, not only in their design, but also in their results. This lack of concordance between the two studies has left a gap in the literature and warrants additional investigations.

# CHAPTER 3

## METHODS

### 3.1 Study Population

All persons living in SC from the years 2005 through 2011 were included in the study and considered at risk of being hospitalized due to UC or CD. Individuals living in neighboring states who were employed in SC, were not included in the study population.

### 3.2 Data Sources

In-patient hospitalization records for CD and UC were obtained through the South Carolina Revenue and Fiscal Affairs office. Cases were determined according to the International Classification of Diseases, 9th edition (ICD-9) codes for CD (555.x) and UC (556.x). Each case included county of residence, age group, sex, ethnicity, and year of diagnosis from the years 2005 through 2011. Only cases with complete information were retained for all analyses. The U.S. Census Bureau provided population counts for all SC Counties for each of the study years. The population counts for the years 2005-2009 and 2011 were estimated counts while the 2010 census was used for the year 2010.

The Outdoor Air Quality – Fine Particulate Matter database, downloaded through CDC Wonder, was used for the PM$_{2.5}$ exposure data. The data are results of a regional

surfacing algorithm developed by the National Aeronautics and Space Administration [NASA] Applied Sciences and Public Health programs. Incorporated into the algorithm were direct land monitored PM$_{2.5}$ data from the United States Environmental Protection Agency [EPA] Air Quality System along with remotely sensed aerosol optical depth data from the NASA moderate Resolution Imaging Spectroradiometer. Fine Particulate matter levels were measured in micrograms per cubic meter ($\mu$g/m$^3$), and given as annual average county-level estimates.

3.3 Rate Standardization

According to the U.S. Census Bureau, in 2005 McCormick County had a population of only 10,049, while Greenville County had a population of 405,608. By using traditional disease rates, counties with smaller populations, such as McCormick County, would be much more susceptible to large and inconsistent rate fluctuations from year to year than larger counties, such as Greenville County. Similarly, the age distributions across SC counties varied from a median age of 32 years in Richland County to 50 years in McCormick County. Since UC and CD are generally diagnosed within the first 40 years of life (Nerich et al., 2006), comparing counties with different age distributions would yield biased results.  In order to address the heterogeneity of population sizes and age distributions across SC counties, UC and CD rates were standardized using the indirect standardization method (Naing, 2000). For each study year and county, all cases and base populations were split into three broad age categories: less than 20 years, between 20 and 64 years, and 65 years or older. Expected counts were calculated through an internal standard population rate, which was the aggregate SC hospitalization rates for each year and disease. The standardized morbidity ratio (SMR)

was then calculated by dividing the observed cases by the expected. All rate standardizations were calculated using the STDRATE procedure in SAS software (SAS. Version 9.4, SAS Institute, Cary, NC).

3.4 Data Visualization

The results of the SMR calculations were then displayed on maps of SC using the ArcGIS software (ESRI 2011. ArcGIS Desktop: Release 10. Redlands, CA: Environmental Systems Research Institute). The SMRs that were significantly different than expected, based on p-values less than 0.05, were displayed on each of the maps. Separate maps were developed for UC and CD for each study year, which yielded 14 individual maps.

3.5 Analysis

To guide the analytic strategy, the Global Moran's I test for spatial autocorrelation was first performed using ArcGIS software. The test used row standardized values of the SMRs for each county and was based off of the Queen spatial weights matrix. Failing to account for spatial autocorrelation, if present, could have potentially led to biased results.

In the primary effects model, the counts of UC and CD within each county were treated as the dependent outcome variables. Because these variables could never take on a negative value, it would have been inappropriate to use any model that was based on the normal distribution assumption. To account for this non-negative problem, it was decided that either a Poisson or Negative Binomial distribution model should be used.

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A Poisson distribution model consists of a single parameter, Lambda, which represents both the mean and the variance of the model. When the variance is greater than the mean, as is often the case when investigating rare diseases, overdispersion is present. Continuing to use the Poisson model with overdispersion would lead to biased results. To test for overdispersion, the SAS procedure GENMOD was used. If zero was contained in the Wald 95% Confidence Limits for the Dispersion parameter, overdispersion would not have been present and a Poisson regression model would have been selected. If zero was not contained, the Negative Binomial distribution model would have been used.

