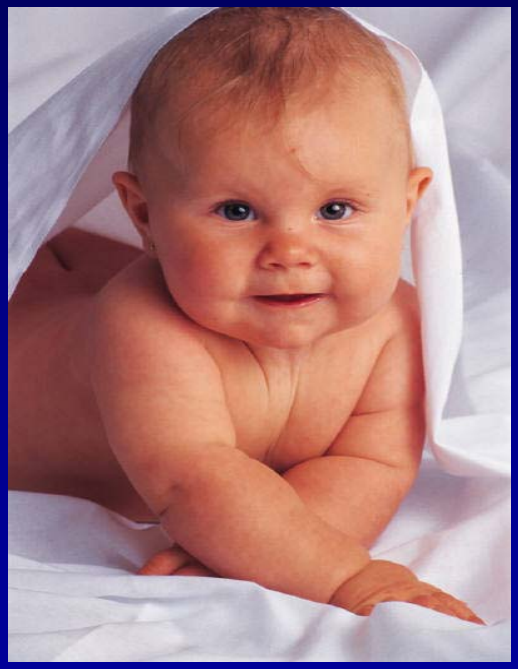
Environmental exposures in asthma: opportunities for prevention



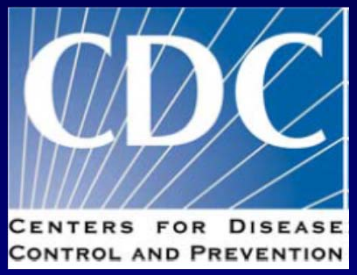
Tim K. Takaro, MD, MPH.
Faculty of Health Sciences
Simon Fraser University

SFU SIMON FRASER UNIVERSITY
ENGAGING THE WORLD

Conflict of Interest

Nothing to declare…

Thank you funders!

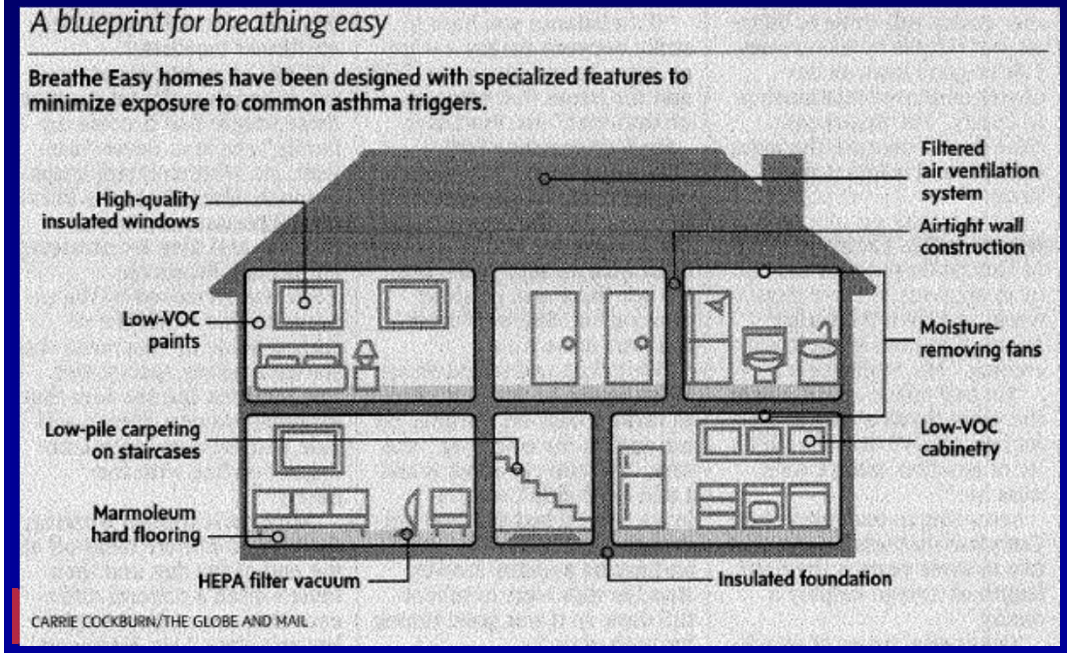


Private donors – Sick Kids Foundation

Chemical Management Program

Story of David

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



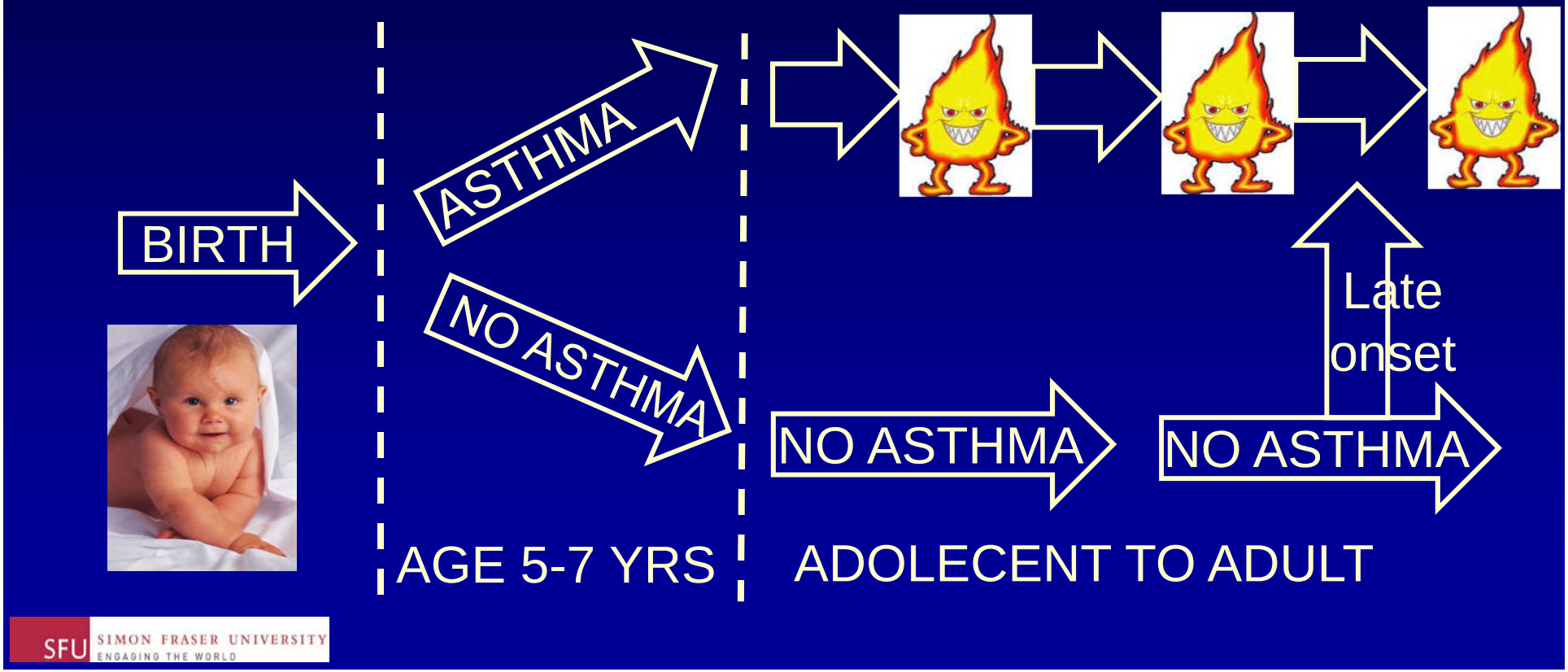
"We still have the inhalers, but he hardly uses them"

- 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



Asthma Development

BIRTH

ASTHMA

NO ASTHMA

AGE 5-7 YRS

NO ASTHMA

ADOLECENT TO ADULT

Late onset

NO ASTHMA

SFU SIMON FRASER UNIVERSITY ENGAGING THE WORLD

Flare-up of Existing Asthma

BIRTH

ASTHMA

NO ASTHMA

AGE 5-7 YRS

NO ASTHMA

Late onset

NO ASTHMA

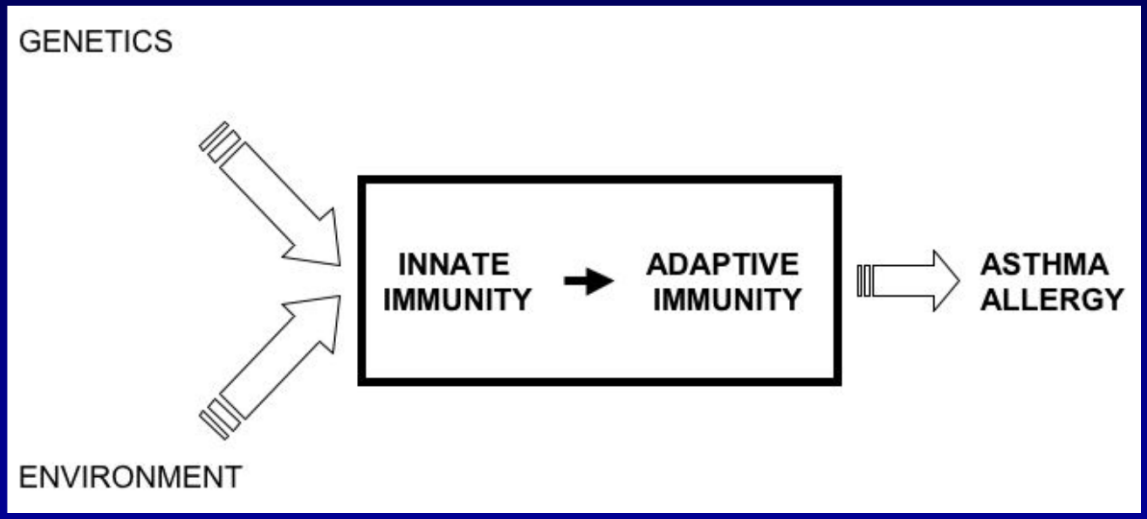
ADOLECENT TO ADULT

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.

