Ambient air pollution and the risk of pediatric inflammatory bowel disease

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EXPOSURE ASSESSMENT SECTION

Presentation overview

BACKGROUND

METHODS

RESULTS

DISCUSSION

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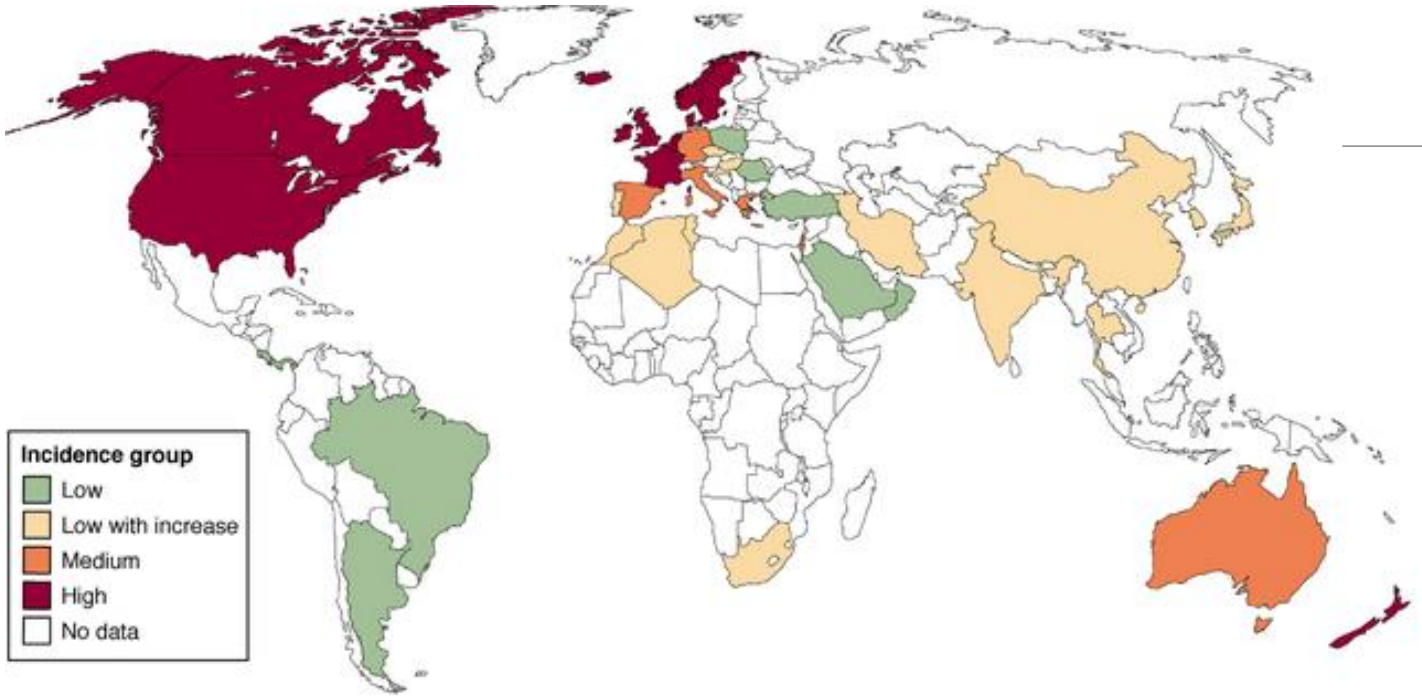
Background

1. WHAT IS IBD?
2. INCREASING INCIDENCE
3. RATIONALE

What is Inflammatory Bowel Disease?