It was determined that the SAS procedure GLIMMIX would be used for the primary analyses. This procedure was chosen based on its flexibility to use either a Poisson Regression or a Negative Binomial model, while incorporating random effects and spatial components if autocorrelation was present. From this procedure, two primary effects models were constructed. The first for UC and the second for CD, modeled the number of cases as the dependent variable, $PM_{2.5}$ (continuous), Year (continuous), and the interaction of the two as the independent variables. The log of the expected cases was used as the offset parameter. The covariance structure of the model was determined through the results of the global Moran's I test. In the presence of spatial autocorrelation, the sp(exp) Latitude Longitude option would have been used, while the unstructured option would have been used if spatial autocorrelation were not detected.

3.6 Covariate Adjustment

In two additional models, seven potential county level confounders were assessed in both of the main effects models for UC and CD. Potential confounders included: percent of residents in each county with no high school diploma, percent of the residents

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in each county who were non-Hispanic white, the median age of residence within each county, the average household size within each county, the percent of the residents in each county who smoked cigarettes, the percent of residence within each county who lived in poverty, and the percent of individuals within each county who were female. A backwards selection procedure was used in both models to determine if each of the potential confounder should be included in each of the final model. The initial adjusted model for each disease included all potential confounders. Each time the model was ran and analyzed, the potential confounder with the highest p-value was removed. The final adjusted models for UC and CD included only the covariates that had a p-value less than 0.05.

# CHAPTER 4

## RESULTS

From 2005 to 2011 there were 21,660 in-patient hospitalizations from either UC or CD. Characteristics of patients are outlined in Table 4.1. Over the study period there were over two times the amount of hospitalizations attributable to CD (n=14,914) than there were UC (n=6,746). The average annual UC hospitalizations increased at a rate of 0.70 cases per 100,000 population per year (p=0.001), from 19.37 (95% CI=17.09, 21.65) in 2005 to 23.48 (95% CI=19.97, 27.00) in 2011. Rates of CD increased by 1.64 cases per 100,000 population per year (p=0.002) from 40.52 (95% CI=35.61, 45.43) in 2005 to 48.16 (95% CI=41.24, 55.09) in 2011. Both gender and racial distributions of UC and CD remained constant over the study period while the proportion of those between the ages of 20 and 64 years significantly decreased and those 65 years or older significantly increased.

Average annual levels of $PM_{2.5}$ decreased by 0.34 $\mu g/m^3$ per year (p<0.0001) in SC over the study period. The highest mean levels of $PM_{2.5}$ were in the year 2005 (Mean 14.45, SD 0.7187), while the lowest mean levels were in the year 2009 (Mean 11.6924, SD 0.17714). A graphical representation of the changes in UC and CD hospitalizations overlaid with the changes in $PM_{2.5}$ are displayed in Figure 4.1.

The SC counties that had a SMR that was significantly different than expected for UC and CD during each of the study years are displayed on maps in Figure 4.2 and Figure 4.3, respectively. Significant spatial autocorrelation was detected for Crohn's Disease in 2007 (Z=1.974, P=0.048) and 2008 (Z=2.521, P=0.012). No spatial autocorrelation was detected for UC. Results of the GENMOD procedure indicated overdispersion for both UC and CD across all study year. As a result, the negative binomial distribution model was chosen over the poisson regression model for all analyses. The results of the random effects statement within both the UC and CD models indicated a statistically significant (p-value <0.0001) difference in the population adjusted number of hospitalizations attributable to UC or CD across SC counties.

None of the main effects models, crude or adjusted, indicated that the annual average levels of $PM_{2.5}$ were associated with UC or CD in-patient hospitalizations. After the backwards elimination selection procedure, the final adjusted models for UC and CD differed in the confounders included in each. The percent of the population within each county who were female was a significant confounder for both models, while the percent of each county who were non-Hispanic white was significant for CD only. Results of the crude and adjusted main effects models are summarized in Table 4.2.

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**Table 4.1.** Summary of demographic statistics for Ulcerative Colitis and Crohn's Disease Hospitalizations in South Carolina, 2005-2011

