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

BY MICHAEL ELTEN

MSc. Epidemiology Candidate – University of Ottawa

Presentation overview

BACKGROUND

METHODS

RESULTS

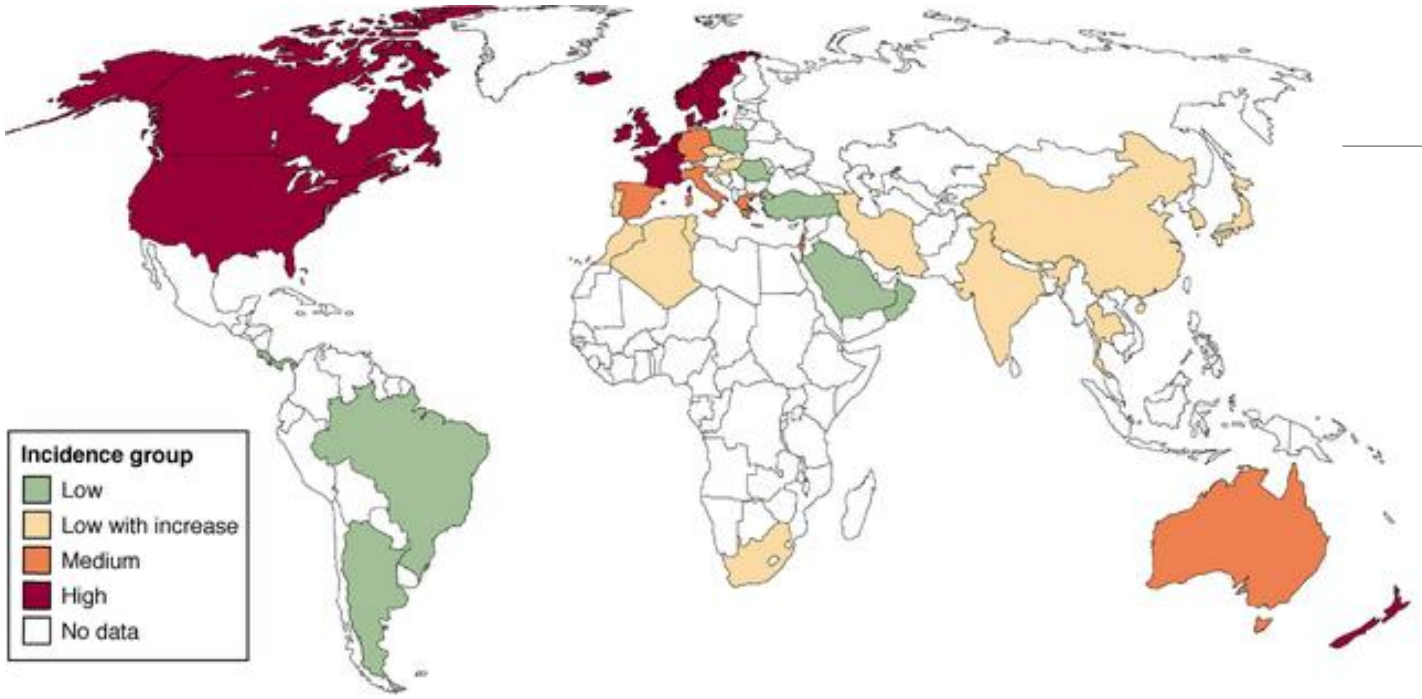
DISCUSSION

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

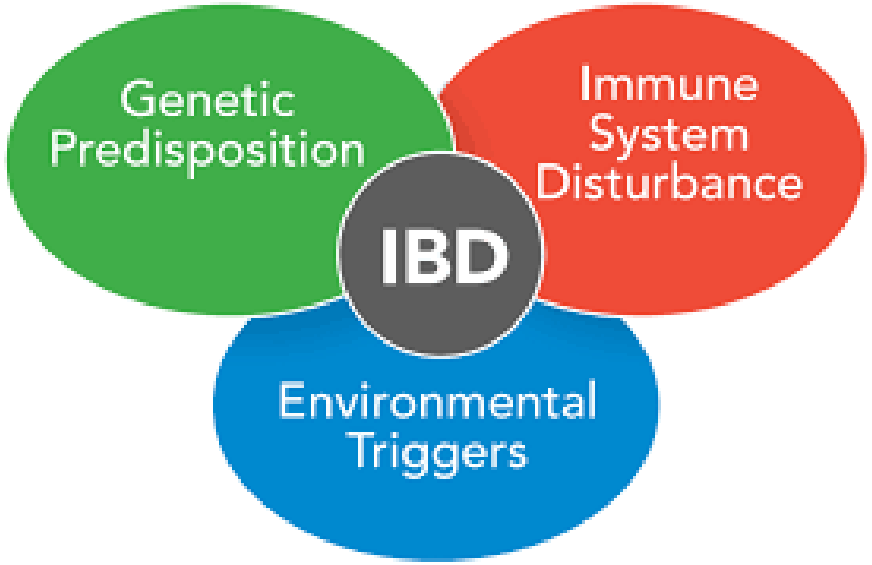


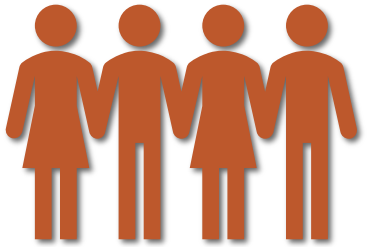
- Incidence of IBD is highest in westernized nations, increasing throughout the 20th century
- Incidence rates in newly industrialized nations are rapidly increasing
- If current trends persist, IBD will soon be a global disease

Cosnes et al. 2011. *Gastroentrology.* 140(6):1785-94

How is it developed?

- Etiology is poorly understood
- There are both genetic and environmental components
- The gut microbiome seems to be implicated



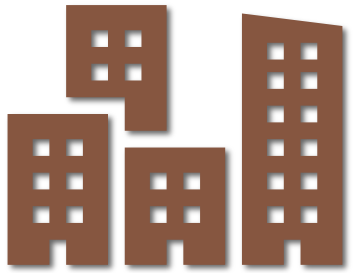


Why this study population?