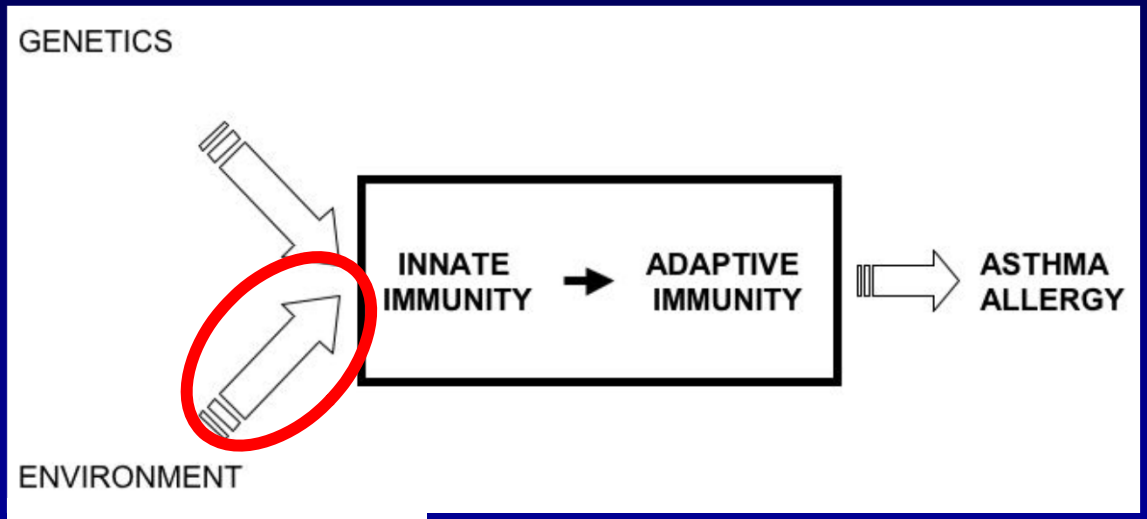
What are the Determinants Asthma Development?



CAUSE ⟶ common pathway ⟶ EFFECT

What are the Determinants Asthma Development?

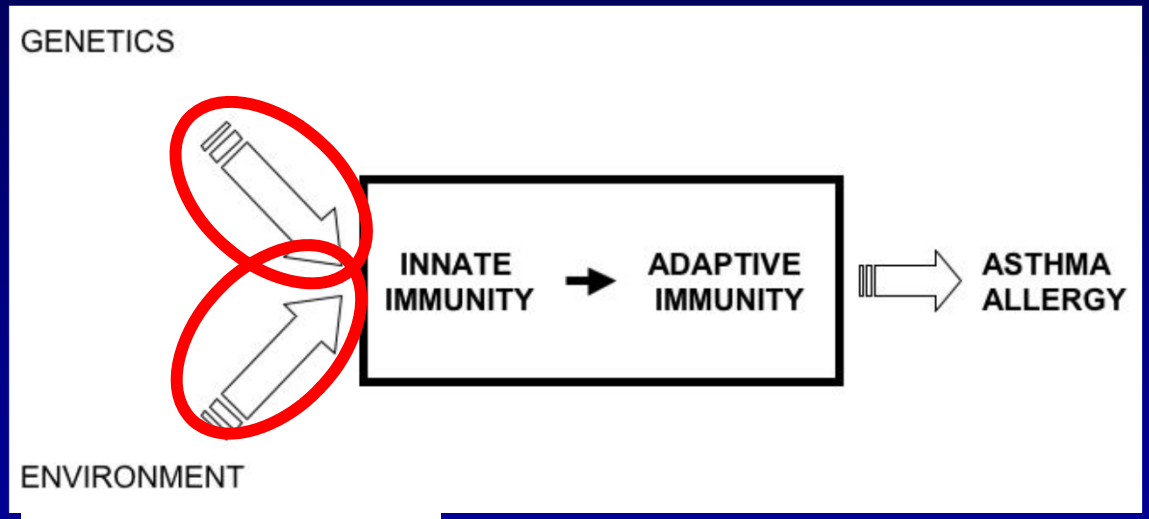
CAUSE ⟶ common pathway ⟶ EFFECT



-physical
-psychosocial
-microbial

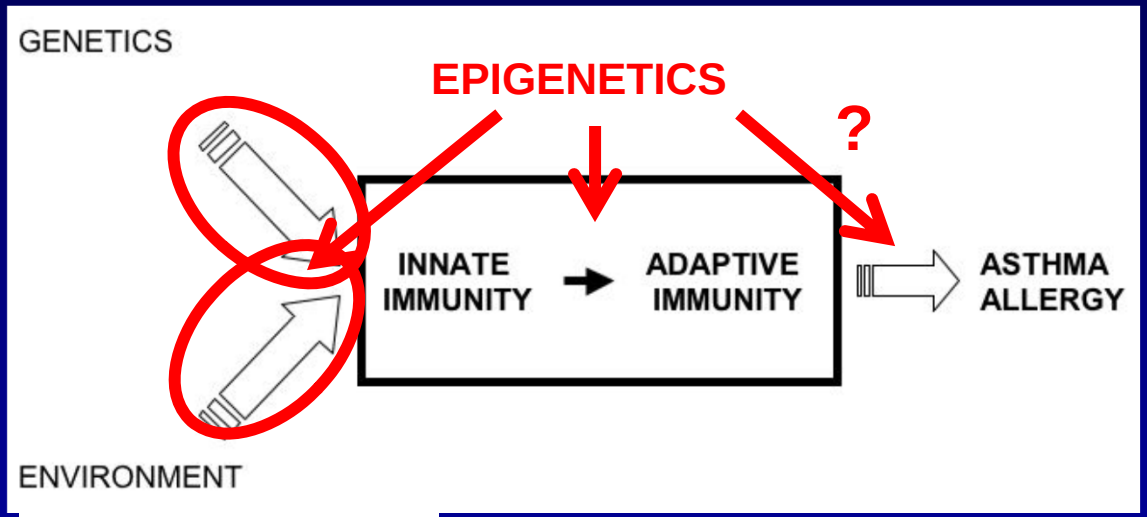
What are the Determinants Asthma Development?

CAUSE ⟶ common pathway ⟶ EFFECT



-physical
-psychosocial
-microbial

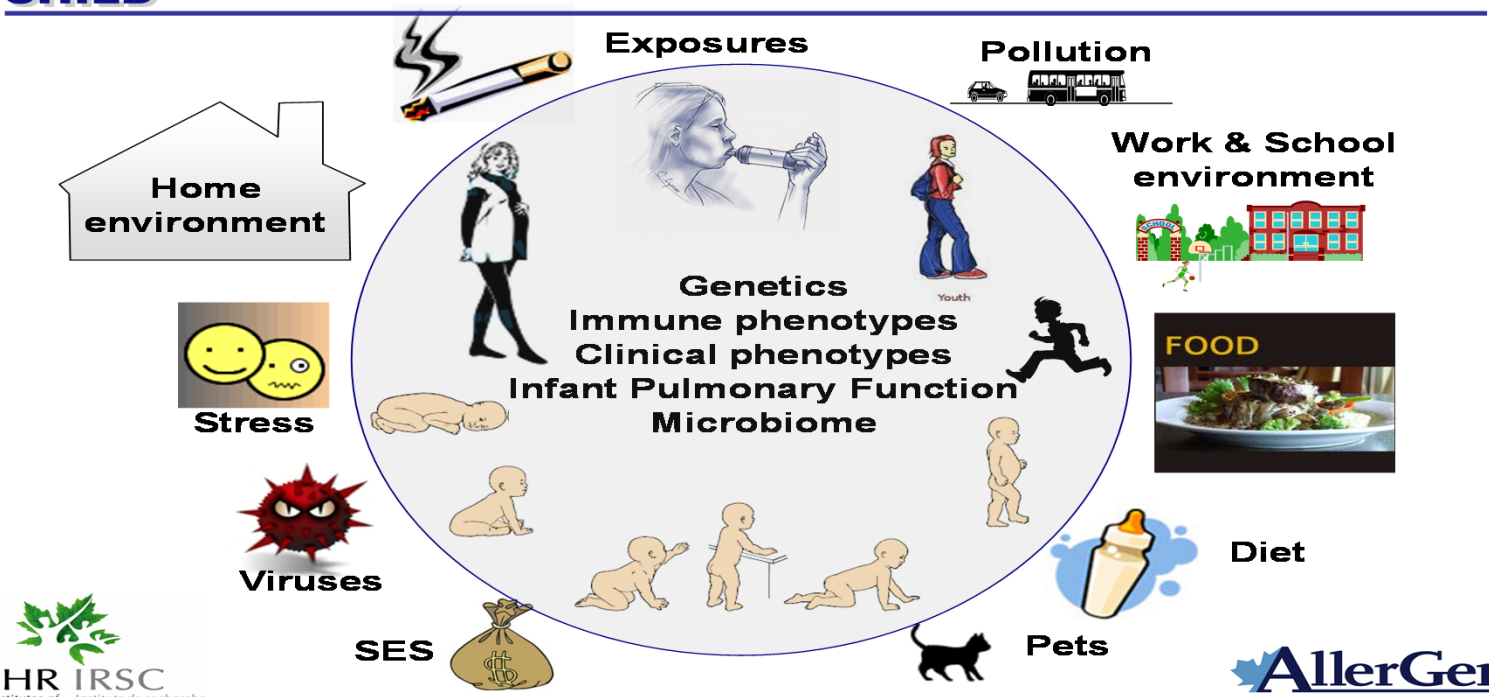
What are the Determinants Asthma Development?