| | 2005 | 2006 | 2007 | Year 2008 | 2009 | 2010 | 2011 | P-value[€] |
|---|---|---|---|---|---|---|---|---|
| **Cases, no.** | | | | | | | | |
| CD | 1,800 | 1,811 | 1,838 | 2,244 | 2,352 | 2,461 | 2,408 | 0.0023 |
| UC | 822 | 772 | 906 | 1,016 | 1,008 | 1,049 | 1,173 | 0.0011 |
| **Gender, %** | | | | | | | | |
| Female | | | | | | | | |
| CD | 61.28 | 58.97 | 59.30 | 60.03 | 60.80 | 60.59 | 59.68 | 0.9906 |
| UC | 55.11 | 55.57 | 57.73 | 56.69 | 56.75 | 57.10 | 55.84 | 0.4329 |
| **Race, %** | | | | | | | | |
| White | | | | | | | | |
| CD | 78.17 | 78.41 | 76.88 | 78.83 | 78.61 | 75.74 | 77.37 | 0.3532[λ] |
| UC | 77.86 | 79.27 | 78.81 | 79.33 | 81.25 | 75.98 | 76.04 | 0.3869[λ] |
| A-A[†] | | | | | | | | |
| CD | 20.72 | 20.38 | 20.95 | 19.43 | 20.15 | 22.55 | 20.72 | 0.5353 |
| UC | 19.34 | 18.52 | 17.66 | 19.09 | 16.77 | 21.54 | 21.74 | 0.2389 |
| Other | | | | | | | | |
| CD | 1.11 | 1.21 | 2.18 | 1.74 | 1.23 | 1.71 | 1.91 | 0.2931 |
| UC | 2.80 | 2.20 | 3.53 | 1.57 | 1.98 | 2.48 | 2.22 | 0.4636[λ] |
| **Age, %** | | | | | | | | |
| < 20 | | | | | | | | |
| CD | 4.50 | 3.92 | 5.77 | 5.30 | 4.04 | 4.35 | 4.19 | 0.6661[λ] |
| UC | 5.96 | 5.70 | 4.19 | 5.91 | 5.65 | 3.34 | 4.18 | 0.1328[λ] |
| 20-64 | | | | | | | | |
| CD | 76.17 | 79.51 | 75.46 | 73.35 | 73.89 | 72.86 | 72.43 | 0.0263[λ] |
| UC | 63.99 | 68.52 | 66.45 | 62.89 | 63.19 | 61.49 | 60.44 | 0.0429[λ] |
| ≥ 65 | | | | | | | | |
| CD | 19.33 | 16.57 | 18.77 | 21.35 | 22.07 | 22.80 | 23.38 | 0.0103 |
| UC | 30.05 | 25.78 | 29.36 | 31.20 | 31.15 | 35.18 | 35.38 | 0.0174 |

† African America

€ Test of trend

λ Negative trend

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**Table 4.2:** Crude and Adjusted Main Effects Model Results for Ulcerative Colitis and Crohn's Disease hospitalizations in South Carolina, 2005-2011

| | Ulcerative Colitis Estimate (P value) | | Crohn's Disease Estimate (P value) | |
|---|---|---|---|---|
| | Crude | Adjusted | Crude | Adjusted |
| Intercept | 0.397 (0.488) | -4.126 (0.018) | -0.029 (0.948) | -5.586 (0.001) |
| $PM_{2.5}$ | -0.035 (0.390) | -0.036 (0.379) | -0.007 (0.827) | -0.010 (0.762) |
| YEAR | -0.082 (0.584) | -0.085 (0.573) | -0.021 (0.853) | -0.019 (0.865) |
| $PM_{2.5}$*YEAR | 0.005 (0.640) | 0.006 (0.628) | 0.001 (0.895) | 0.001 (0.915) |
| FEMALE%[†] | - | 8.874 (0.006) | - | 9.900 (0.002) |
| NHW%[€] | - | - | - | 0.940 (0.010) |