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 NO2 were associated with increased risk of Crohn's disease in those <23 years

Kaplan et al. 2010. Am J Gastro. 105(11):2412

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

Jones et al 2008. Am J Gastro. 103(9):2382

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

Benchimol et al 2017. Am J Gastro. 112(9):1412

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:

- NO_2, $PM_{2.5}$, O_3 data – modelled pollutant data
- Greenness (NDVI) – a measure of greenness a short distance from a given residence

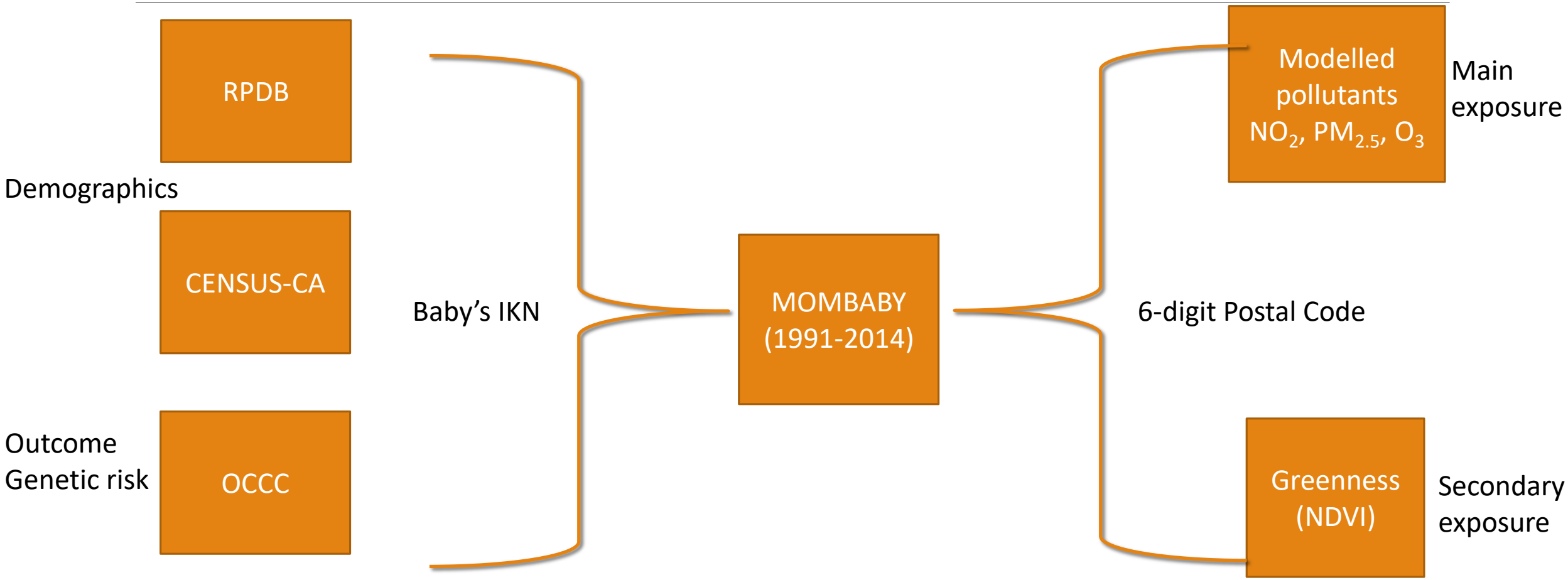
Exposure Assessment – Air pollution

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 estimates with geographically weighted regression
   - 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



Baseline characteristics

Characteristic	IBD (n=3464)	Non-IBD (n=2,722,530)
Sex		
Male	1991 (57%)	1,395,884 (51%)
Female	1473 (43%)	1,326,646 (49%)
Mean birthweight (g)		
	3,442.43	3,410.53
Mean maternal age (years)		
	30.0	29.5
Area of residence		
Rural	333 (10%)	347,710 (13%)
Urban	3131 (90%)	2,374,820 (87%)
Median neighborhood income quintile		
5 (Highest)	798 (23.0%)	540,140 (19.8%)
4	699 (20.2%)	540,092 (19.8%)
3	692 (20.0%)	540,304 (19.9%)
2	698 (20.2%)	540,239 (19.8%)
1 (Lowest)	564 (16.3%)	540,363 (19.9%)
Missing	13 (0.4%)	21,392 (0.8%)
Mother or sibling with IBD		
Yes	206 (6%)	14,410 (0.5%)
No	3258 (94%)	2,708,120 (99.5%)

Cohort IBD breakdown

Disease subtype	Number of cases	Percent of total
Crohn’s disease	1915	55%
Ulcerative colitis	1253	36%
Unclassifiable	296	9%
Total IBD	3464	100%

