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AllerGen
Allergy, Genes and Environment Network

The Canadian Healthy Infant Longitudinal Development Study: Exploring the origins of asthma

CHILD

Feb 19, 2016

Padmaja Subbarao, MD, MSc FRCP(C)
Clinician-Scientist
Co-Director, CHILD Study
Hospital for Sick Children
University of Toronto
Toronto, Canada

Disclosures

No commercial or other interests other than a bias towards pulmonary function outcomes!

SickKids®

UNIVERSITY of TORONTO

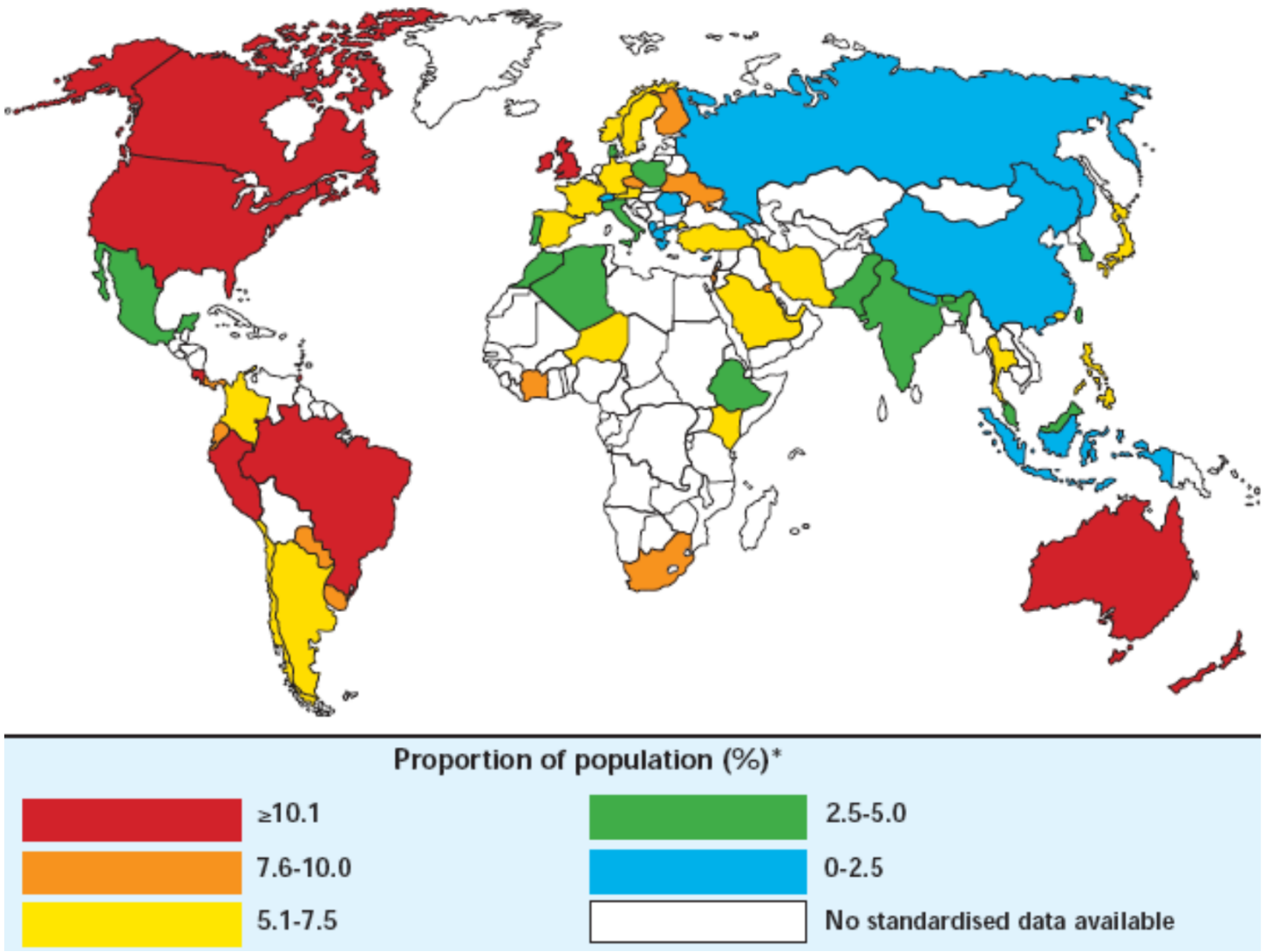
Objectives

- To understand the epidemiology and natural history of asthma
- To understand the role of the environment in the development of asthma
- To update the community about the CHILD study and its value in answering key questions about the role of the environment in asthma and allergy