† Percent of the population within each SC county that are female

€ Percent of the population within each SC county that are non-Hispanic white
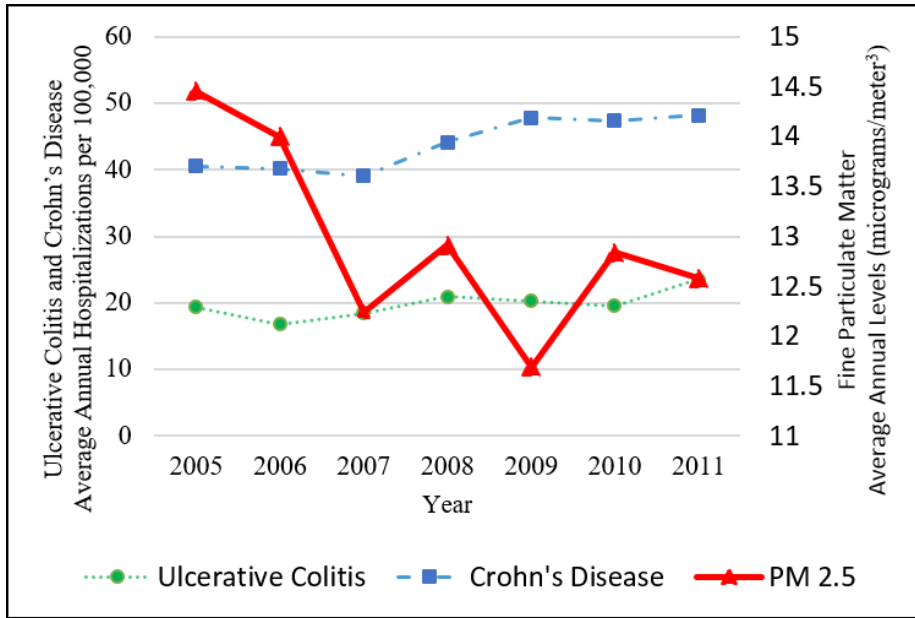
**Figure 4.1:** Ulcerative Colitis and Crohn's Disease Average Annual Hospitalizations per 100,000 population compared to Average Annual Levels of Fine Particulate Matter in South Carolina, 2005-2011
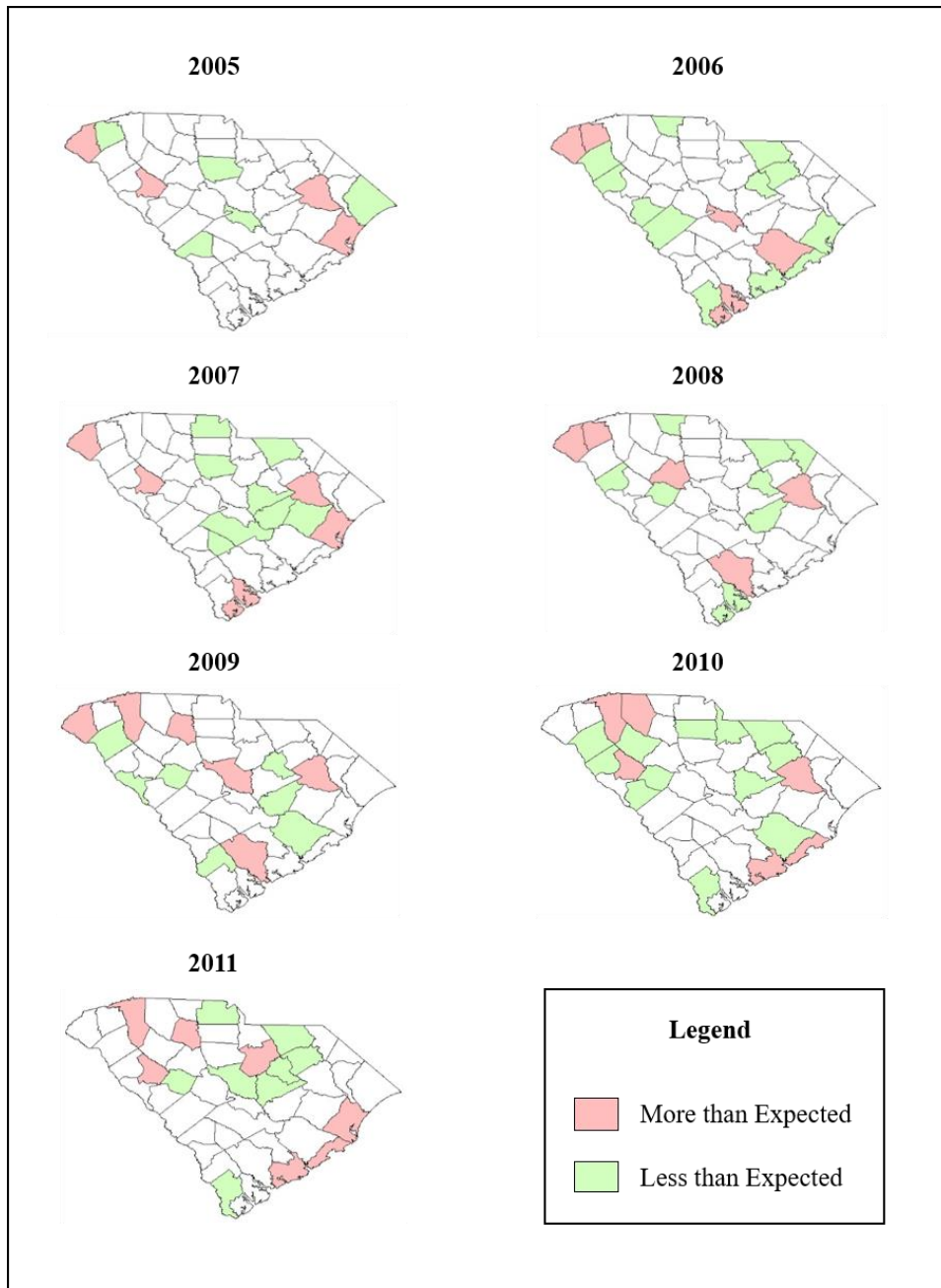
**Figure 4.2:** Ulcerative Colitis Significant Age Standardized Morbidity Ratios in South Carolina, 2005-2011