Research Question 1

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

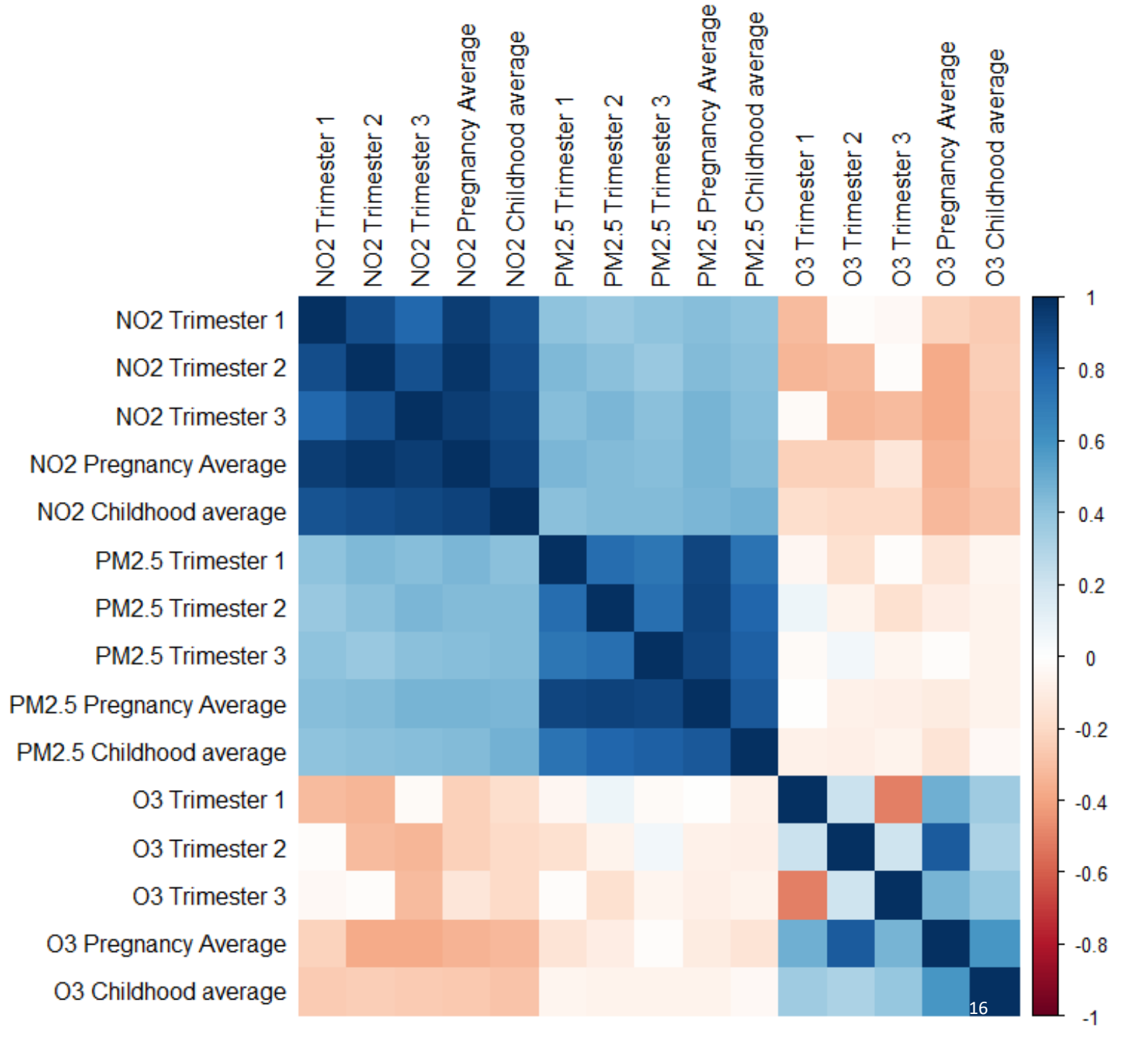
Exposure correlation matrix

Mean childhood exposures:

NO_2 : 12.2 ppb

$PM_{2.5}$: 7.9 ug/m^3

O_3 : 24.5 ppb



Statistical Analysis

In-utero exposures

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

Childhood exposures

- 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:

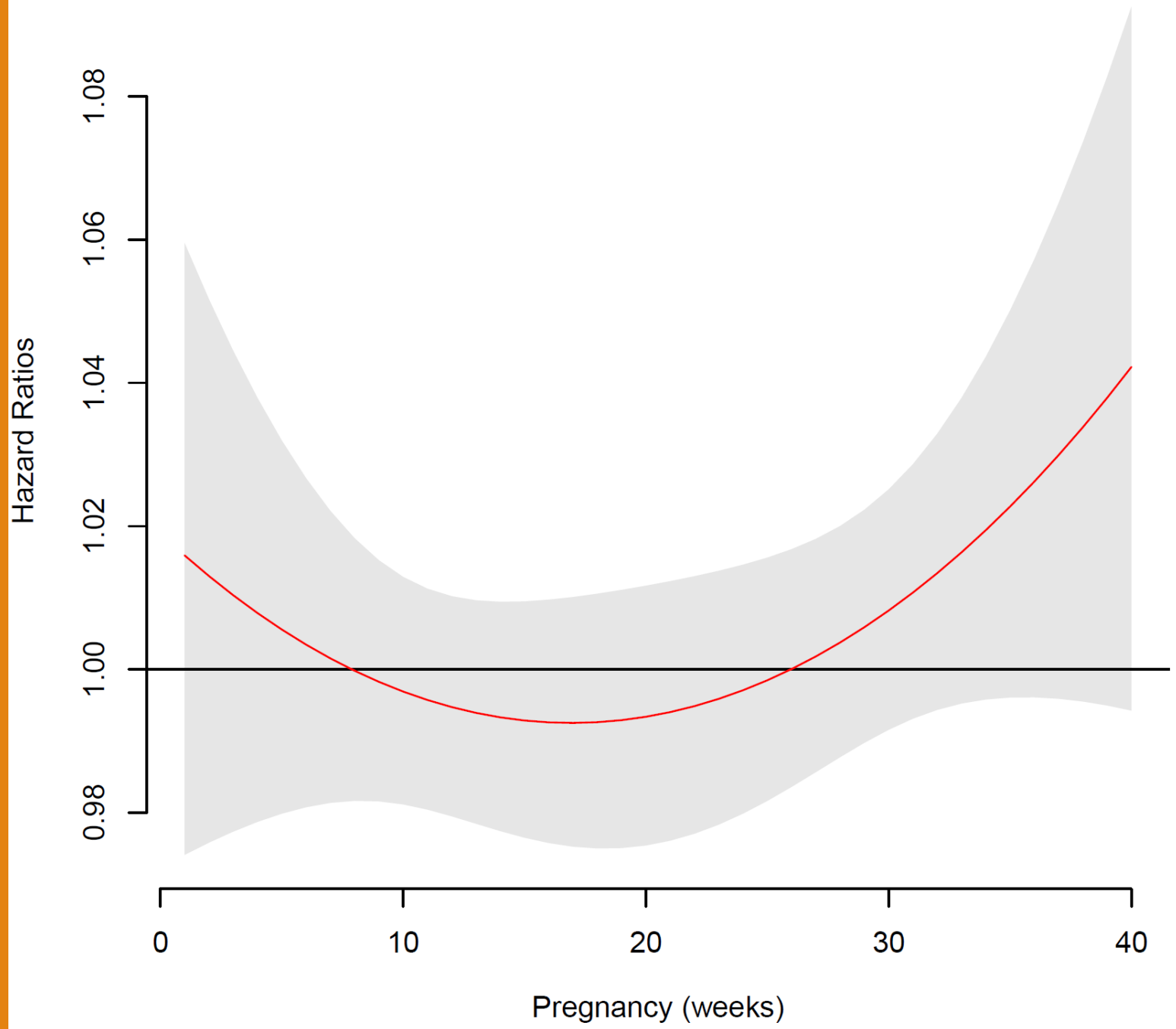
- ×Sex
- ×Greenness during pregnancy
- ×Greenness during childhood
- ×Maternal age
- ×Season of conception
- ×Parity

