Environmental exposures in asthma: opportunities for prevention

Tim K. Takaro, MD, MPH.
Faculty of Health Sciences
Simon Fraser University
Conflict of Interest

Nothing to declare…
Thank you funders!
Story of David

David was a 15 year old with severe asthma growing up in a housing project in Seattle’s High Point neighborhood.

“We still have the inhalers, but he hardly uses them”
- David’s mom two years after moving into a Breathe Easy Home
Questions for today’s talk

- What is the difference between asthma exacerbation and asthma development?
- What are exposures that influence asthma development and exacerbation?
- Why are exposures important in asthma?
- What about multiple exposures in asthma?
- Can exposure reduction improve health?
Development of asthma compared to flare-up of existing asthma

- **BIRTH**
  - NO ASTHMA
  - AGE 5-7 YRS
- ASTHMA
- NO ASTHMA
- NO ASTHMA
- NO ASTHMA
- ADOLESCENT TO ADULT
  - Late onset
Asthma Development

- **BIRTH**: Asthma or No Asthma
- **AGE 5-7 YRS**: No Asthma
- **ADOLESCENT TO ADULT**: Late Onset

Diagram shows the progression of asthma development from birth to adulthood.
Flare-up of Existing Asthma

- **BIRTH**
  - ASTHMA
  - NO ASTHMA

- **AGE 5-7 YRS**
  - NO ASTHMA

- **ADOLESCENT TO ADULT**
  - NO ASTHMA
  - NO ASTHMA

Late onset

SFU

Simon Fraser University
Engaging the World
Development of asthma compared to flare-up of existing asthma

Why is this distinction important?

- Flare-ups or exacerbations have been much easier to study until recent large birth cohorts so most of our knowledge of exposure-response relationships comes from these studies.

- Opportunities for primary prevention vs. secondary prevention have very different human health and economic value, i.e. prevent one case of asthma and all downstream costs (medication, time-loss, QOL) are saved for a lifetime.
What are the Determinants Asthma Development?

CAUSE  common pathway  EFFECT
What are the Determinants Asthma Development?

CAUSE ➔ common pathway ➔ EFFECT

- genetic
- environmental
  - physical
  - psychosocial
  - microbial

GENETICS
ENVIRONMENT
INNATE IMMUNITY ➔ ADAPTIVE IMMUNITY ➔ ASTHMA ALLERGY
What are the Determinants of Asthma Development?

CAUSE — common pathway — EFFECT

- physical
- psychosocial
- microbial

 common pathway
What are the Determinants of Asthma Development?

- Physical
- Psychosocial
- Microbial
Exposure Measurement in CHILD Study

Canadian Healthy Infant Longitudinal Development Study

Genetics
Immune phenotypes
Clinical phenotypes
Infant Pulmonary Function
Microbiome

Exposures
Pollution
Work & School environment

Home environment

Stress
Viruses
SES
Diet
Pets

AllerGen

In utero
3 months
6 months
1 year
1 1/2 years
2 years
2 1/2 years
3 years
4 years
5 years

Recruitment, material and parental study of children, stress, environment and health assessment questionnaire
delivery outcomes, blood, maternal
Health questionnaire, home assessment, breast milk, urine, infant lung Function, stress
Clinic tests on skin, blood, lung function, infections, urine, need medical, asthma, material balance
Questionnaire follow-up
Questionnaire follow-up
Questionnaire follow-up
Clinic visits, urine, skin, lung function, clinical assessment, questionnaires
Questionnaire follow-up
Questionnaire follow-up
Questionnaire follow-up
# CHILD Exposure Assessment for the Physical Environment

Takaro, et al. JESEE 2015

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Questionnaires</th>
<th>house dust</th>
<th>Home Assessment (3mo)</th>
<th>biomarkers</th>
<th>geographic models</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common allergens (pets, pests)</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Environmental tobacco smoke</td>
<td>✓</td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Endotoxin</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Home dampness</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mould in home</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indoor semivolatile organic compounds</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Traffic air pollution</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outdoor air pollution</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Outdoor Air Pollution

- 92% of the world’s population lives where air quality levels exceed the World Health Organization’s ambient air quality guidelines for annual mean particulate matter (PM) with a diameter of less than 2.5 mm (PM2.5).

- PM 2.5 is definitively associated with asthma flare-ups and may cause asthma
Traffic-related air pollution at home estimated from land-use regression maps for each of four centres

Indoor and outdoor exposures related to asthma

Dust mites † *
Mold (moisture)
Tobacco Smoke *
Pets (?)
Cockroaches*
Rhinovirus
Respiratory syncycial virus
Indoor cleaning chemicals

Rodents
Stove and heater emissions
Respiratory irritants (e.g. endotoxin, phthalates, fragrances, diesel particulates)
Traffic Related Air Pollutants *
Aero-allergens (pollen, fungi)

Burbank et al. 2017. JACI. 140: 1-12
But Wait… Pets have a question mark

Why is this so complicated?
But Wait… Pets have a question mark

Why is this so complicated?

1) Genetic differences
But Wait… Pets have a question mark

Why is this so complicated?