Asthma: Definition

- **Chronic** inflammatory disorder of the airways resulting in reversible episodes of airway obstruction and airway hyperresponsiveness.
- **Characterized clinically by recurrent wheezing.**
- **It is the most common chronic disease of childhood**
- **Lifetime risk is 1/3**

World Map of the Prevalence of Clinical Asthma



From GINA Report, www.ginaasthma.com

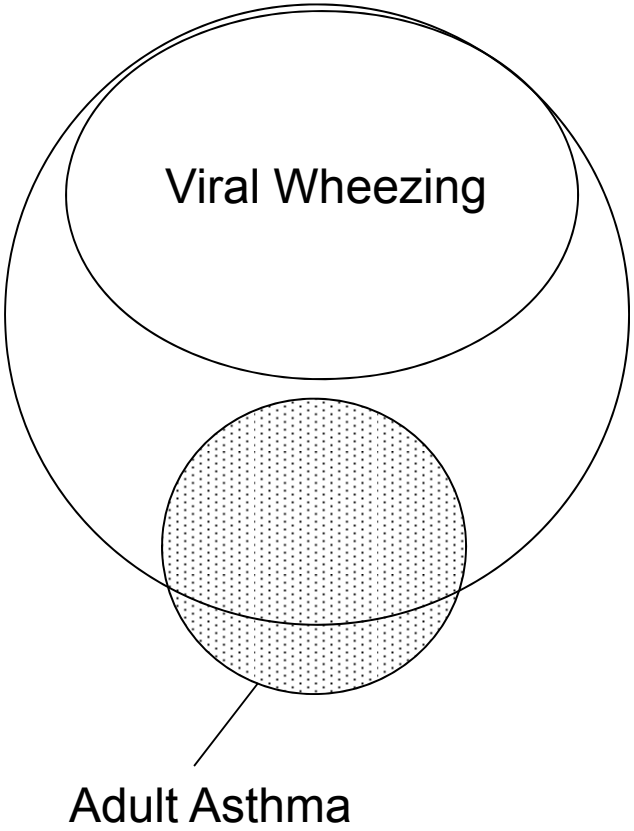
Worldwide Variation In Prevalence of Asthma Symptoms

International Study of Asthma and Allergies in Children (ISAAC)

Lancet 1998;351:1225

All that wheezes…

Wheezing in Childhood



- 50% of all children wheeze < 6y.
- 40-60% children wheeze after viral lower respiratory illness.
- Majority of children with early wheezing resolve.
- 75% of adult asthmatics trace their symptoms to early childhood.

Many "ASTHMAS"

Phenotypes of asthma

Previous descriptions

- Extrinsic vs. intrinsic
- Transient vs. persistent
- Mild vs. severe
- Childhood vs. adult onset
- Seasonal vs. perennial
- Eosinophilic vs. neutrophilic
- Occupational asthma
- Exercise induced asthma
- Aspirin-sensitive asthma

Recent methodologies

- Cluster analysis
- Latent class analysis
- Latent class growth analysis
- Multiple factor analysis
- Unsupervised statistical learning techniques
- Trajectories

The New England
Journal of Medicine

Volume 332 JANUARY 19, 1995 Number 3

ASTHMA AND WHEEZING IN THE FIRST SIX YEARS OF LIFE

FERNANDO D. MARTINEZ, M.D., ANNE L. WRIGHT, PH.D., LYNN M. TAUSSIG, M.D., CATHARINE J. HOLBERG, M.SC., MARILYN HALONEN, PH.D., WAYNE J. MORGAN, M.D., AND THE GROUP HEALTH MEDICAL ASSOCIATES*