In-utero exposure – Nitrogen Dioxide (NO_2)

Weeks	HR*	95% CI
1-12	1.00	0.97 - 1.03
13-26	1.00	0.98 – 1.03
27-40	1.02	0.99 – 1.05

*adjusted for:

- Childhood exposure to pollutant
- Rural / urban residence
- Mother or sibling with IBD
- Median neighborhood household income quintile

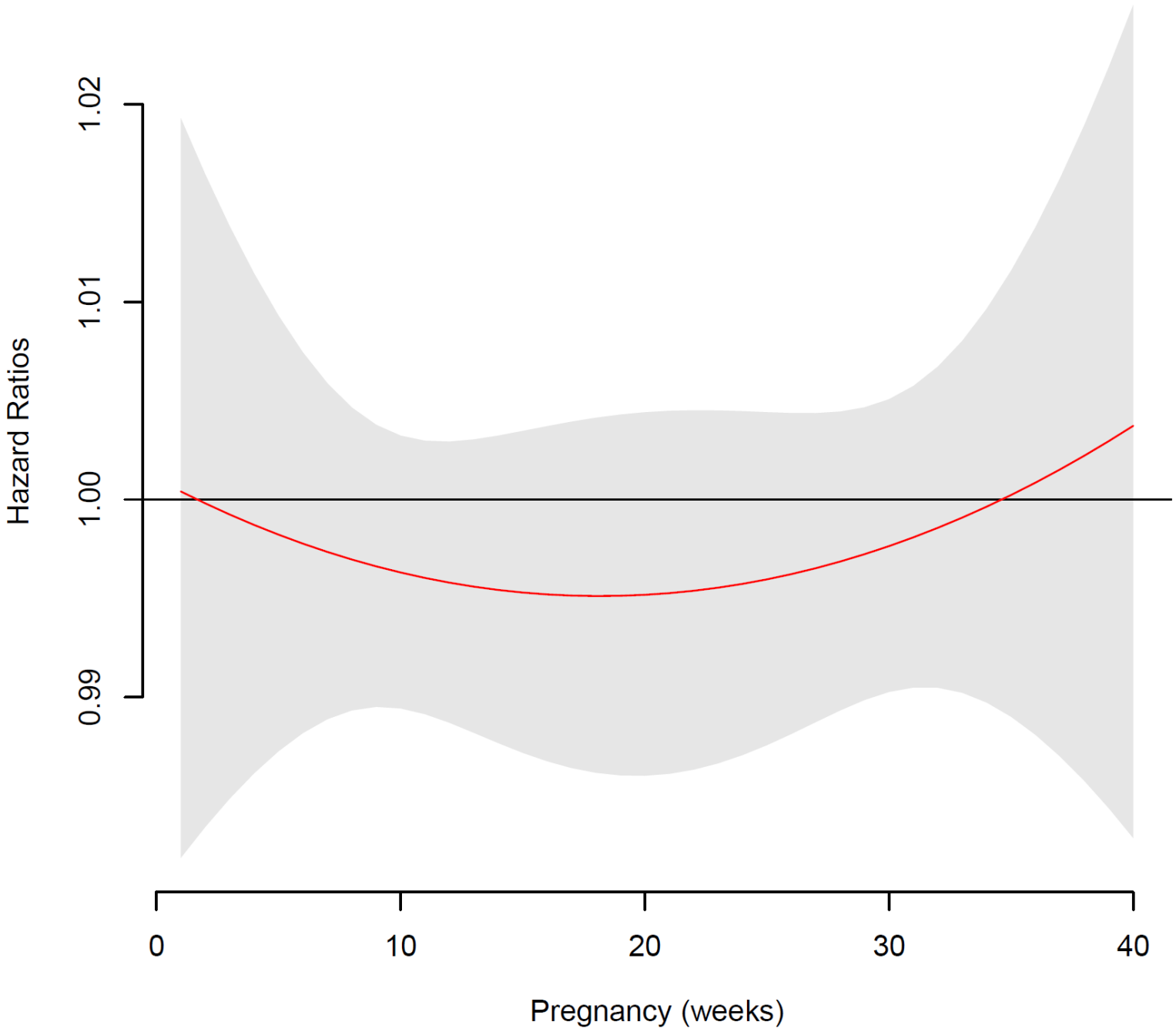


In-utero exposure – Fine Particulate Matter ($PM_{2.5}$)

Weeks	HR*	95% CI
1-12	0.98	0.85 – 1.11
13-26	0.94	0.83 – 1.05
27-40	1.00	0.87 – 1.14

*adjusted for:

- Childhood exposure to pollutant
- Rural / urban residence
- Mother or sibling with IBD
- Median neighborhood household income quintile