- A chronic immune-mediated disease affecting the digestive tract
- No current cure, can only treat symptoms with varying success
- Two subtypes:
  - Crohn's disease
  - Ulcerative colitis
- Cause of many symptoms that lead to poorer quality of life, and increased burden to the healthcare system, particularly with childhood-onset IBD
- Etiology is poorly understood, but it is known that there are both genetic (20%) and environmental (80%) components to disease development, probably inter-related

Increasing Incidence of IBD



Cosnes et al. *Gastroentrology.* 2011

- The incidence of IBD is highest in westernized nations such as Canada
- Incidence in these countries was seen to have increased during the 20th century
- Recent studies have shown that the incidence rates in newly industrialized nations are rapidly increasing
- If current trends persist, IBD will soon be a global disease with an increasing prevalence worldwide

Motivation for the study

- Why here?
  - Ontario has one of the highest incident rates of IBD in the world, and rates are continuing to climb amongst those aged 0-9 years
- Why air?
  - It is hypothesized that an environmental factor, perhaps related to industrialization, may help explain the increased risk for IBD
  - Air pollution is being increasingly linked to other immune-mediated diseases and may be implicated here

Air pollution?! How?

- Direct dysregulation of immune system development
  - Many immune system elements thought to be implicated in IBD pathology such as mesenteric lymph nodes (MLN) and gut associated lymphoid tissue (GALT), begin developing at week 14, and continue to develop postnatally
  - Evidence suggests that in-utero exposure to NO2 may cause an immune response in the child
- Disruption of the gut microbiome
  - There are differences in gut microbe diversity in pediatric ulcerative colitis cases vs controls
  - PM_{10} has been seen to significantly change the gut microbiome composition, and introduce an inflammatory response when fed to mice

Review of Previous Literature

- One previous epidemiological study:
  - Looked at NO_2, PM_{10} and SO_2 in a UK general population
  - Found that increased levels of NO2 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

Research question

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

Methods

1. DATA SOURCES AND LINKAGE
2. EXPOSURE ASSESSMENT
3. STATISTICAL ANALYSES

Data Sources

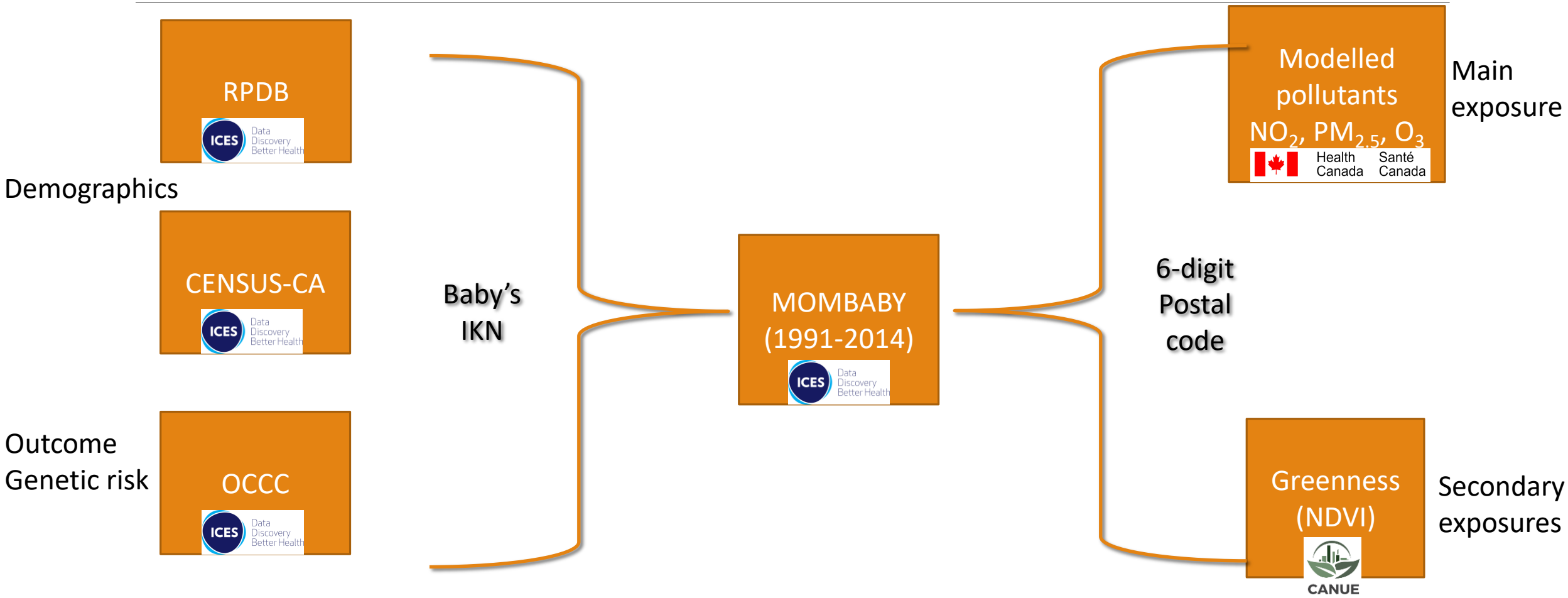
Cohort data:

