Ambient air pollution, greenness and the risk of pediatric inflammatory bowel disease

BY MICHAEL ELTEN

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Presentation overview

BACKGROUND  METHODS  RESULTS  DISCUSSION  NEXT STEPS
What is Inflammatory Bowel Disease?

- A chronic immune-mediated disease affecting the digestive tract
- Two subtypes:
  - Crohn’s disease (CD)
  - Ulcerative colitis (UC)
- No current cure, treatments target inflammation
- Childhood-onset IBD tends to be more severe
Increasing Incidence of IBD

- Incidence of IBD is highest in westernized nations, increasing throughout the 20th century
- Incidence rates in newly industrialized nations are rapidly increasing
- If current trends persist, IBD will soon be a global disease

How is it developed?

- Etiology is poorly understood
- There are both genetic and environmental components
- The gut microbiome seems to be implicated
Why this study population?

Ontario has a high incident rate of IBD
Ontario is the largest IBD-linked cohort
Children have had less environmental exposure

Why air pollution and greenness?

Air pollution exposures increase during industrialization
Urbanization has led to loss of available greenspace
Potential mechanisms

▪ Disruption of the gut microbiome
  ▪ Differences in gut microbe diversity in pediatric UC cases vs healthy controls
  ▪ Oxidative stress from air pollution has been seen to affect the gut function
  ▪ Greenspace alters the outdoor microbial environment

▪ Dysregulation of fetal development
  ▪ Many immune system elements that are thought to be involved in IBD begin developing in 2nd and 3rd trimesters
  ▪ In-utero exposure to pollution can activate the fetal immune response
Review of Previous Literature

- **Previous epidemiological study:**
  - Looked at postnatal NO$_2$, PM$_{10}$ and SO$_2$ exposures in a UK general population
  - Found that increased levels of NO$_2$ were associated with increased risk of Crohn’s disease in those <23 years

- **Meta-analysis of passive smoking and IBD**
  - Weak positive association with Crohn’s disease
  - No association with ulcerative colitis

- **Rural vs urban study**
  - Found that rurality was protective against IBD
  - Strongest association in children
Data Sources

Cohort data:
- MOMBABY – has information on all mother/infant pairs
- RPDB – has additional demographic information
- CENSUS-CA has some census variables used for modelling
- OCCC – database that has cases of IBD up to Mar. 31, 2017

Exposure data:
- NO₂, PM₂.₅, O₃ data – modelled pollutant data
- Greenness (NDVI) – a measure of greenness a short distance from a given residence
Exposure Assessment – Air pollution

1. Initial pollutant estimates for each 6-digit postal code were derived as follows:
   ▪ NO$_2$ - national land use regression (LUR) model
   ▪ PM$_{2.5}$ - satellite-based geographically weighted regression techniques
   ▪ O$_3$ - an optimal interpolation technique

2. Obtain weekly estimates of the pollutants through temporal interpolation

3. Assign exposures to the cohort for each week of gestation, and each year of childhood
Exposure Assessment - Greenness

1. Estimates of greenness from the Landsat satellite were obtained using NDVI measures (values ranged from 0-1)

2. The growing season maximum estimate within a 250m buffer of each 6-digit postal code was assigned

3. Annual estimates were averaged to get simple measures of pregnancy and childhood exposures to greenness
Data Linkage

Demographics
- RPDB
- CENSUS-CA

Outcome
- OCCC
- Genetic risk

Baby’s IKN

MOMBABY (1991-2014)

Modelled pollutants
- NO$_2$
- PM$_{2.5}$
- O$_3$

6-digit Postal Code

Greenness (NDVI)