1) Genetic differences
2) Timing of exposure matters (early life vs. after asthma established)
But Wait… Pets have a question mark

Why is this so complicated?

1) Genetic differences i.e. variable susceptibility
2) Timing of exposure matters (early life vs. after asthma established)
3) We’re exposed to many things at the same time and we’re bad at measuring everything together.
But Wait… Pets have a question mark

Why is this so complicated?

1) Genetic differences i.e. variable susceptibility
2) Timing of exposure matters (early life vs. after asthma established)
3) We’re exposed to many things at the same time and we’re bad at measuring everything together.
4) Some exposure risk curves are not linear
Non-linear dust mite exposure-response curves

Dust mite
exposure
quintiles

Tovey et al.
JACI 2008;
122:114
But Wait… Weren’t Pets on this List?

Why is this so complicated?

1) Genetic differences i.e. variable susceptibility
2) Timing of exposure matters (early life vs. after asthma established)
3) We’re exposed to many things at the same time and we’re bad at measuring everything together
4) Some exposure risk curves are not linear
5) These factors interact in complicated ways
Diesel plus allergen exposure

Kramer et. al. 2017
Translational Res.
182:49–60
The Hygiene Hypothesis – or Let ‘em Eat Dirt

- Overcrowding, unhygienic conditions, and larger family size are associated with a lower asthma prevalence.
- Infections and exposures to specific pro-inflammatory microbial agents e.g. endotoxin are implicated.
- Such exposure activate innate immunity through toll-like receptor pathway and thereby suppress the Th2 response.
- Attempts to explain recent increases in asthma as due to increased cleanliness, smaller family size and overuse of antibiotics in kids.
The Hygiene Hypothesis

CAUSE                 common pathway                 EFFECT

GENETICS

ENVIRONMENT

INNATE IMMUNITY → ADAPTIVE IMMUNITY

‘good germs’ normal immune function

ASTHMA ALLERGY
Genetic Determinants of Asthma: The Confusing Role for Endotoxin

Endotoxin (aka lipopolysaccharide or LPS) is a potent inflammatory agent found primarily in gram-negative bacterial cell walls.

Role in asthma is confusing
1) Protective effect with early exposure (hygiene hypothesis)
2) Clearly exacerbates existing asthma acting as an inflammatory agent
Dose-Response for Endotoxin Depends Upon CD14 Genetic Variant

Simpson et al. Respir Crit Care Med 2006;174:386–392
Population study: Genetically similar Hutterite and Amish homes

Stein et al. 2016 NEJM 375: 411-421

endotoxin levels
Some conclusions

- A wide range of exposures can be measured relatively inexpensively in early life in birth cohorts.
- BUT .... the health impact is complicated by:
  - Genetic differences in susceptibility to exposure
  - Timing of exposure during development
  - Non-linear dose-response
  - The multiplicity and interactions of exposures
Remember David and the Breathe Easy Home?

Takaro et al. 2011; AJPH 101:55
Opportunities for Interventions to prevent asthma flare-ups and asthma development

Burbank et al. JACI. 2017; 140:1
Opportunities for Interventions to prevent asthma flare-ups and asthma development

Burbank et al. JACI. 2017; 140:1
Breathe Easy Homes
Limitations and Conclusions

- Necessity of Pre-Post Design limits the ability to interpret the relationship between trigger reduction and clinical response. Hard to dissect building effects from other effects.
- Though home environmental assessment not performed by the same CHW engaged in educational visits, assessor knew status of subject.
- We did not control for outdoor asthma triggers e.g. air pollution.

CONCLUSIONS:
- In this population of low-income children, modest improvements in housing design, materials & construction ($5,000-7000) had a dramatic effect on asthma triggers, symptoms & exacerbations, FEV1 & PC20 and a modest improvement in caretaker QOL.
Canadian Asthma Primary Prevention Study

Mothers of high-risk infants recruited during third trimester in Vancouver (n = 545) and Winnipeg (n = 274)

*High-risk* > first-degree relative with asthma (or two first-degree relatives with IgE-mediated allergic disease)

RCT: control (usual care) or intervention

- avoidance of HDM, pet allergen, and ETS
- breast-feeding encouraged
- formula supplementation if necessary
- introduction of solid foods delayed
Canadian Asthma Primary Prevention Study

Percent Physician Diagnosed Asthma

Age 1 & 2
Age 7

Control
Intervention

Chan-Yeung, et al JACI 2005
Becker et al JACI 2004
Inner-city Asthma Study
Symptom Days (Flare-ups) in Previous 2 Weeks