-physical
-psychosocial
-microbial

Exposure Measurement in CHILD Study

Canadian Healthy Infant Longitudinal Development Study



CHILD Exposure Assessment for the Physical Environment

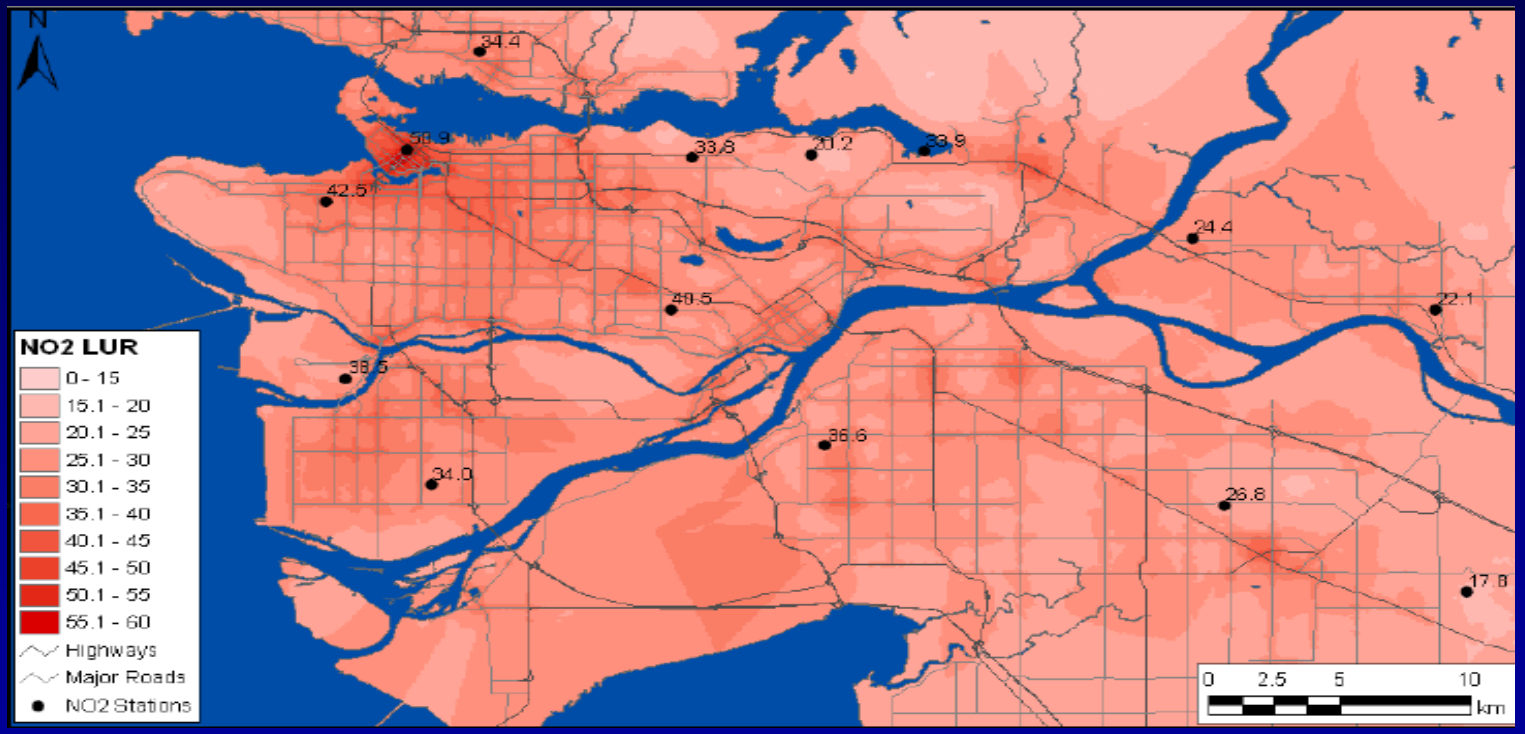
Exposure	Questionnaires	house dust	Home Assessment (3 mo)	biomarkers	geographic models
Common allergens (pets, pests)	✓	✓			
Environmental tobacco smoke	✓			✓	
Endotoxin	✓	✓			
Home dampness	✓		✓		
Mould in home	✓	✓	✓		
Indoor semivolatile organic compounds	✓	✓	✓	✓	
Traffic air pollution	✓	✓			✓
Outdoor air pollution	✓	✓			✓

Takaro, et al. JESEE 2015

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



Vancouver LUR (2003) Sbihi, et al. 2015

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)

SFU SIMON FRASER UNIVERSITY ENGAGING THE WORLD

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.**

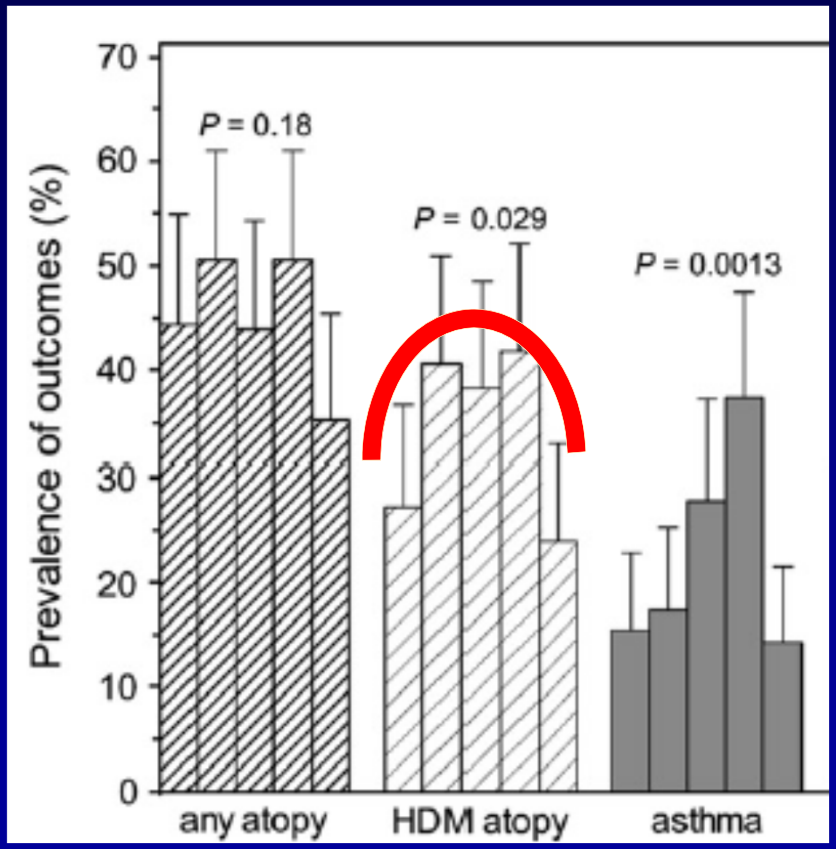
But Wait… Pets have a question mark

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

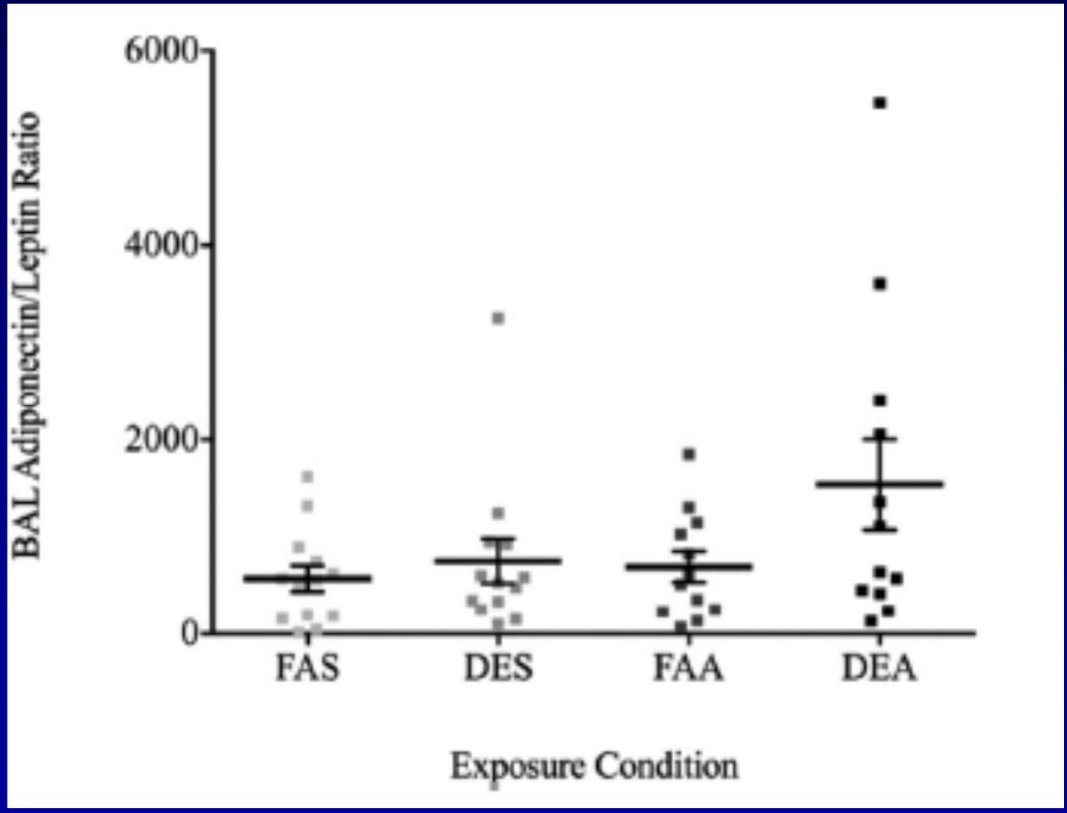
But Wait… Weren't Pets on this List?