Main exposure

Secondary exposure
### Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>IBD (n=3464)</th>
<th>Non-IBD (n=2,722,530)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1991 (57%)</td>
<td>1,395,884 (51%)</td>
</tr>
<tr>
<td>Female</td>
<td>1473 (43%)</td>
<td>1,326,646 (49%)</td>
</tr>
<tr>
<td><strong>Mean birthweight (g)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3,442.43</td>
<td>3,410.53</td>
</tr>
<tr>
<td><strong>Mean maternal age (years)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>30.0</td>
<td>29.5</td>
</tr>
<tr>
<td><strong>Area of residence</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>333 (10%)</td>
<td>347,710 (13%)</td>
</tr>
<tr>
<td>Urban</td>
<td>3131 (90%)</td>
<td>2,374,820 (87%)</td>
</tr>
<tr>
<td><strong>Median neighborhood income quintile</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 (Highest)</td>
<td>798 (23.0%)</td>
<td>540,140 (19.8%)</td>
</tr>
<tr>
<td>4</td>
<td>699 (20.2%)</td>
<td>540,092 (19.8%)</td>
</tr>
<tr>
<td>3</td>
<td>692 (20.0%)</td>
<td>540,304 (19.9%)</td>
</tr>
<tr>
<td>2</td>
<td>698 (20.2%)</td>
<td>540,239 (19.8%)</td>
</tr>
<tr>
<td>1 (Lowest)</td>
<td>564 (16.3%)</td>
<td>540,363 (19.9%)</td>
</tr>
<tr>
<td>Missing</td>
<td>13 (0.4%)</td>
<td>21,392 (0.8%)</td>
</tr>
<tr>
<td><strong>Mother or sibling with IBD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>206 (6%)</td>
<td>14,410 (0.5%)</td>
</tr>
<tr>
<td>No</td>
<td>3258 (94%)</td>
<td>2,708,120 (99.5%)</td>
</tr>
<tr>
<td>Disease subtype</td>
<td>Number of cases</td>
<td>Percent of total</td>
</tr>
<tr>
<td>-----------------------</td>
<td>-----------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td>1915</td>
<td>55%</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>1253</td>
<td>36%</td>
</tr>
<tr>
<td>Unclassifiable</td>
<td>296</td>
<td>9%</td>
</tr>
<tr>
<td><strong>Total IBD</strong></td>
<td><strong>3464</strong></td>
<td><strong>100%</strong></td>
</tr>
</tbody>
</table>
Research Question 1

Is there an association between maternal or childhood exposures to ambient air pollution, and the risk of developing childhood-onset IBD?
Exposure correlation matrix

Mean childhood exposures:

\( \text{NO}_2 \) : 12.2 ppb

\( \text{PM}_{2.5} \) : 7.9 ug/m\(^3\)

\( \text{O}_3 \) : 24.5 ppb
Statistical Analysis

- **Distributed lag non-linear models (DLNM)**
  - Adapted from time-series analyses
  - Take into account lagged effects of an exposure on an outcome

- **Cox proportional hazards models**
  - Follow-up time: from birth until event (or age 18)
  - Exposure: continuous time-dependent variable
  - Annual exposure to pollutants was considered as a time-dependent variable
  - Hazard ratios (HR) show the risk of a child developing IBD per IQR increase
Model Building

Entered into the model based on previous literature:
- ✓ Family history of IBD
- ✓ Rural/Urban status
- ✓ Median neighborhood household income quintile

Considered as potential confounders through change in estimate (CIE) method:
- ✗ Sex
- ✗ Greenness during pregnancy
- ✗ Greenness during childhood
- ✗ Maternal age
- ✗ Season of conception
- ✗ Parity
In-utero exposure – Nitrogen Dioxide (NO$_2$)

<table>
<thead>
<tr>
<th>Weeks</th>
<th>HR*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-12</td>
<td>1.00</td>
<td>0.97 - 1.03</td>
</tr>
<tr>
<td>13-26</td>
<td>1.00</td>
<td>0.98 – 1.03</td>
</tr>
<tr>
<td>27-40</td>
<td>1.02</td>
<td>0.99 – 1.05</td>
</tr>
</tbody>
</table>

*adjusted for:
- Childhood exposure to pollutant
- Rural / urban residence
- Mother or sibling with IBD
- Median neighborhood household income quintile
In-utero exposure

—

Fine Particulate Matter (PM$_{2.5}$)

<table>
<thead>
<tr>
<th>Weeks</th>
<th>HR*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-12</td>
<td>0.98</td>
<td>0.85 – 1.11</td>
</tr>
<tr>
<td>13-26</td>
<td>0.94</td>
<td>0.83 – 1.05</td>
</tr>
<tr>
<td>27-40</td>
<td>1.00</td>
<td>0.87 – 1.14</td>
</tr>
</tbody>
</table>

*adjusted for:
- Childhood exposure to pollutant
- Rural / urban residence
- Mother or sibling with IBD
- Median neighborhood household income quintile
In-utero exposure — Ozone (O₃)