- 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 validated cases of IBD up to Mar. 31, 2017

Exposure data:

- NO2, PM2.5, O3 data – modelled pollutant data obtained through Health Canada
- Greenness (NDVI) – a measure of greenness a short distance from a given residence

Data Linkage



Exposure Assessment

1. Initial pollutant estimates for each 6-digit postal code were derived as follows:
   - NO2 derived using the national land use regression (LUR) model
   - PM2.5 derived using satellite-based geographically weighted regression techniques
   - O3 derived using an optimal interpolation technique adapted to air pollutants
2. Temporal interpolation to get weekly estimates of the above pollutants for each week of gestation and childhood of all the study population
3. Exposure assignments were calculated as follows:
   - In-utero: estimates were averaged by trimester (and pregnancy average was taken as well)
   - Childhood: estimates were averaged for each year of life, and a running average was taken for the cumulative childhood exposure

Statistical Analysis

Mixed effects Cox proportional hazards models

- Follow-up time is birth until age 18 or end of ascertainment period
- Evaluate the effect of an increase in exposure of a pollutant on the risk of developing IBD, while controlling for confounders
- Hazard ratios (HR) can roughly be interpreted as the increased risk of a child developing IBD per interquartile range (IQR) increase in a given pollutant
- Random effects control for spatial confounding

Model Building

Entered into the model based on previous literature:

- Family history of IBD
- Rural/Urban status
- Median neighborhood household income quintile