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

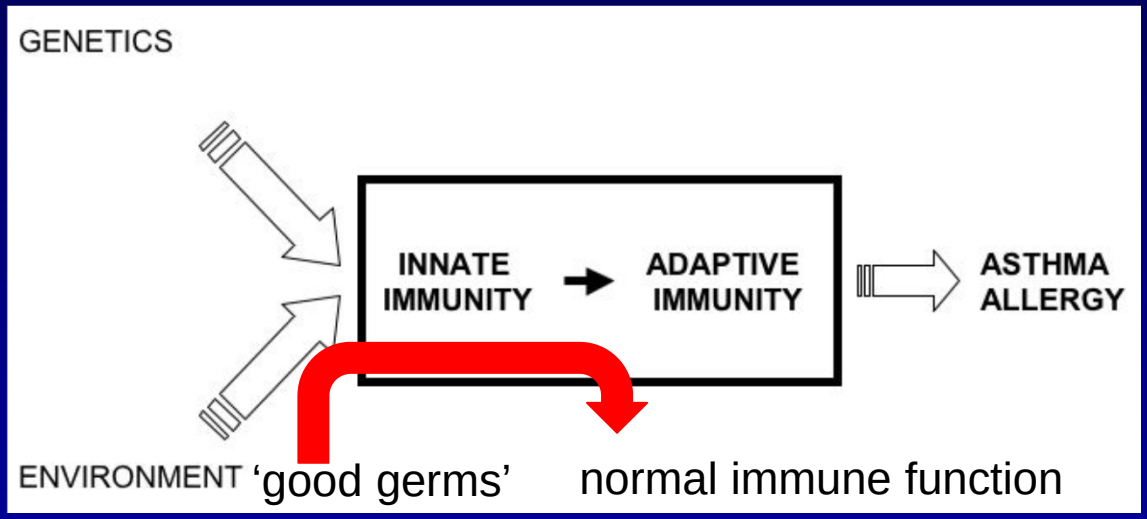
Kramer et. al. 2017
Translational Res.
182:49–60



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

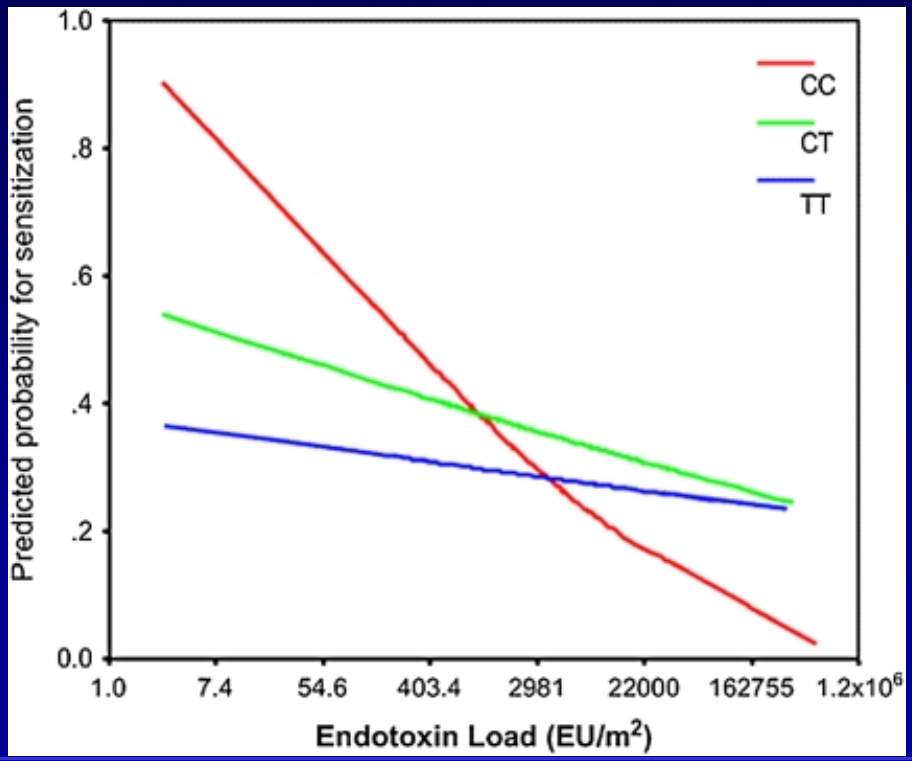
Genetic Determinants of Asthma: The Confusing Role for Endotoxin

Endotoxin (aka lipopolysaccaride 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 asthma acting as an inflammatory agent

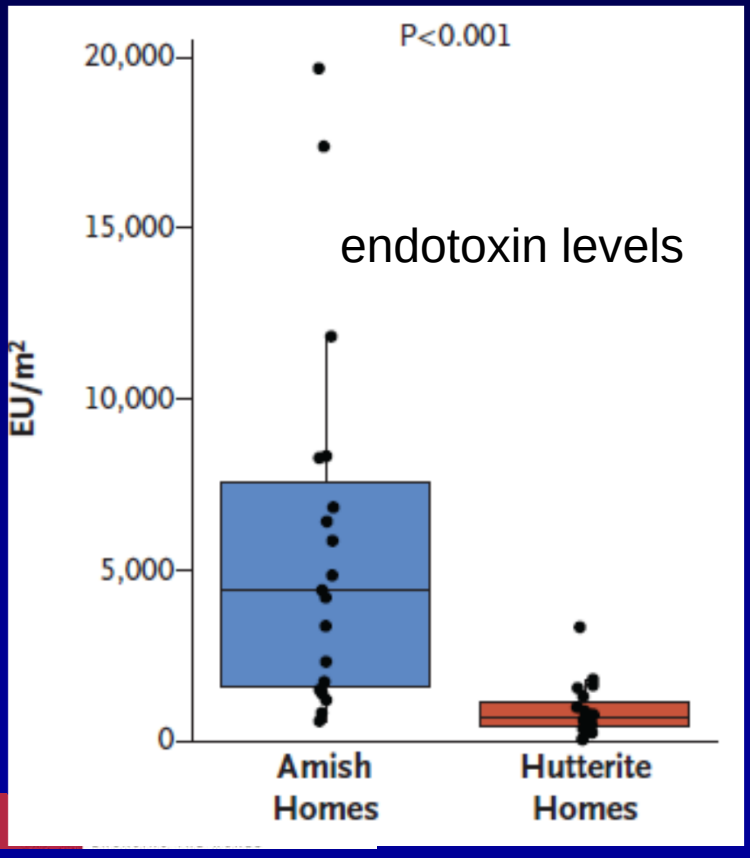
Dose-Response for Endotoxin Depends Upon CD14 Genetic Variant

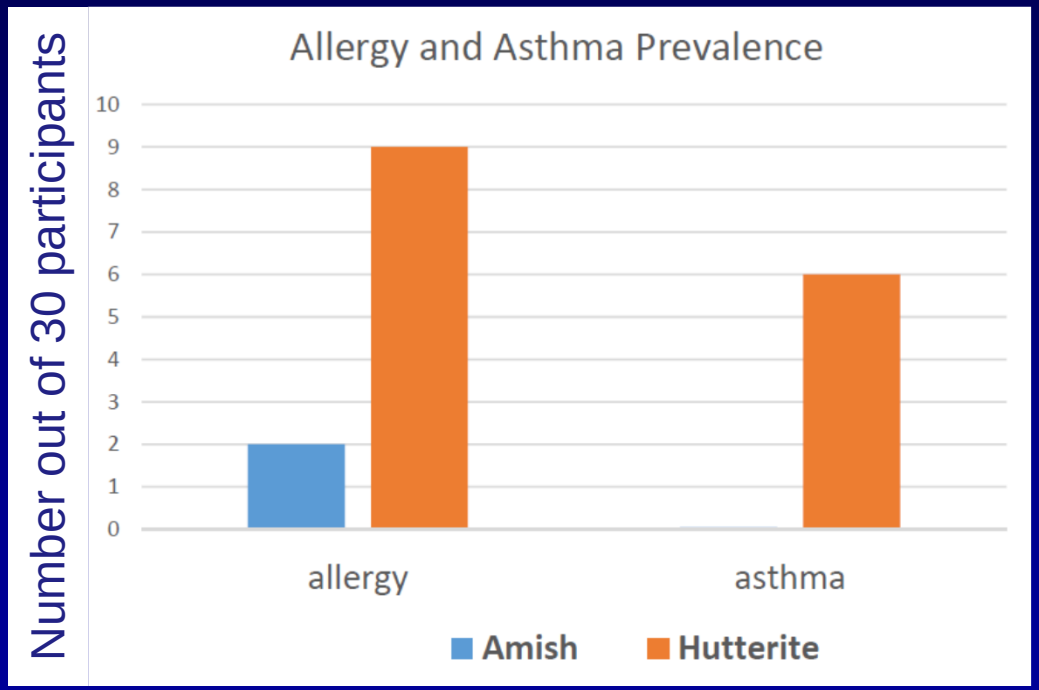


SFU SIMON FRASER UNIVERSITY ENGAGING THE WORLD

Simpson et al. Respir Crit Care Med 2006;174:386–392

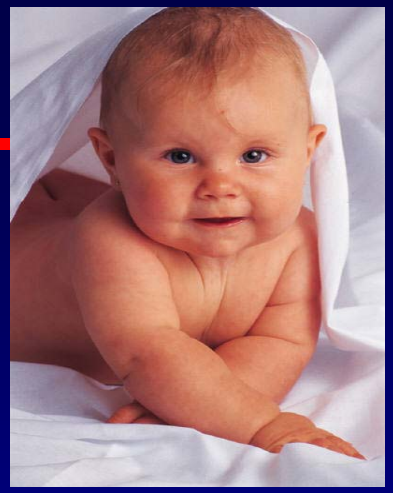
Population study: Genetocally simil Hutterite and Amish homes