## CDC Expert Panel Review on Housing Interventions

<table>
<thead>
<tr>
<th>Panel</th>
<th>Sufficient Evidence for Implementation</th>
<th>Needs More Field Evaluation</th>
</tr>
</thead>
</table>
| Interior Biological Agents (Toxins) | 1. Multifaceted, in-home, tailored interventions for asthma (reduce exposure to triggers, decrease symptoms and health care use, improve quality of life)  
2. Cockroach control through integrated pest management (reduce allergens)  
3. Combined elimination of moisture intrusion and leaks and removal of moldy items | 1. Improved insulation (reduce moisture and mold exposure and improve general and respiratory health status)  
2. Repeated vacuuming and steam cleaning of carpeting and furnishings (reduce allergens)  
3. HEPA air filtration (to reduce asthma)  
4. Ventilation and dehumidification | 1. Radon mitigation in drinking water  
2. Portable HEPA cleaners to reduce indoor particulates  
3. Attached garage sealing to limit VOC intrusion  
4. Particulate control by envelope sealing |
| Interior Chemical Agents (Toxics)   | 1. Active radon air mitigation strategies (to reduce exposure to radon in air)  
2. Integrated pest management (pesticide reduction)  
3. Smoke-free policies  
4. Residential lead hazard control to reduce lead hazards and children's blood lead levels |                                                                                               | 1. Radon mitigation in drinking water  
2. Portable HEPA cleaners to reduce indoor particulates  
3. Attached garage sealing to limit VOC intrusion  
4. Particulate control by envelope sealing | 1. Radon mitigation in drinking water  
2. Portable HEPA cleaners to reduce indoor particulates  
3. Attached garage sealing to limit VOC intrusion  
4. Particulate control by envelope sealing |
Public Health Policy & Practice to Reduce Impact of Asthma

- Test housing interventions on larger scale
- Increase availability of healthy housing for low income families (focus on FN housing)
- Educate primary care providers on linkage of IEQ efforts to clinical asthma management
- Promote healthcare coverage of exposure control resources and community health worker driven interventions
- Integrate housing and health at Ministry policy making level
Some recent findings from the CHILD Study

- Air pollution exposure increases early childhood atopy
  - Traffic-related air pollution is a risk factor for childhood asthma
- Health Canada / Chemical Management Plan analyses:
  - Cotinine is detectable in urine of almost all infants at 3-4 months
  - Phthalate metabolites in urine are associated with early atopy
- The early infant microbiome varies among children:
  - The microbiome is affected by mode of delivery, breastfeeding, antibiotic use, household pets and the presence of siblings
- The early infant microbiome is associated with atopy and wheezing
  - Changes in infant microbiome are associated with food sensitization
  - CHILD data and animal models show deficiency of certain microbiota (FLVR) is associated with clinical asthma and airway inflammation
Traffic exposure linked to atopy in CHILD

Sbihi, et al. 2015 EHP
Traffic exposure linked to atopy in CHILD

Sbihi, et al. 2015 EHP
Day care appears protective against air pollution effect in childhood atopy

Sbihi, et al. 2015 EHP
New CHILD findings: Cleaning products exposure in early life may increase asthma risk

Questionnaire responses at 3 months of age used for Frequency of Use Score (FUS)
0=none, 1=less than monthly, 2=monthly, 3=weekly, 4=daily

<table>
<thead>
<tr>
<th>Frequency of Use Score</th>
<th>Frequency of Use Level</th>
<th># Subjects in sample (n=1884)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score &gt;=37.0</td>
<td>“Very High Use”</td>
<td>515</td>
</tr>
<tr>
<td>Score &gt;= 31.0, &lt;37.0</td>
<td>“High Use”</td>
<td>431</td>
</tr>
<tr>
<td>Score &gt; 24.0, &lt;31.0</td>
<td>“Moderate Use”</td>
<td>509</td>
</tr>
<tr>
<td>Score &lt;=24.0</td>
<td>“Low Use”</td>
<td>429</td>
</tr>
</tbody>
</table>
New CHILD finding: Cleaning products exposure in early life may increase asthma risk

Frequency of Use
Highest
Toronto 33
Lowest
Vancouver 28
Opportunities for Interventions to prevent asthma flare-ups and asthma development

Burbank et al. JACI. 2017; 140:1
Adding FLVR to CHILD

RESEARCH ARTICLE

Early infancy microbial and metabolic alterations affect risk of childhood asthma

Marie-Claire Arrieta,1,2* Leah T. Stiemisma,2,3* Pedro A. Dimitriu,2 Lisa Thorson,1 Shannon Russell,1,2 Sophie Yurist-Doucet,1,2 Boris Kuzeljevic,3 Matthew J. Gold,4 Heidi M. Britton,1 Diana L. Lefebvre,5 Padmaja Subbarao,6,7 Pius Mandhane,8,9 Allan Becker,10 Kelly M. McNagny,4 Malcolm R. Sears,5 Tobias Kollmann,3,11 the CHILD Study Investigators,† William W. Mohn,2 Stuart E. Turvey,3,11‡§ B. Brett Finlay1,2,12†§

Atopy

- 87 subjects Atopy only
- 22 subjects Atopy + Wheeze (AW)
- Positive allergen skin prick test at 1 year

Wheeze

- 136 subjects Wheeze only
- ≥1 episode of wheezing by 1 year of age

Asthma by 3 years of age (odds ratio)

1 2 5 10 15 20 25

74 subjects Controls

SFU SIMON FRASER UNIVERSITY ENGAGING THE WORLD
Adding FLVR to CHILD
We were all much younger then...
Thanks for your attention! Questions?