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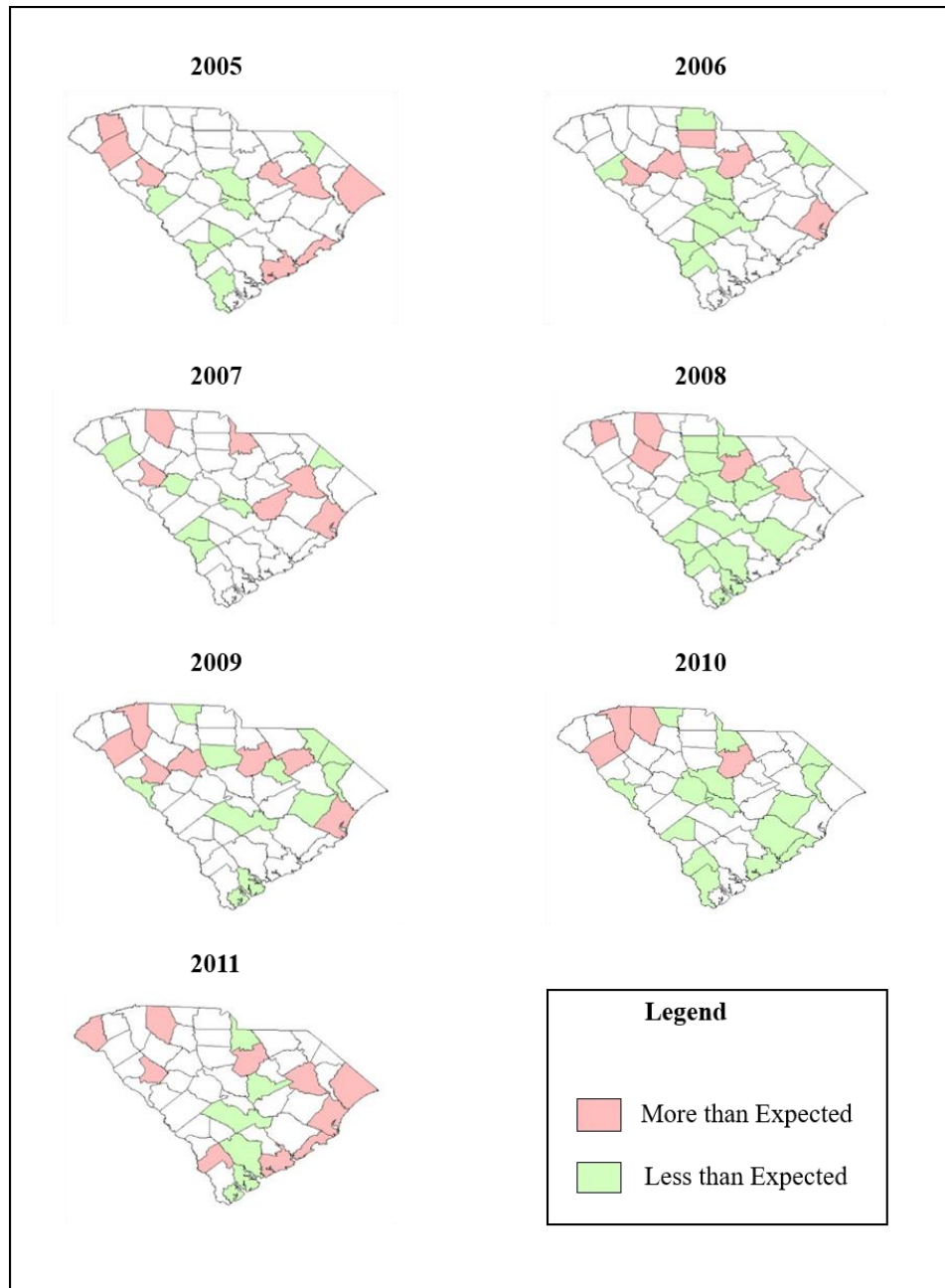
**Figure 4.3:** Crohn's Disease Significant Age Standardized Morbidity Ratios in South Carolina, 2005-2011