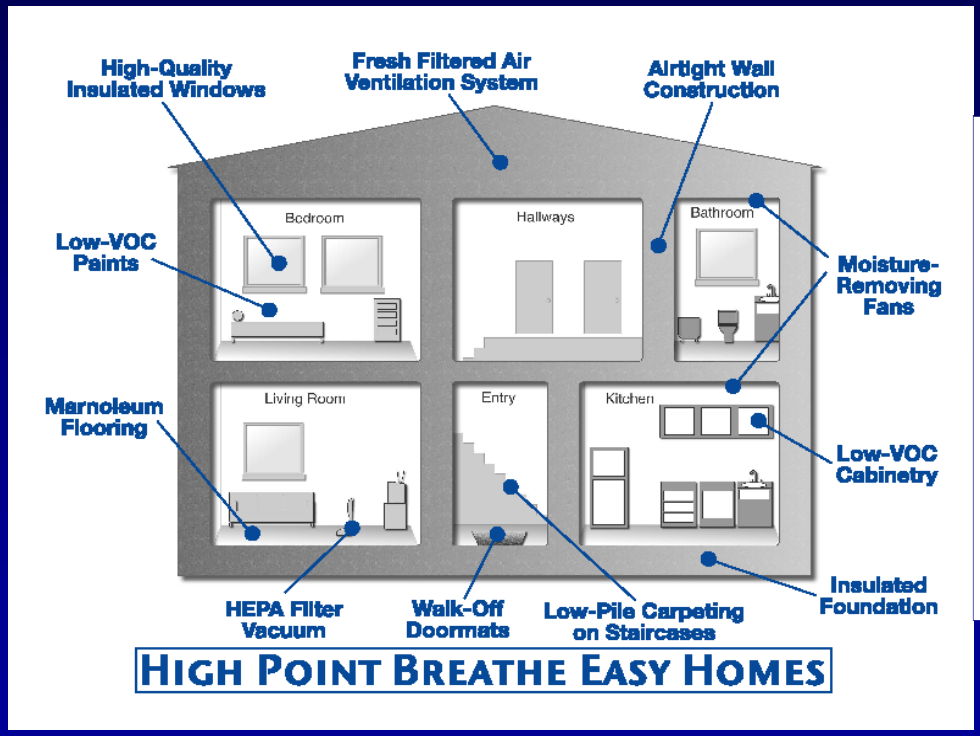
Stein et al. 2016 NEJM 375: 411-421

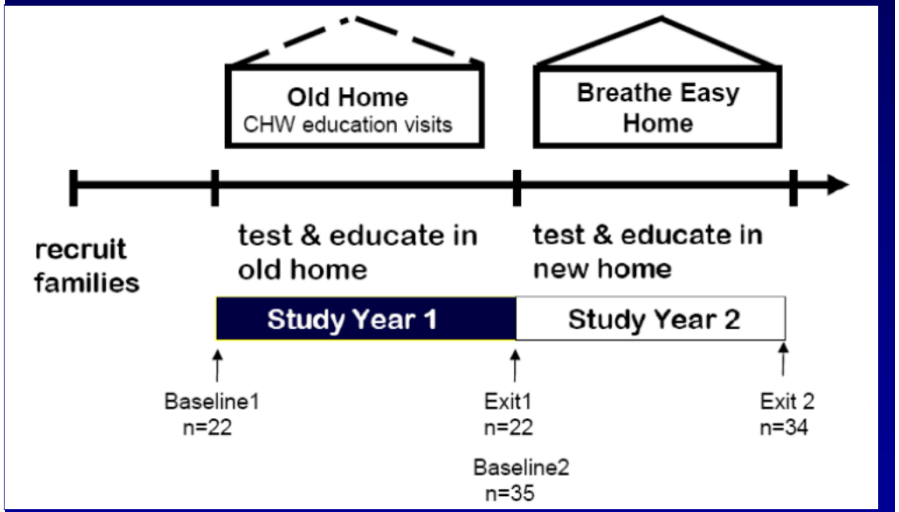
Some conclusions



- 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?