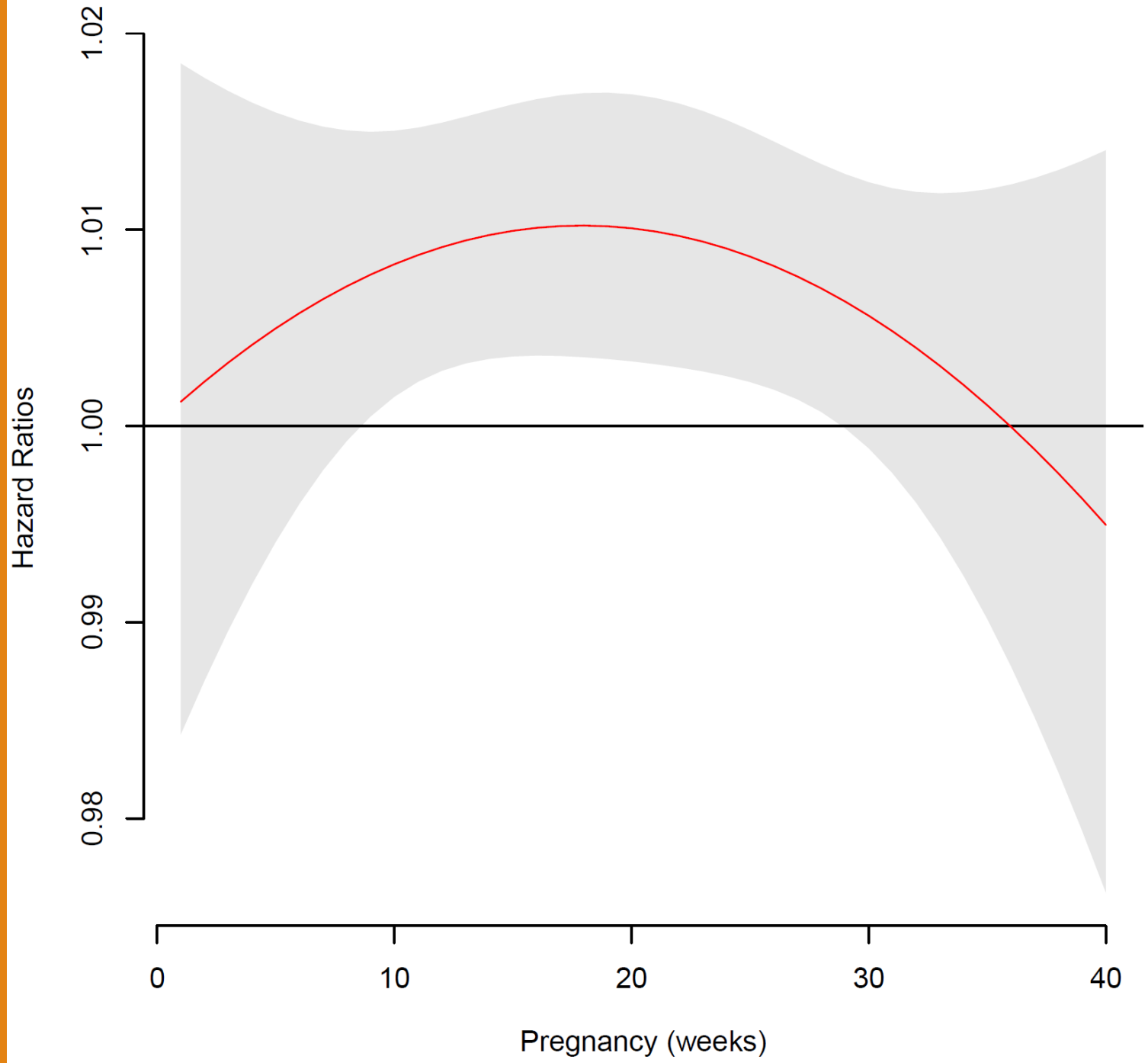


In-utero exposure – Ozone (O_3)

Weeks	HR*	95% CI
1-12	1.07	0.94 - 1.22
13-26	1.14	1.05 – 1.25
27-40	1.03	0.90 – 1.18