CHAPTER 5

DISCUSSION

Our data did not indicate that average annual levels of $PM_{2.5}$ had any impact on UC or CD hospitalizations in SC from the years 2005 through 2011. Rates of UC and CD in-patient hospitalizations were found to be steadily increasing while the annual levels of $PM_{2.5}$ were found to be decreasing. Even when the temporality aspects of our data were ignored, counties with highest levels of $PM_{2.5}$ were not the same counties with the highest levels of in-patient UC or CD hospitalizations.

The lack of association between fine particulate matter and UC or CD in-patient hospitalizations demonstrated in our study strengthen the inferences made by Kaplan et al. who also was unable to find a statistically significant association between air pollutants and UC or CD. Even though a more similar study design, the results of our study do not support those from Ananthakrishnan et al.. Our studies differed primarily in the number of variables accounted for and the analyses performed. While our study concentrated solely on levels of $PM_{2.5}$, Ananthakrishnan et al. investigated five separate environmental pollutants along with $PM_{2.5}$. Also, the study by Ananthakrishnan et al. only examined data across a single year while we looked at data across a seven year period.

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Several limitations should be considered. First, the ecological nature of the study did not allow for inferences to be made about individuals. Second, aggregate administrative based ICD-9 codes were used for case ascertainment. Without validation, this source of case data is prone to disease misclassification. Also, the aggregate-level data limited our ability to control for rehospitalizations, thus making our study susceptible to cases being counted multiple times. Third, no individual-level monitoring of $PM_{2.5}$ was conducted. This limitation assumed that everyone in a particular county received the same level of exposure to $PM_{2.5}$ regardless if they were employed in the same county or if they spent most of their time indoors, opening up the possibility of exposure misclassification. Lastly, the use of annual average $PM_{2.5}$ did not capture seasonal variations or acute spikes brought on by fires and other industrial sources that could have potentially led to acute spikes in UC or CD hospitalizations.

A few strengths of the study were also evident. First, in-patient hospitalizations and levels of $PM_{2.5}$ were monitored over a seven-year period allowing for temporality to be assessed and trends to be demonstrated. Second, a geostatistical analysis was utilized, which accounted for the spatial autocorrelation exhibited by our data. Third, our study consisted of a relatively large sample size which allowed for sub-analyses to be performed.

The results from this study did not indicate any association between rates of UC or CD hospitalizations and $PM_{2.5}$. Rates of UC and CD were observed to be increasing over the seven-year period while levels of $PM_{2.5}$ decreased. In order to rule out $PM_{2.5}$ as a potential piece in the complex web of causation of UC and CD, future studies would need

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to include more individual-level monitoring of $PM_{2.5}$ and a more accurate case

ascertainment strategy.

# REFERENCES

Aamodt, G., Bukholm, G., Jahnsen, J., Moum, B., Vatn, M. H., & Group, I. S. (2008). The association between water supply and inflammatory bowel disease based on a 1990-1993 cohort study in southeastern Norway. *Am J Epidemiol, 168*(9), 1065-1072. doi:10.1093/aje/kwn218

Aamodt, G., Jahnsen, J., Bengtson, M. B., Moum, B., Vatn, M. H., & Group, I. S. (2008). Geographic distribution and ecological studies of inflammatory bowel disease in southeastern Norway in 1990-1993. *Inflamm Bowel Dis, 14*(7), 984-991. doi:10.1002/ibd.20417

Ananthakrishnan, A. N., McGinley, E. L., Binion, D. G., & Saeian, K. (2011). Ambient air pollution correlates with hospitalizations for inflammatory bowel disease: an ecologic analysis. *Inflamm Bowel Dis, 17*(5), 1138-1145. doi:10.1002/ibd.21455

Armitage, E. L., Aldhous, M. C., Anderson, N., Drummond, H. E., Riemersma, R. A., Ghosh, S., & Satsangi, J. (2004). Incidence of juvenile-onset Crohn's disease in Scotland: Association with northern latitude and affluence. *Gastroenterology, 127*(4), 1051-1057. doi:10.1053/j.gastro.2004.06.024

Baumgart, D.-C. (2008). What's new in inflammatory bowel disease in 2008? *World Journal of Gastroenterology, 14*(3), 329. doi:10.3748/wjg.14.329