<table>
<thead>
<tr>
<th>Weeks</th>
<th>HR*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-12</td>
<td>1.07</td>
<td>0.94 - 1.22</td>
</tr>
<tr>
<td>13-26</td>
<td>1.14</td>
<td>1.05 – 1.25</td>
</tr>
<tr>
<td>27-40</td>
<td>1.03</td>
<td>0.90 – 1.18</td>
</tr>
</tbody>
</table>

*adjusted for:
- Childhood exposure to pollutant
- Rural / urban residence
- Mother or sibling with IBD
- Median neighborhood household income quintile
Childhood Exposure

Overall IBD

<table>
<thead>
<tr>
<th>Pollutant</th>
<th>HR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO₂</td>
<td>1.11 (0.99 – 1.25)</td>
</tr>
<tr>
<td>PM₂₅</td>
<td>1.15 (1.01 – 1.32)</td>
</tr>
<tr>
<td>O₃</td>
<td>1.11 (1.05 – 1.16)</td>
</tr>
</tbody>
</table>

*adjusted for:
- Average pregnancy exposure
- Rural / urban residence
- Mother or sibling with IBD
- Median neighborhood household income quintile
Disease Subtypes

Pollutant | HR* (95% CI)
---|---
NO$_2$ | 1.14 (0.97 – 1.33)
 | 1.12 (0.91 – 1.36)
PM$_{2.5}$ | 1.18 (0.98 – 1.42)
 | 1.13 (0.91 – 1.4)
O$_3$ | 1.08 (1.02 – 1.09)
 | 1.10 (1.02 – 1.19)

*adjusted for:
- Average pregnancy exposure
- Rural / urban residence
- Mother or sibling with IBD
- Median neighborhood household income quintile

Legend:
Crohn’s | IBD | Ulcerative Colitis

Childhood Exposure
Interpretation

- For in-utero exposures, seems to be a positive association with $O_3$ during the second trimester.
- Increased exposure to all pollutants during childhood period was consistently associated with IBD before age 18.
- No differences seen by disease subtype.
Research Question 2

Is there an association between childhood exposure to residential greenness, and the risk of developing childhood-onset IBD?
Greenness Correlation Matrix
Statistical Analysis

- Cox proportional hazards models
  - Follow-up time: from birth until event (or age 18)
  - Exposure: time-varying quartile of residential greenness
  - Hazard ratios (HR) show the risk of a child developing IBD for a given quartile compared to lowest level of greenness
Overall IBD

Quartile (ref=1st) | HR* (95% CI)
--- | ---
2nd quartile | 0.95 (0.87 – 1.05)
3rd quartile | 0.93 (0.85 – 1.02)
4th quartile | 0.89 (0.81 – 0.98)

*adjusted for:
- Rural / urban residence
- Mother or sibling with IBD
- Median neighborhood household income quintile
Disease Subtypes

Legend:

Crohn’s
IBD
Ulcerative Colitis

Quartile (ref=1st)  HR* (95% CI)

2nd quartile  1.00 (0.88 – 1.14)
             0.84 (0.72 – 0.98)

3rd quartile  1.04 (0.92 – 1.18)
             0.83 (0.72 – 0.97)

4th quartile  0.95 (0.83 – 1.09)
             0.80 (0.68 – 0.95)

*adjusted for:
➢ Rural / urban residence
➢ Mother or sibling with IBD
➢ Median neighborhood household income quintile
Interpretation

- Childhood exposure to greenness may be protective of ulcerative colitis
- No evidence for association with Crohn’s disease
- Suggestion of a dose-response relationship
Overall Conclusions

- Interesting results, but can’t make any causal statements from one study
- The findings here strengthen the proposed relevance of the environment in IBD etiology
- Childhood exposures to both air pollution, and greenness should be investigated further
Next steps

1. Examine early childhood exposure period
2. Test other measures of greenness
3. Replicate study in other populations
Acknowledgements

Thesis advisory committee:
- Dr. Eric Lavigne
- Dr. Eric Benchimol
- Dr. Deshayne Fell

Unofficial advisory committee:
- Dr. Ellen Kuenzig
- Dr. Gilaad Kaplan
- Dr. Hong Chen
- Dr. Antonio Gasparini