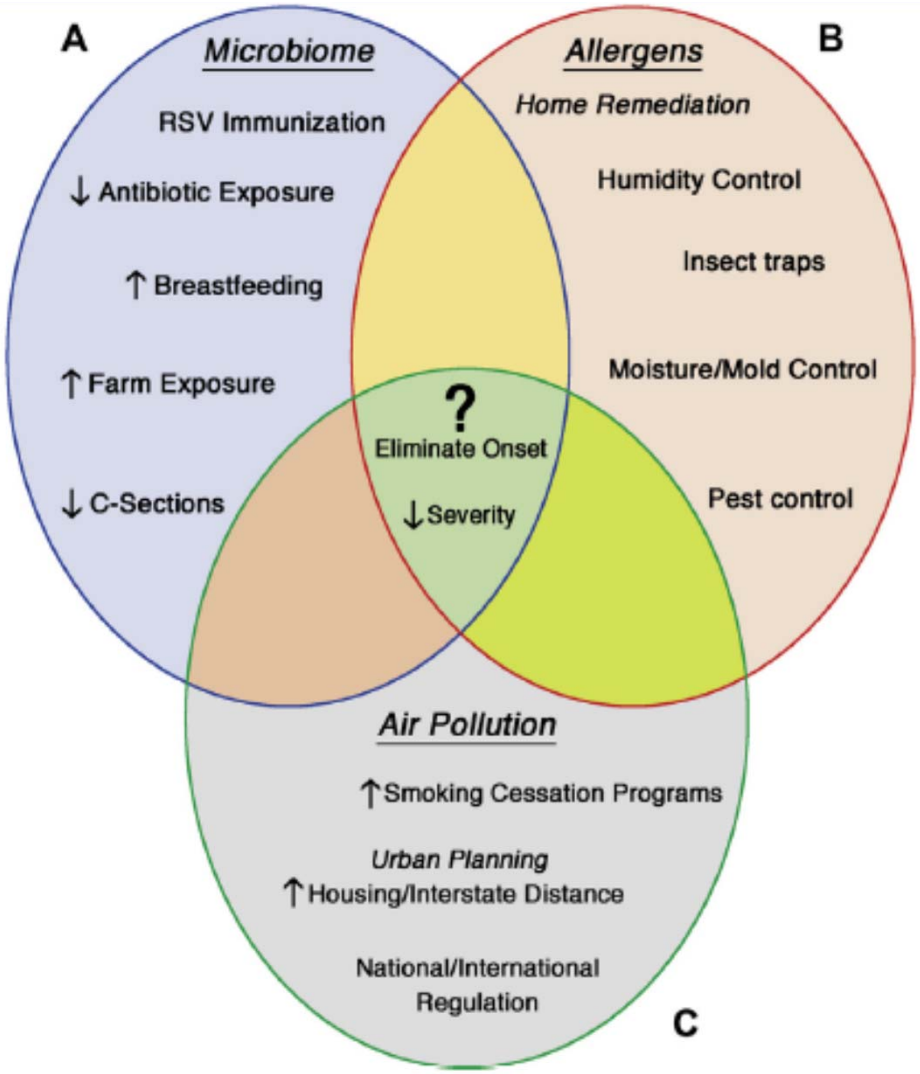




SFU SIMON FRASER UNIVERSITY ENGAGING THE WORLD

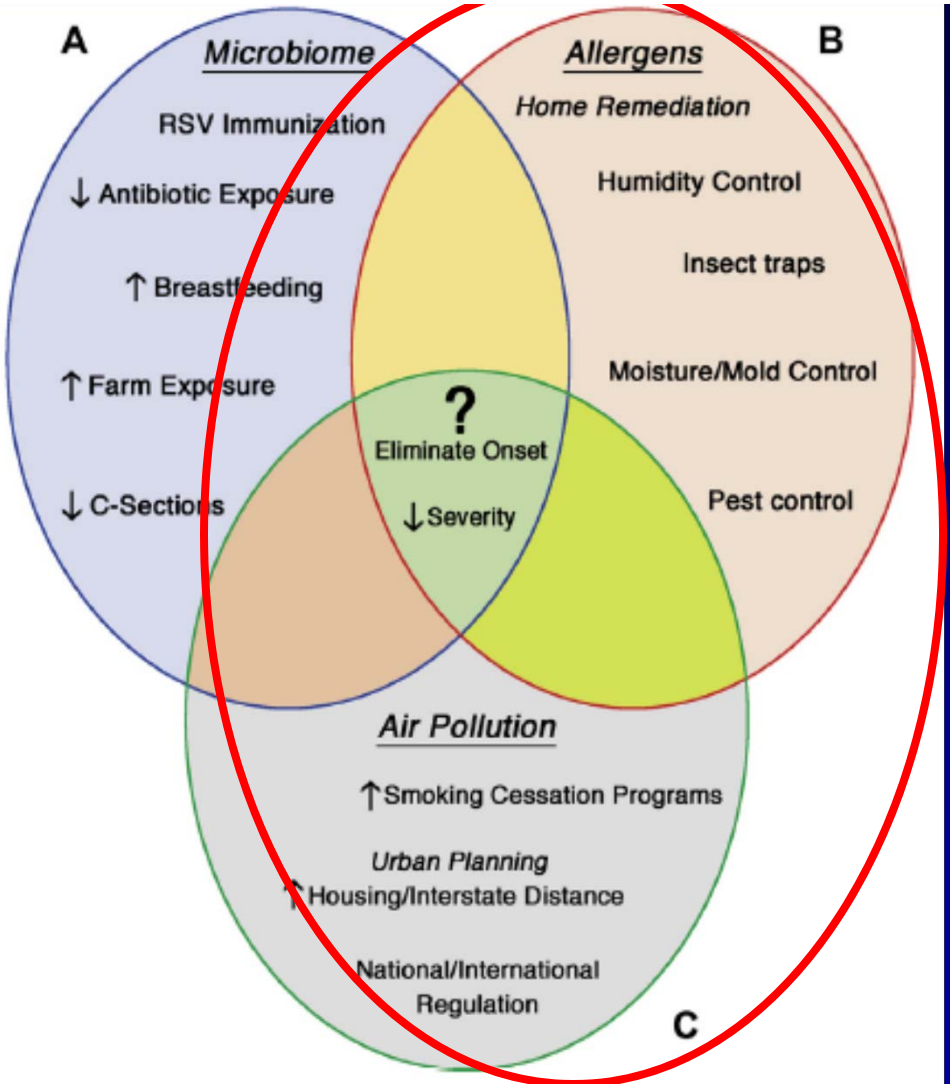
Takaro et al. 2011; AJPH 101:55

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

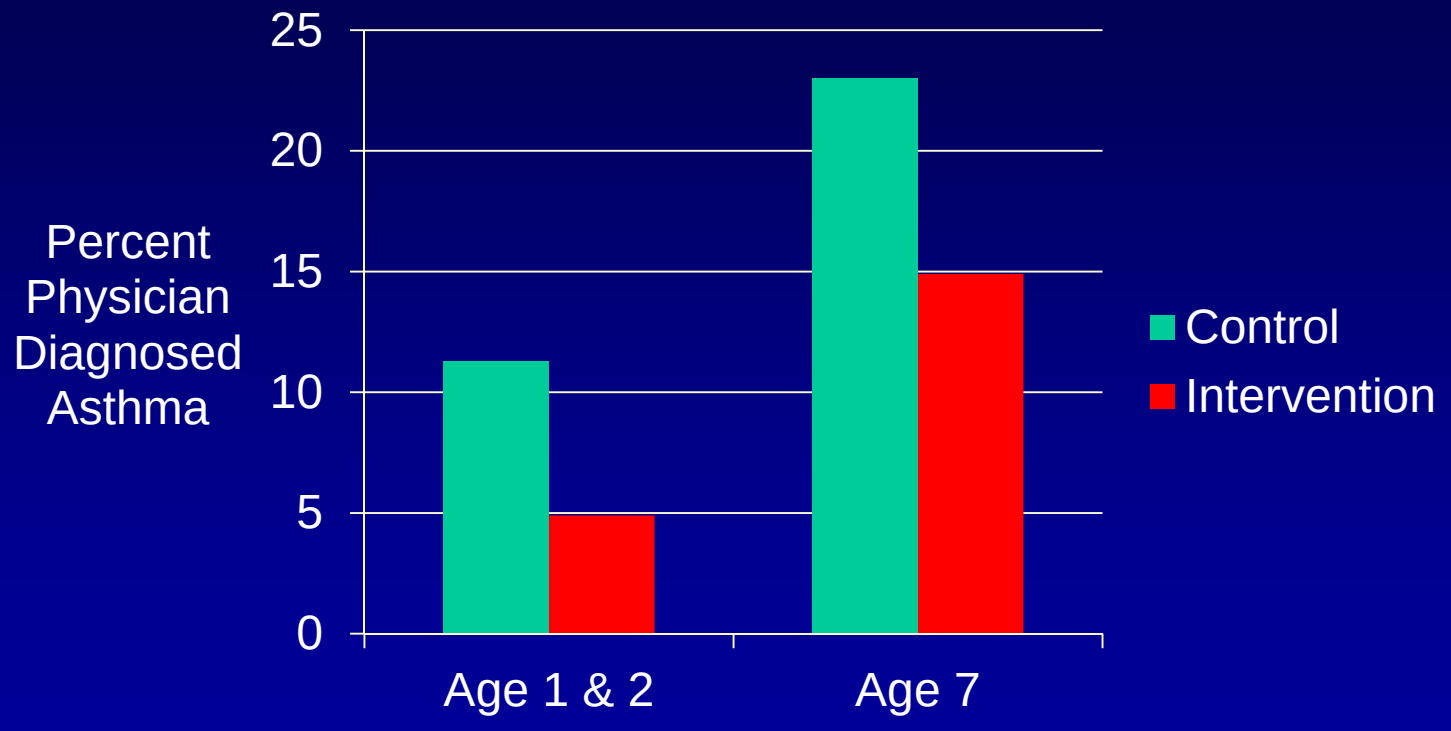
Mothers of high-risk infants recruited during third trimester in Vancouver (n = 545) and Winnipeg (n = 274)

High-risk **$\geq$ 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**

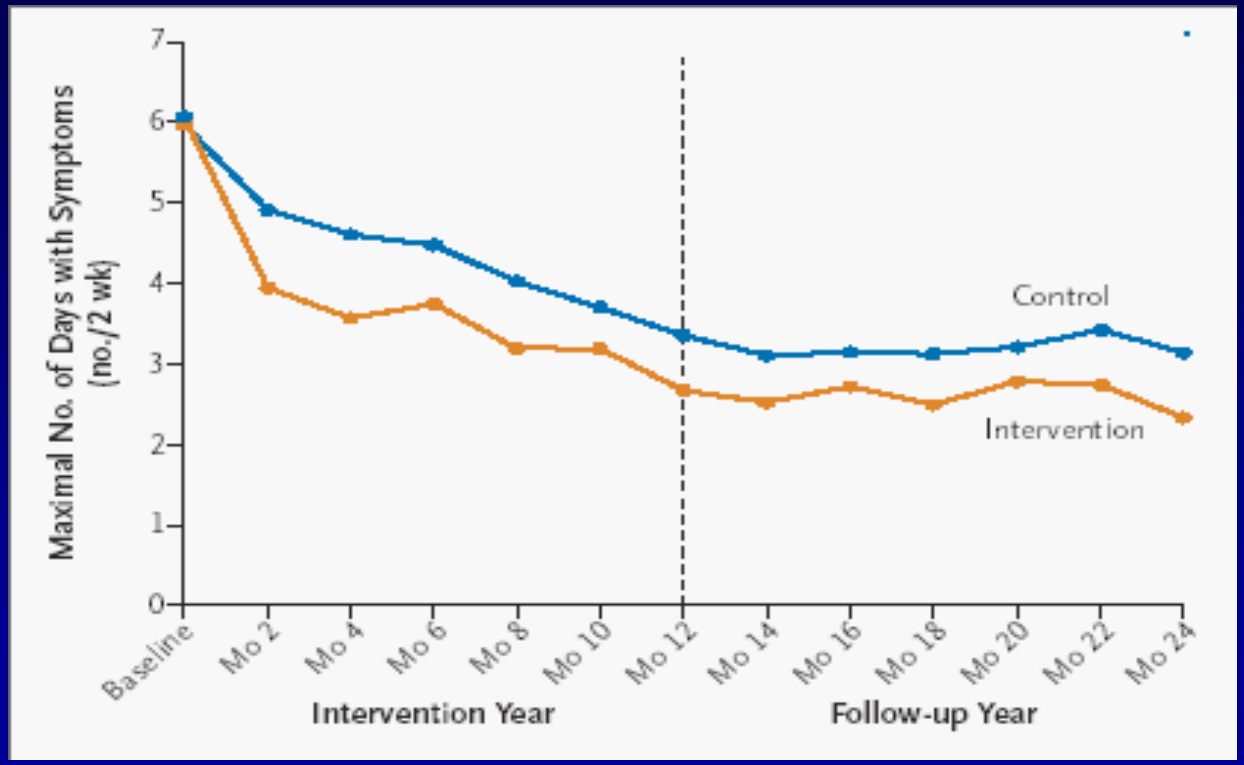
Canadian Asthma Primary Prevention Study



Chan-Yeung, et al JACI 2005

Becker et al JACI 2004

Inner-city Asthma Study
Symptom Days (Flare-ups) in Previous 2 Weeks



2004. NEJM 531: 1068-1080.

CDC Expert Panel Review on Housing Interventions

Panel	Sufficient Evidence for Implementation	Needs More Field Evaluation
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
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

Jacobs D, et al. 2010 J Pub Hlth Mgt Prac. 16: S5-S10

Public Health Policy & Practice to Reduce Impact of Asthma

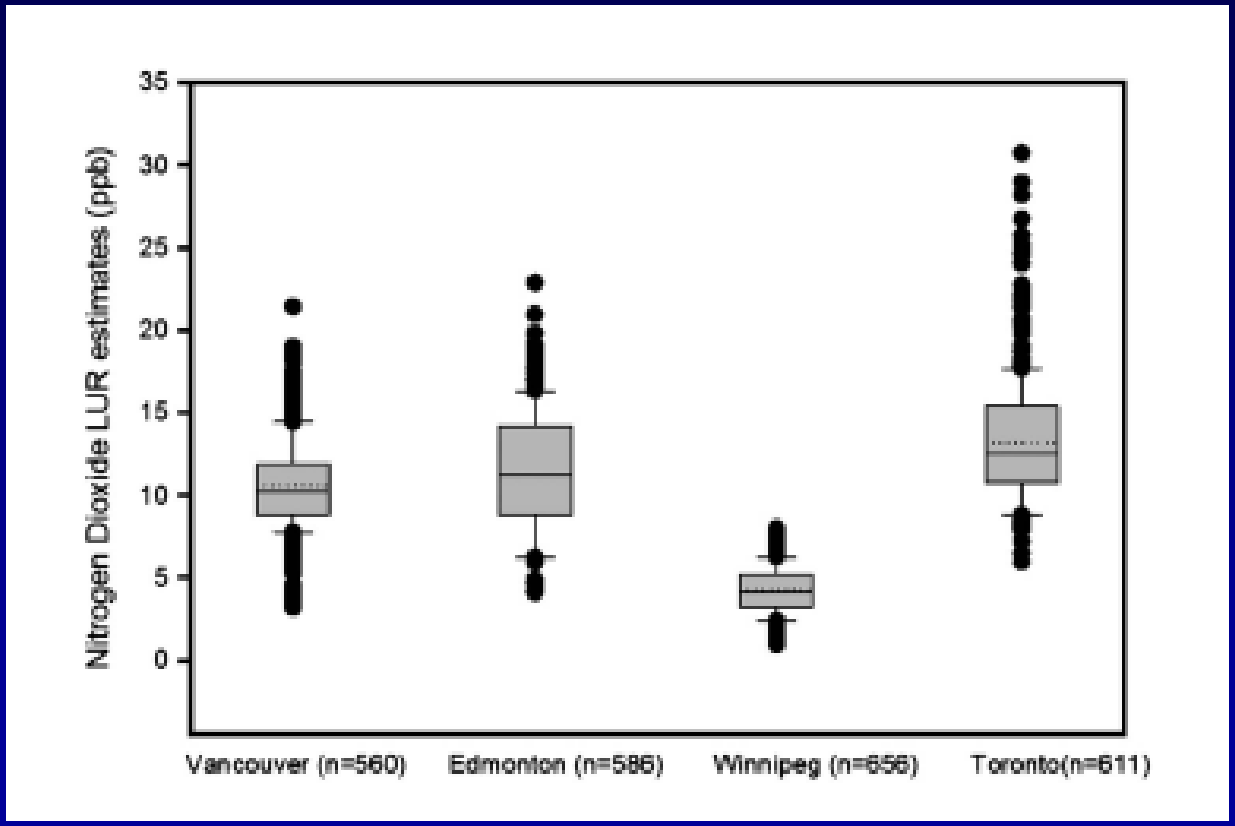
- Test housing interventions on larger scale
- Increase availability of healthy housing for low income families (focus on FN housing)
- Educate primary care providers on linkage of IEQ efforts to clinical asthma management
- Promote healthcare coverage of exposure control resources and community health 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