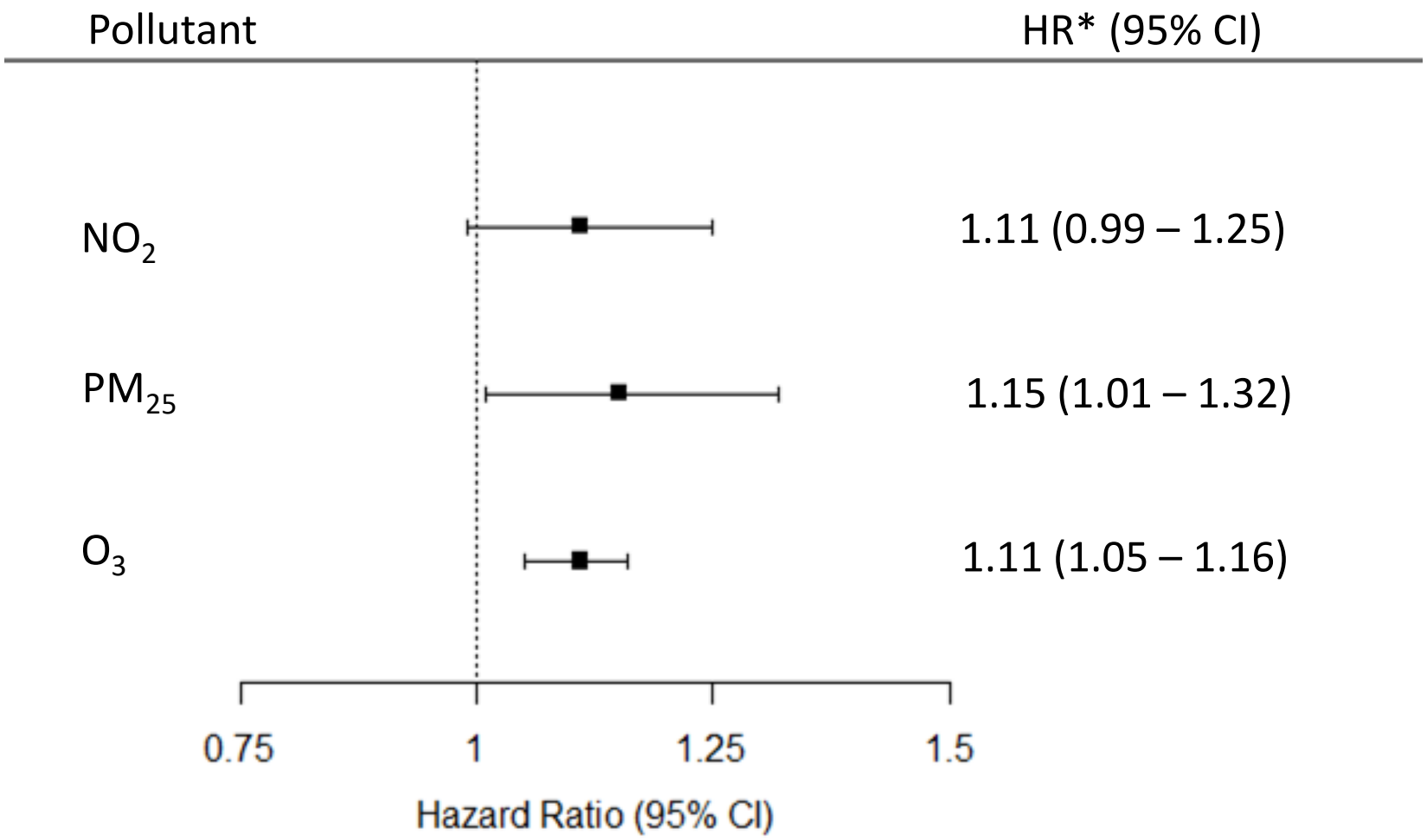
*adjusted for:

- Childhood exposure to pollutant
- Rural / urban residence
- Mother or sibling with IBD
- Median neighborhood household income quintile



Childhood Exposure

Overall IBD



*adjusted for:

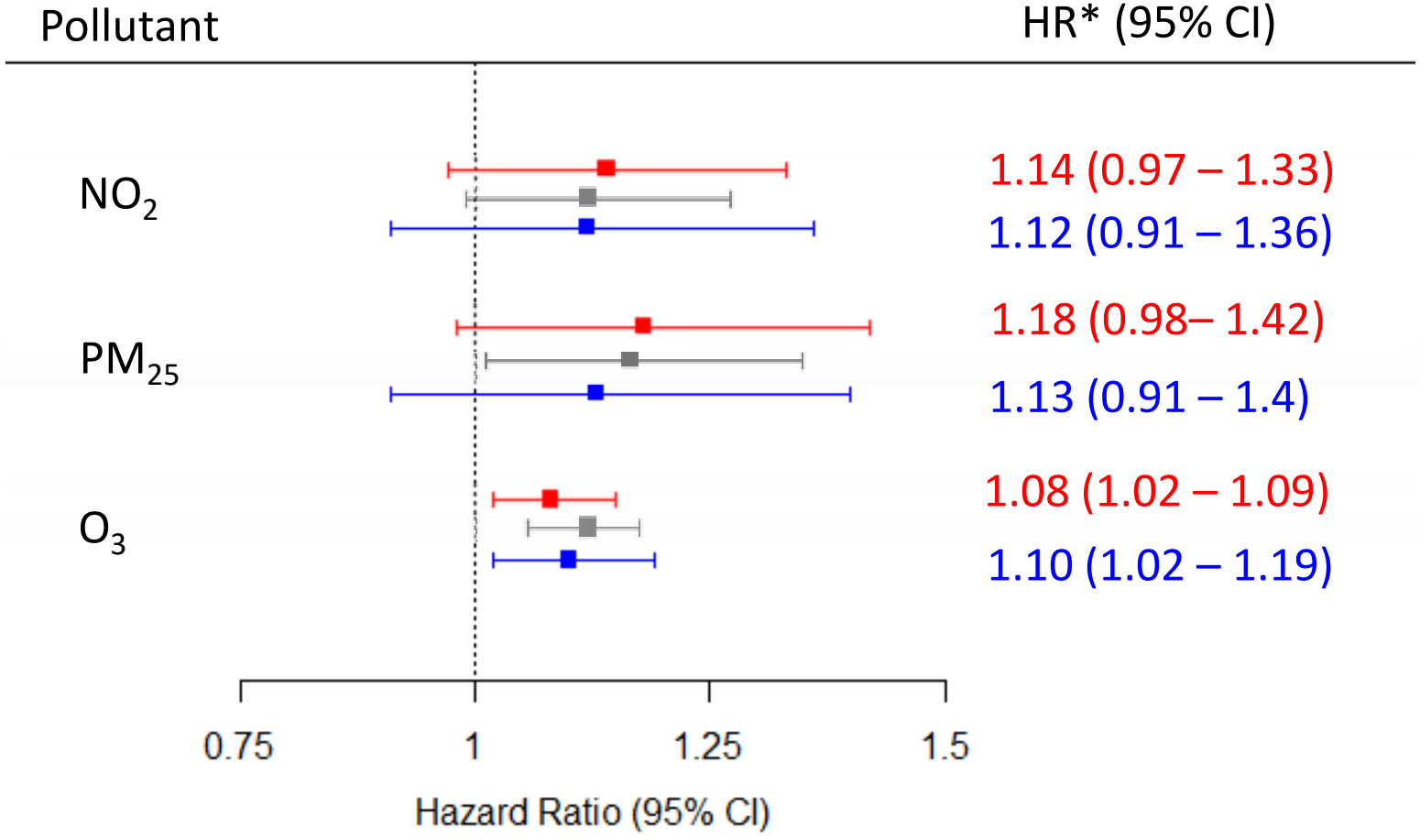
- Average pregnancy exposure
- Rural / urban residence
- Mother or sibling with IBD
- Median neighborhood household income quintile