Beamish, L. A., Osornio-Vargas, A. R., & Wine, E. (2011). Air pollution: An environmental factor contributing to intestinal disease. *J Crohns Colitis, 5*(4), 279-286. doi:10.1016/j.crohns.2011.02.017

Bilski, J., Brzozowski, B., Mazur-Bialy, A., Sliwowski, Z., & Brzozowski, T. (2014). The role of physical exercise in inflammatory bowel disease. *Biomed Res Int, 2014*, 429031. doi:10.1155/2014/429031

Blanchard, J. F., Bernstein, C. N., Wajda, A., & Rawsthorne, P. (2001). Small-area Variations and Sociodemographic Correlates for the Incidence of Crohn's Disease and Ulcerative Colitis. *American Journal of Epidemiology, 154*(4), 328-335.

Brook, R. D., Rajagopalan, S., Pope, C. A., 3rd, Brook, J. R., Bhatnagar, A., Diez-Roux, A. V., . . . Metabolism. (2010). Particulate matter air pollution and cardiovascular disease: An update to the scientific statement from the American Heart Association. *Circulation, 121*(21), 2331-2378. doi:10.1161/CIR.0b013e3181dbece1

Calderon-Garciduenas, L., Franco-Lira, M., Torres-Jardon, R., Henriquez-Roldan, C., Barragan-Mejia, G., Valencia-Salazar, G., . . . Reed, W. (2007). Pediatric respiratory and systemic effects of chronic air pollution exposure: nose, lung, heart, and brain pathology. *Toxicol Pathol, 35*(1), 154-162. doi:10.1080/01926230601059985

Crohn, B., Ginzburg, L., & Oppemjeo, G. (1984). Landmark article Oct 15, 1932. Regional ileitis. A pathological and clinical entity. By Burril B. Crohn, Leon

25

Ginzburg, and Gordon D. Oppenheimer. *The Journal of the American Medical Association, 251*, 73-79.

Economou, M., & Pappas, G. (2008). New global map of Crohn's disease: Genetic, environmental, and socioeconomic correlations. *Inflamm Bowel Dis, 14*(5), 709-720. doi:10.1002/ibd.20352

Fan, Z. T., Meng, Q., Weisel, C., Laumbach, R., Ohman-Strickland, P., Shalat, S., . . . Black, K. (2009). Acute exposure to elevated PM2.5 generated by traffic and cardiopulmonary health effects in healthy older adults. *J Expo Sci Environ Epidemiol, 19*(5), 525-533. doi:10.1038/jes.2008.46

Geerling, B. J., Dagnelie, P. C., Badart-Smook, A., Russel, M. G., Strockbrugger, R. W., & Brummer, R.-J. M. (2000). Diet as a Risk Factor for the Development of Ulcerative Colitis. *The American Journal of Gastroenterology, 95*(4), 1008-1013.

Green, C., Elliott, L., Beaudoin, C., & Bernstein, C. N. (2006). A Population-based Ecologic Study of Inflammatory Bowel Disease: Searching for Etiologic Clues. *American Journal of Epidemiology, 164*(7), 615-623.

Hou, J. K., El-Serag, H., & Thirumurthi, S. (2009). Distribution and manifestations of inflammatory bowel disease in Asians, Hispanics, and African Americans: a systematic review. *Am J Gastroenterol, 104*(8), 2100-2109. doi:10.1038/ajg.2009.190

Kaplan, G. G., Dixon, E., Panaccione, R., Fong, A., Chen, L., Szyszkowicz, M., . . . Villeneuve, P. J. (2009). Effect of ambient air pollution on the incidence of appendicitis. *CMAJ, 181*(9), 591-597. doi:10.1503/cmaj.082068

Kaplan, G. G., Hubbard, J., Korzenik, J., Sands, B. E., Panaccione, R., Ghosh, S., . . . Villeneuve, P. J. (2010). The inflammatory bowel diseases and ambient air pollution: a novel association. *Am J Gastroenterol, 105*(11), 2412-2419. doi:10.1038/ajg.2010.252

Kaplan, G. G., Szyszkowicz, M., Fichna, J., Rowe, B. H., Porada, E., Vincent, R., . . . Storr, M. (2012). Non-specific abdominal pain and air pollution: a novel association. *PLoS One, 7*(10), e47669. doi:10.1371/journal.pone.0047669

Kappelman, M. D., Rifas-Shiman, S. L., Kleinman, K., Ollendorf, D., Bousvaros, A., Grand, R. J., & Finkelstein, J. A. (2007). The prevalence and geographic distribution of Crohn's disease and ulcerative colitis in the United States. *Clin Gastroenterol Hepatol, 5*(12), 1424-1429. doi:10.1016/j.cgh.2007.07.012