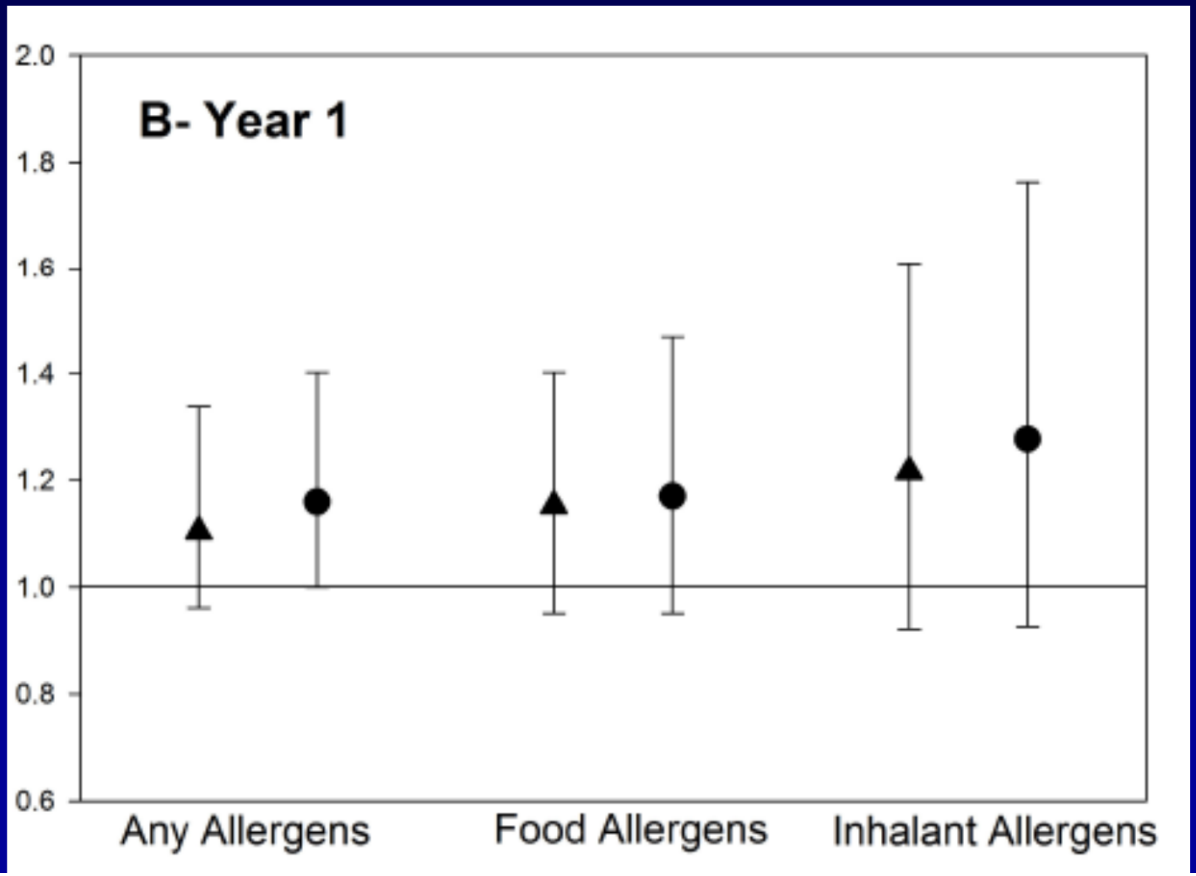
Traffic exposure linked to atopy in CHILD

Sbihi, et al.
2015 EHP



Traffic exposure linked to atopy in CHILD

Sbihi, et al.
2015 EHP

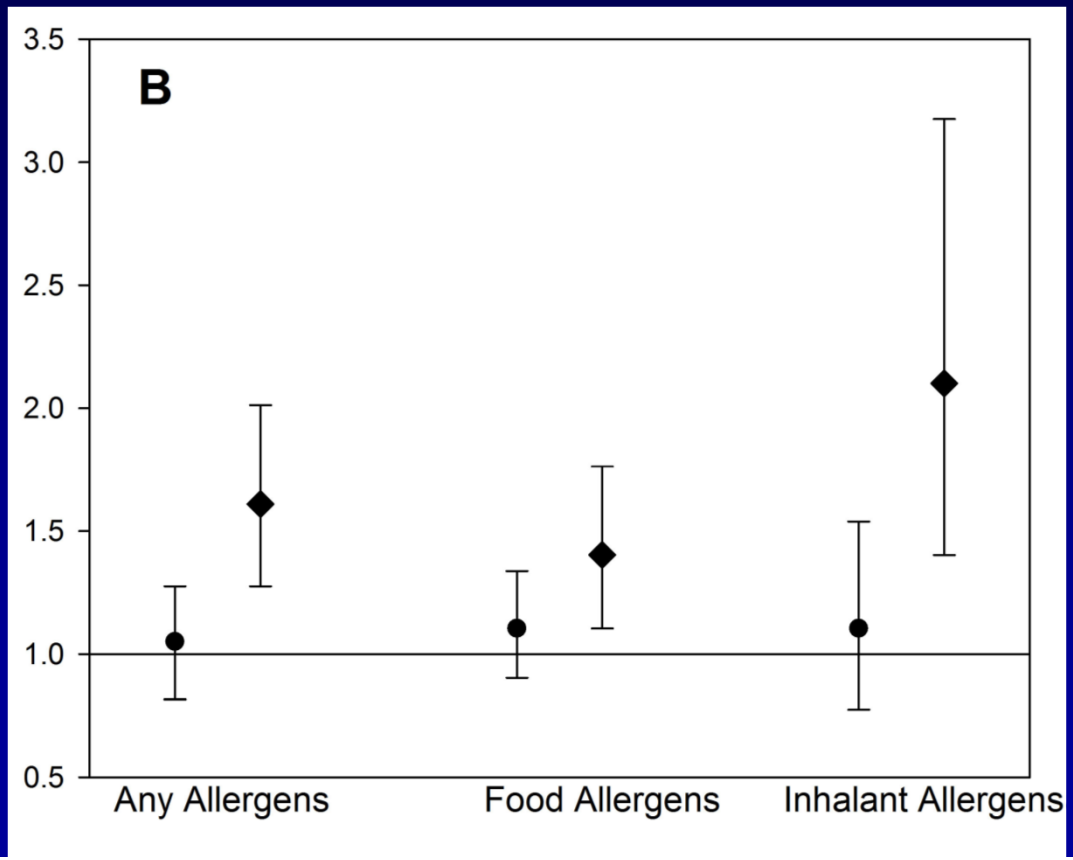


▲ Birth Address
● All Addresses

SFU SIMON FRASER UNIVERSITY
ENGAGING THE WORLD

Day care appears protective against air pollution effect in childhood atopy

Sbihi, et al. 2015 EHP



SFU SIMON FRASER UNIVERSITY ENGAGING THE WORLD

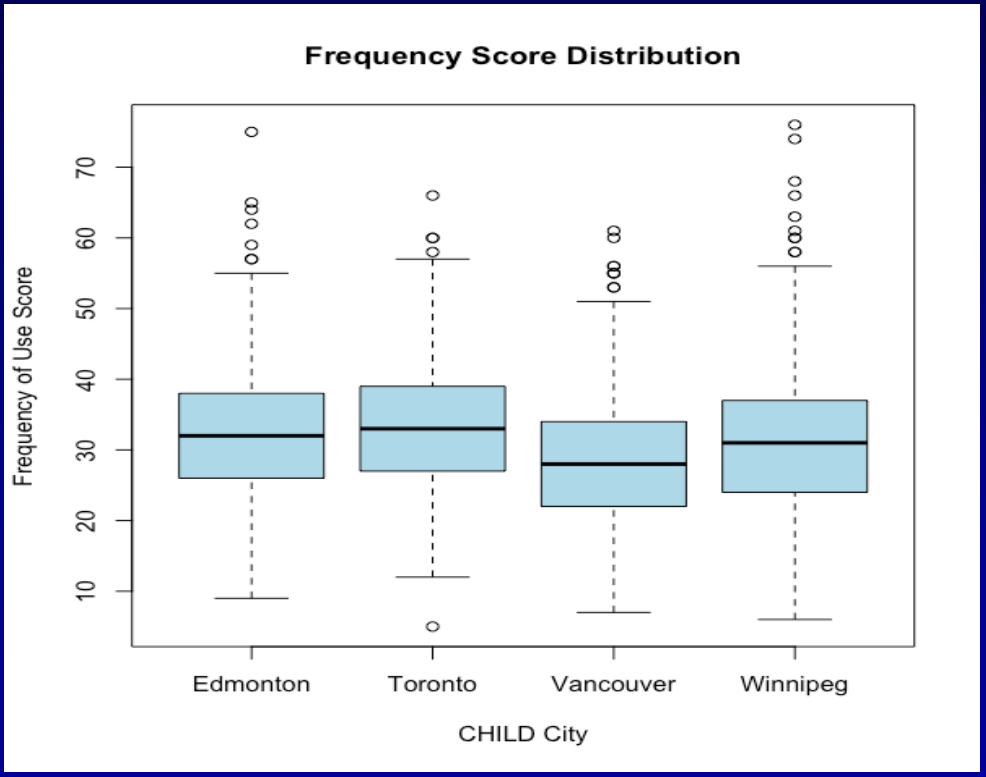
New CHILD findings: Cleaning products exposure in early life may increase asthma risk