Childhood Exposure

*adjusted for:

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

Disease Subtypes



Legend:

Crohn's IBD **Ulcerative Colitis**

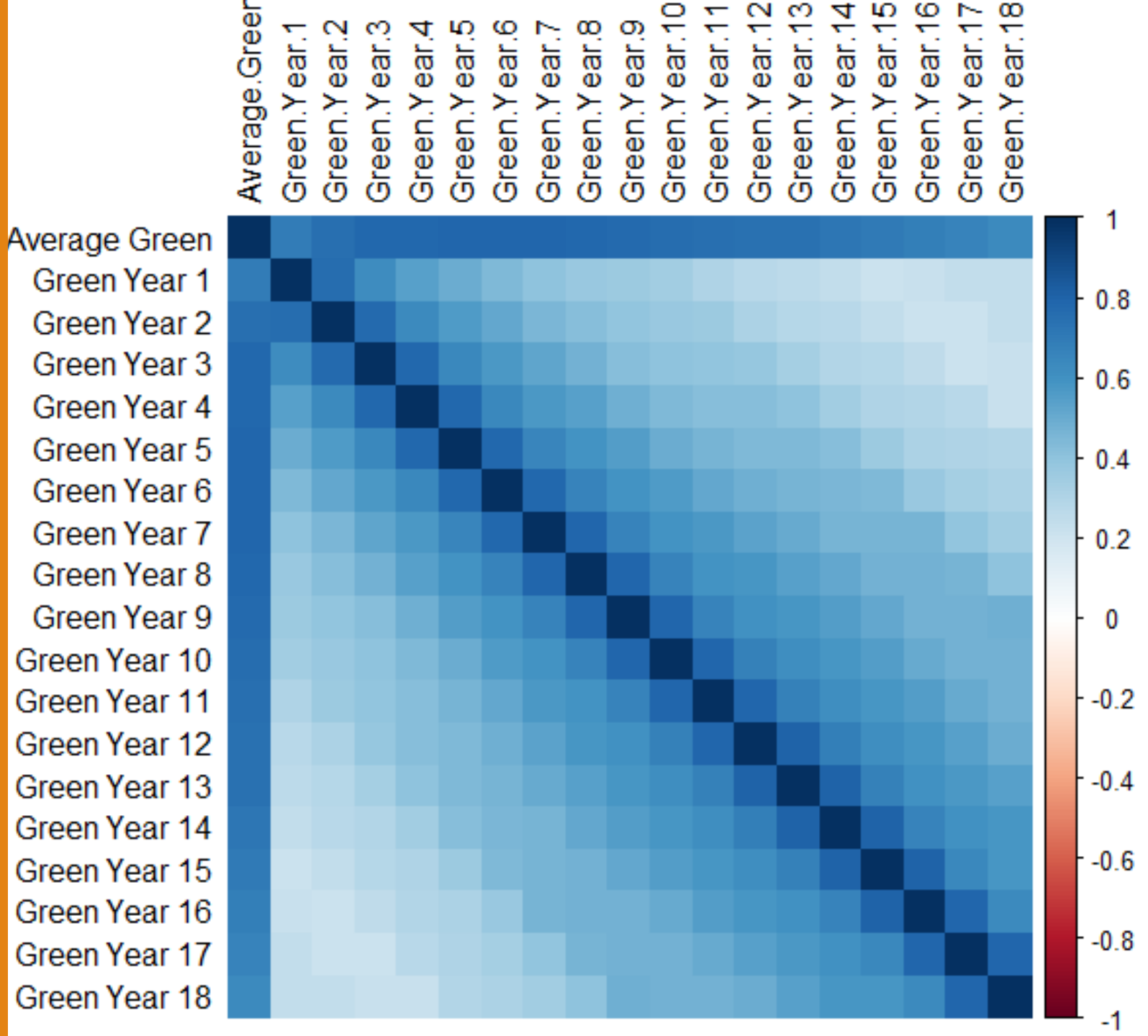
Interpretation

- 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

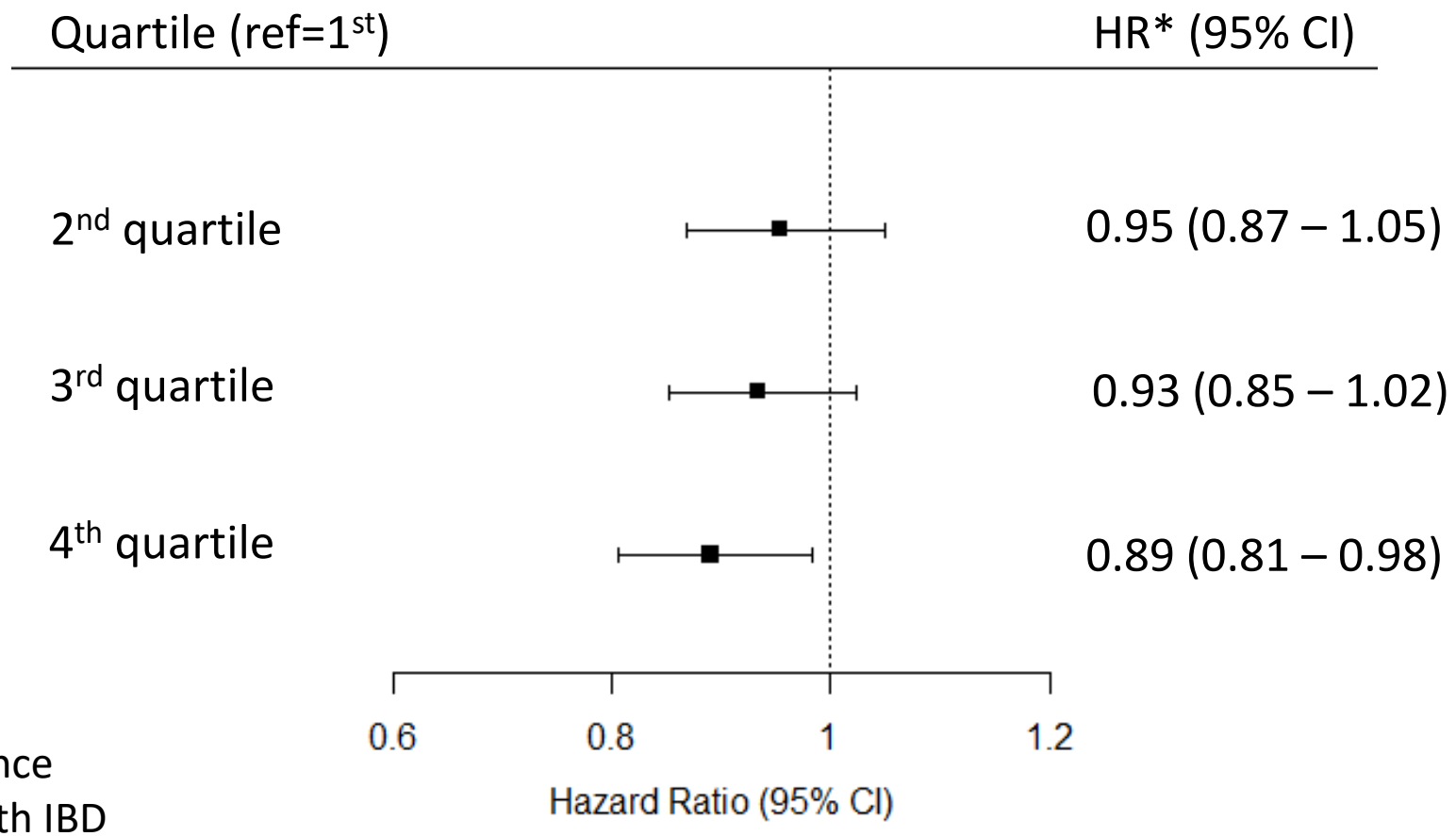


Statistical Analysis

Childhood exposures

- 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