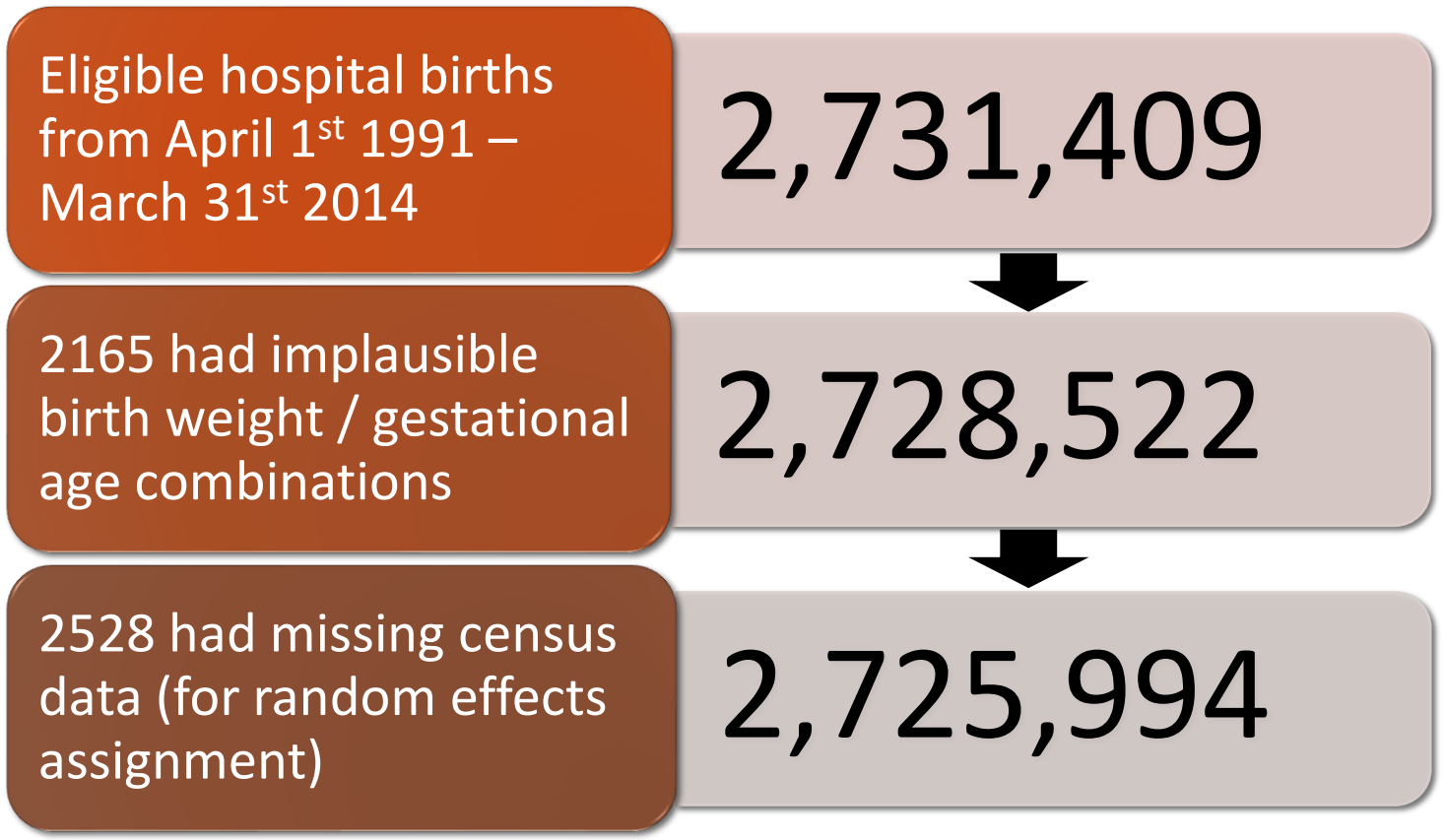
Considered as potential confounders through change in estimate (CIE) method:

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

Results

1. STUDY POPULATION
2. DESCRIPTIVE STATISTICS
3. MODELLING RESULTS

Study Population



Cohort IBD prevalence

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

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)	29.98	29.51
Area of residence		
Rural	333 (10%)	347,710 (13%)
Urban	3131 (90%)	2,374,820 (87%)
Parity (previous children by mother)		
0	1,747 (50%)	1,321,672 (49%)
1	1,288 (37%)	965,840 (35%)
2+	419 (12%)	427,403 (16%)
Missing	10 (0.3%)	7,615 (0.3%)
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)
IBD in immediate family*		
Yes	1139 (33%)	14,410 (0.5)
No	2,325 (67%)	2,708,120 (99.5)