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

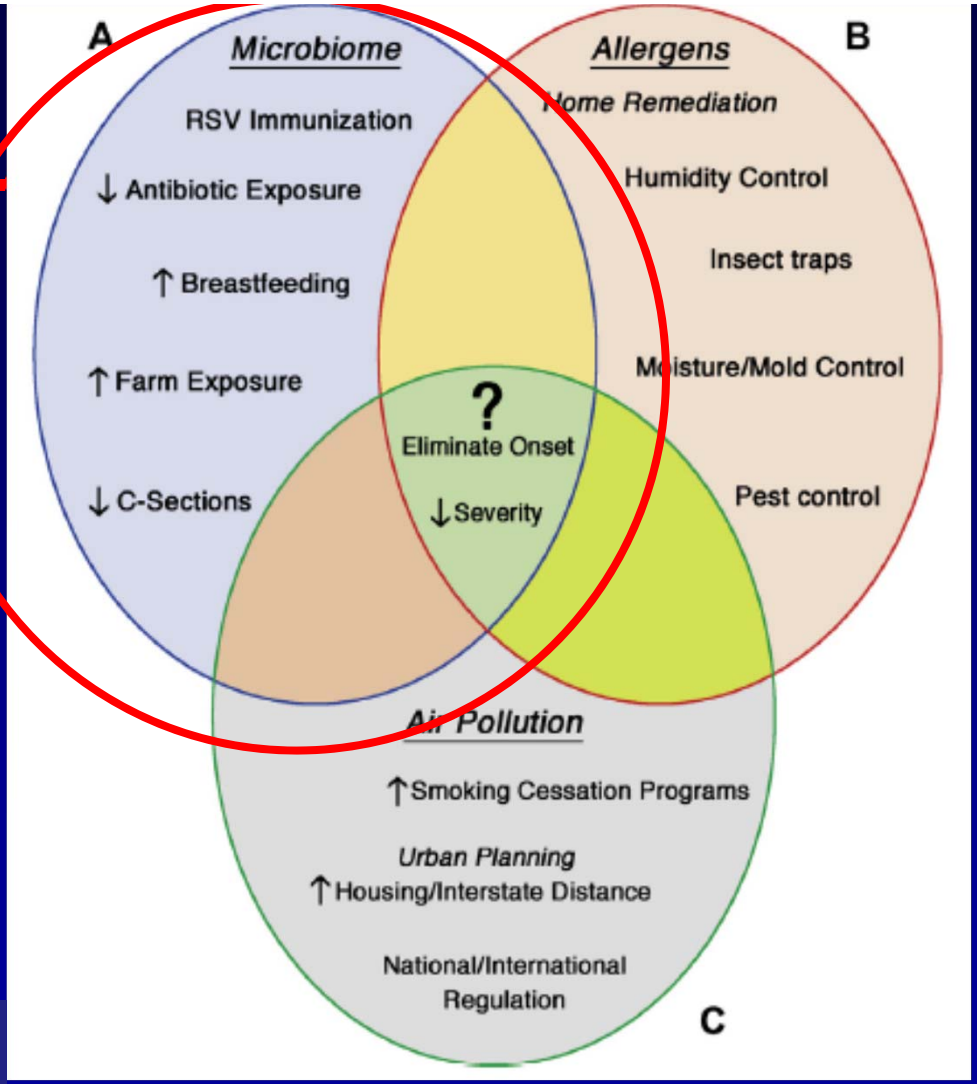
Frequency of Use Score	Frequency of Use Level	# Subjects in sample (n=1884)
Score >=37.0	"Very High Use"	515
Score >= 31.0, <37.0	"High Use"	431
Score > 24.0, <31.0	"Moderate Use"	509
Score <=24.0	"Low Use"	429

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

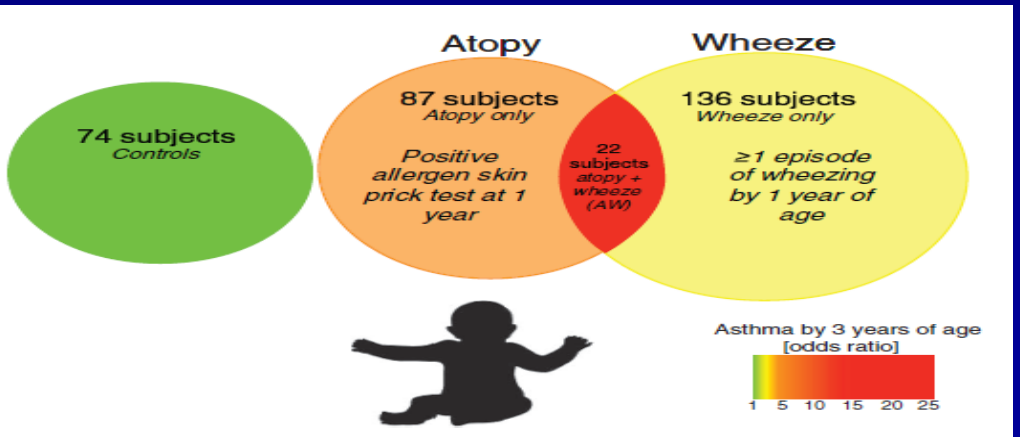
Adding FLVR to CHILD

RESEARCH ARTICLE

ASTHMA www.ScienceTranslationalMedicine.org 30 September 2015 Vol 7 Issue 307 307ra152

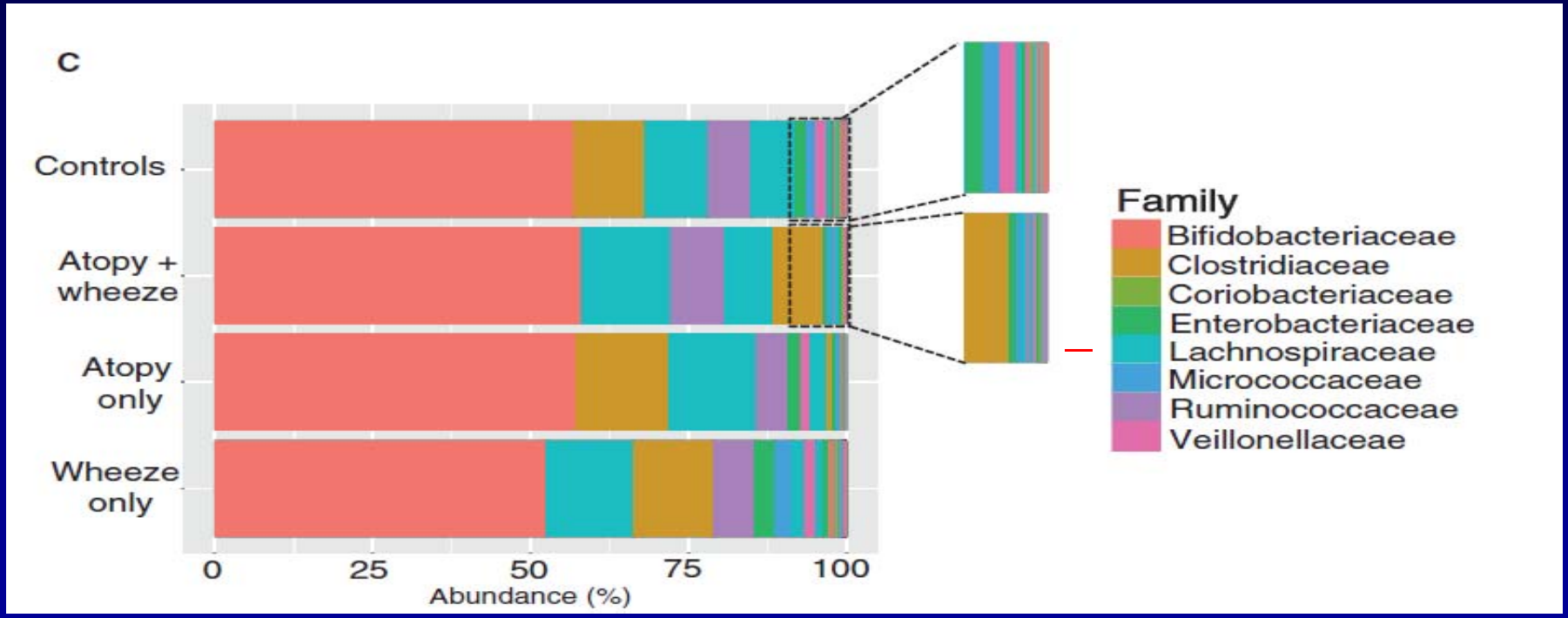
Early infancy microbial and metabolic alterations affect risk of childhood asthma

Marie-Claire Arrieta,[1,2]* Leah T. Stiemsma,[2,3]* Pedro A. Dimitriu,[2] Lisa Thorson,[1] Shannon Russell,[1,2] Sophie Yurist-Doutsch,[1,2] Boris Kuzeljevic,[3] Matthew J. Gold,[4] Heidi M. Britton,[1] Diana L. Lefebvre,[5] Padmaja Subbarao,[6,7] Piush 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 Finlay[1,2,12‡§]



SFU SIMON FRASER UNIVERSITY ENGAGING THE WORLD

Adding FLVR to CHILD



www.ScienceTranslationalMedicine.org 30 September 2015 Vol 7 Issue 307 307ra152

CHILD Investigators

We were all much younger then…

Thanks for your attention! Questions?

SFU SIMON FRASER UNIVERSITY
ENGAGING THE WORLD