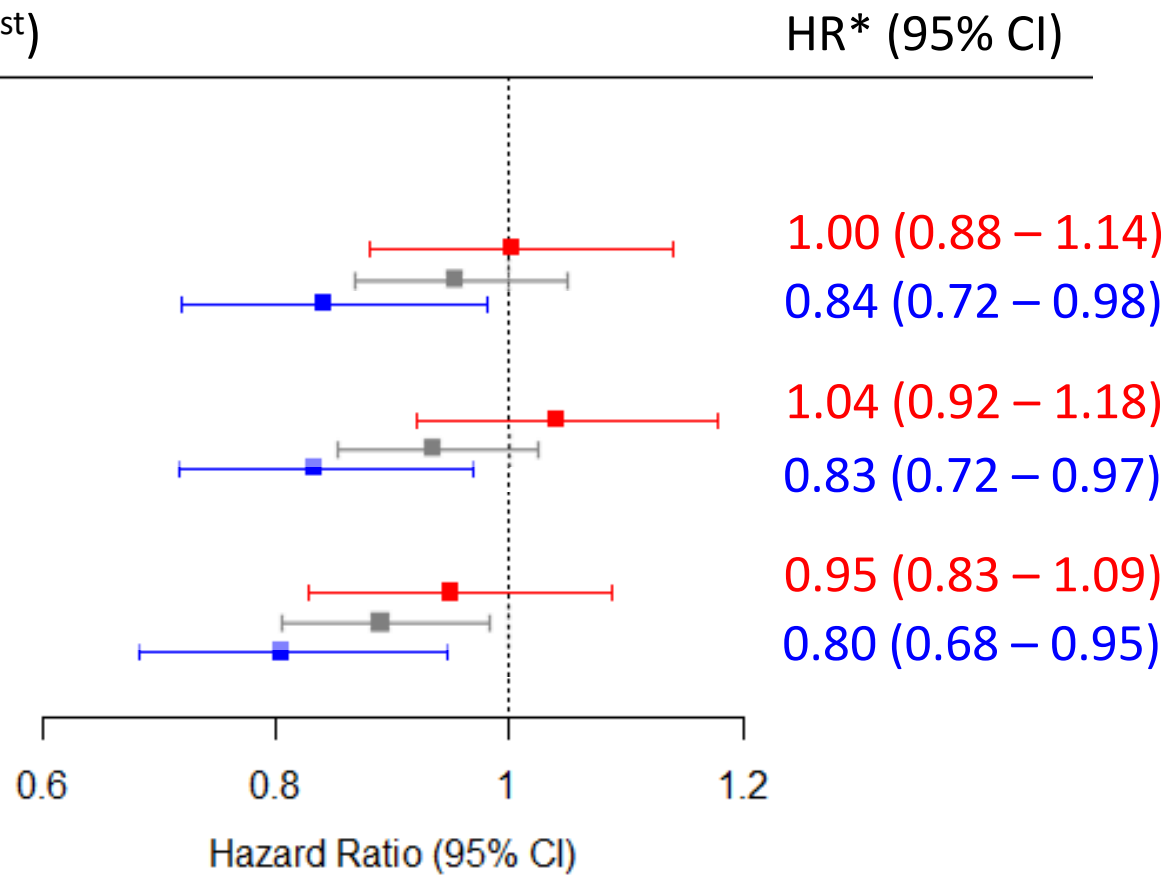
Overall IBD



*adjusted for:

- Rural / urban residence
- Mother or sibling with IBD
- Median neighborhood household income quintile

Disease Subtypes



Legend:

Crohn's

IBD

Ulcerative Colitis

*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

Health Canada Santé Canada

Questions / Feedback?

melte087@uottawa.ca

@MichaelElten