Khalili, H., Huang, E. S., Ananthakrishnan, A. N., Higuchi, L., Richter, J. M., Fuchs, C. S., & Chan, A. T. (2012). Geographical variation and incidence of inflammatory bowel disease among US women. *Gut, 61*(12), 1686-1692. doi:10.1136/gutjnl-2011-301574

Laden, F., Neas, L. M., Dockery, D., W., & Schwartz, J. (2000). Association of Fine Particulate Matter from Different Sources with Daily Mortality in Six U.S. Cities. *Environmental Health Perspectives, 108*(10), 941-947.

Loftus, E. V., & Sandborn, W. J. (2002). Epidemiology of Inflammatory Bowel Disease. *Gastroenteron Clin North Am., 31*, 1-20.

Moller, W., Haussinger, K., Winkler-Heil, R., Stahlhofen, W., Meyer, T., Hofmann, W., & Heyder, J. (2004). Mucociliary and long-term particle clearance in the airways of healthy nonsmoker subjects. *J Appl Physiol (1985), 97*(6), 2200-2206. doi:10.1152/japplphysiol.00970.2003

Molodecky, N. A., Soon, I. S., Rabi, D. M., Ghali, W. A., Ferris, M., Chernoff, G., . . . Kaplan, G. G. (2012). Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. *Gastroenterology, 142*(1), 46-54 e42; quiz e30. doi:10.1053/j.gastro.2011.10.001

Munkholm, P. (2012). Review Article: The Incidence and Prevalence of Coloretal Cancer in Inflammatory Bowel Disease. *Aliment Pharmacol Ther, 18*(2), 1-5.

Naing, N. (2000). EASY WAY TO LEARN STANDARDIZATION: DIRECT AND INDIRECT METHODS. *Malaysian Journal of Medical Sciences, 7*(1), 10-15.

Nerich, V., Monnet, E., Etienne, A., Louafi, S., Ramee, C., Rican, S., . . . Carbonnel, F. (2006). Geographical Variations of Inflammatory Bowel Disease in France: A Study Based on National Health Insurance Data. *Inflamm Bowel Diseases, 12*(3), 218-226.

Orazzo, F., Nespoli, L., Ito, K., Tassinari, D., Giardina, D., Funis, M., . . . Zanobetti, A. (2009). Air pollution, aeroallergens, and emergency room visits for acute respiratory diseases and gastroenteric disorders among young children in six Italian cities. *Environ Health Perspect, 117*(11), 1780-1785. doi:10.1289/ehp.0900599

Salim, S. Y., Jovel, J., Wine, E., Kaplan, G. G., Vincent, R., Thiesen, A., . . . Madsen, K. L. (2014). Exposure to Ingested Airborne Pollutant Particulate Matter Increases Mucosal Exposure to Bacteria and Induces Early Onset of Inflammation in Neonatal IL-10-Deficient Mice. *Inflamm Bowel Disease, 20*(7), 1129-1138.

Salim, S. Y., Kaplan, G. G., & Madsen, K. L. (2014). Air pollution effects on the gut microbiota: a link between exposure and inflammatory disease. *Gut Microbes, 5*(2), 215-219. doi:10.4161/gmic.27251

Sonnenberg, A. (1990). Occupational distribution of inflammatory bowel disease among German employees. *Gut, 31*, 1037-1040.

Sonnenberg, A., McCarty, D. J., & Jacobsen, S. J. (1991). Geographic Variation of Inflammatory Bowel Disease Within the United States. *Gastroenterology, 100*, 143-149.

Thirumurthi, S., Chowdhury, R., Richardson, P., & Abraham, N. S. (2010). Validation of ICD-9-CM diagnostic codes for inflammatory bowel disease among veterans. *Dig Dis Sci, 55*(9), 2592-2598. doi:10.1007/s10620-009-1074-z

Tornqvist, H., Mills, N. L., Gonzalez, M., Miller, M. R., Robinson, S. D., Megson, I. L., . . . Blomberg, A. (2007). Persistent endothelial dysfunction in humans after diesel exhaust inhalation. *Am J Respir Crit Care Med, 176*(4), 395-400. doi:10.1164/rccm.200606-872OC

Wilks, S. (1859). Morbid appearances in the intestine of Miss Bankes. *London Medical Times & Gazette, 2*, 264.