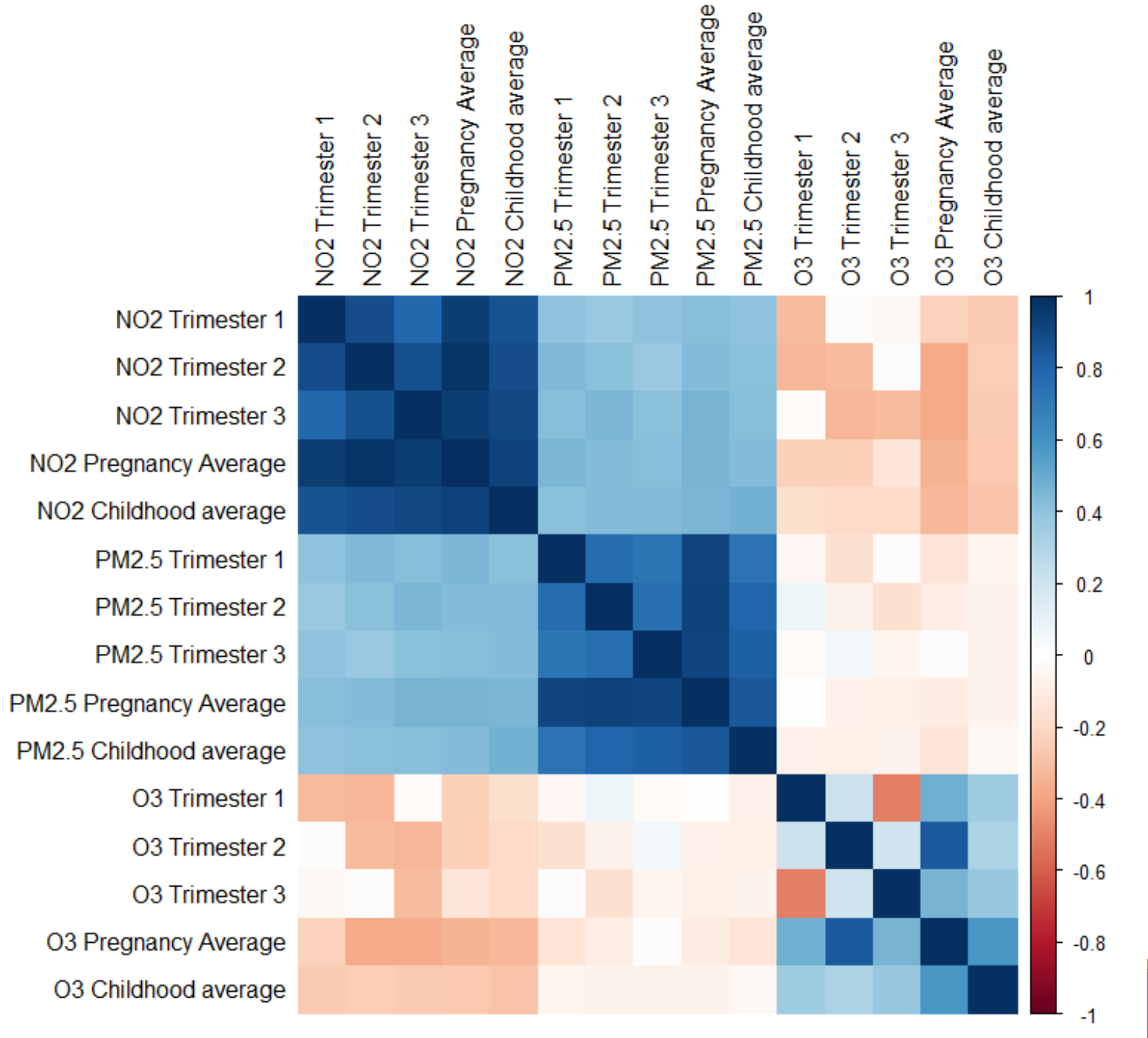
Exposure correlation matrix

Mean long-term exposures:

NO_2 : 12.2 ppb

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

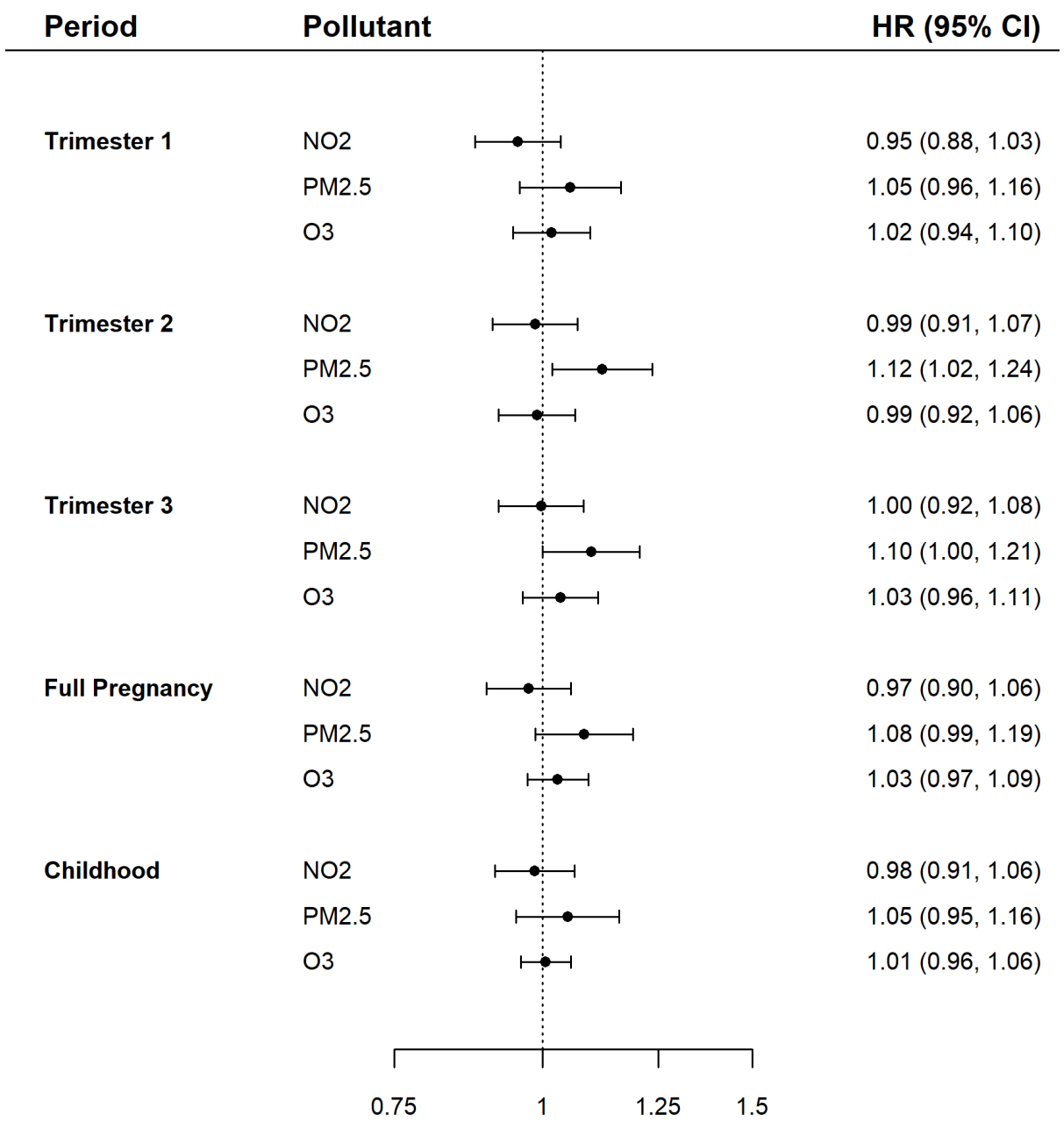
O_3 : 24.5 ppb



Forest plot - Adjusted associations

All hazard ratios are adjusted for:

- Rural / urban residence
- Family history of IBD
- Median neighborhood household income quintile



Discussion

1. DISCUSSION OF RESULTS
2. LIMITATIONS

Interpretation of results

- Based on current analyses:
  - There may be something going on with PM2.5 during the mid-late pregnancy, though effect appears to be unexpectedly strong!
  - Exposure to pollutants during childhood is not really associated with increased risk

Limitations

- There are several limitations of this study:
  - Residential mobility
  - Personal exposure
  - No adjustment for other exposure periods / pollutants
  - Arbitrary classification of trimesters

Next steps:

- Mutually adjust models for other exposure periods and pollutants
- Increase precision in the in-utero analyses
- Look at results stratified by disease subtype
- Look at “early” early-life exposures

Conclusions

- While results are interesting, can't make any causal statements from one study
- Particulate matter exposures in mid-to-late pregnancy should be investigated further in higher resolution
- Future analyses both in this current study, and in other studies should ensure that the observed associations are robust to adjustment to other pollutants, and adjustment for multiple periods

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Questions / Feedback?