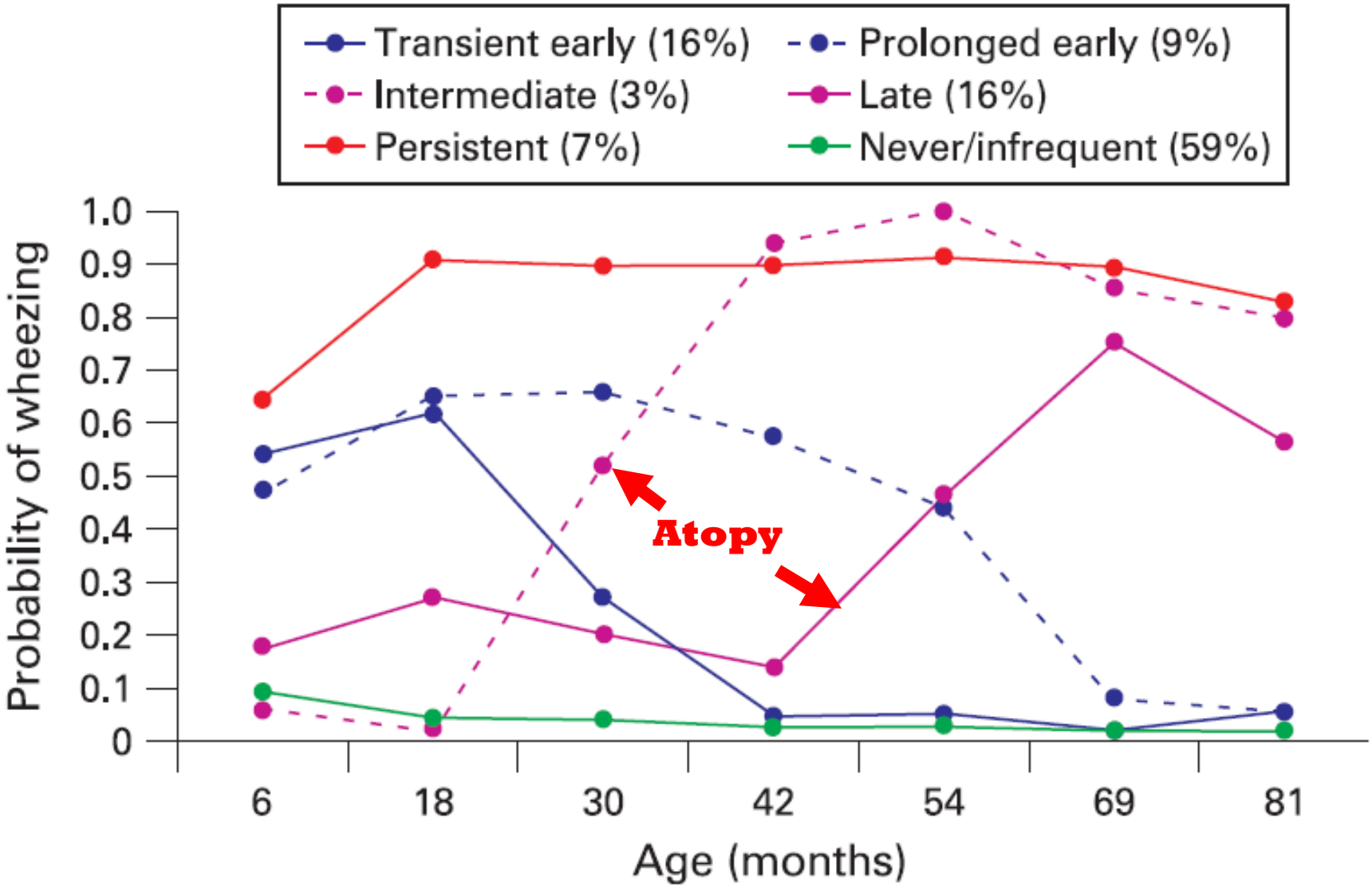
Four "phenotypes" identified:

- No wheeze (51.5%)
- Early-onset wheeze (19.9%)
  (before 3 years, not persisting to 6 years)
- Late-onset wheeze (15.0%)
  (onset between 3 and 6 years)
- Early onset persistent wheeze (13.7%)
  (onset before 3 years, persisting to 6 years)

Associations of wheezing phenotypes in the first 6 years of life with atopy, lung function and airway responsiveness in mid-childhood.

Henderson J, et al. Thorax 2008;63:974-980

- ALSPAC (Avon Longitudinal Study of Parents and Children)
- Symptom data collected at 7 time points from birth to age 7 years (n = 6,265)
- Measures of atopy, airway responsiveness (AHR) and airflow rates were made at ages 7-9 years
- Latent class analysis based on pattern of wheezing
- Six phenotypes were identified
- Atopy most strongly associated with intermediate onset wheezing and late onset wheezing


Transient early (16%)
Prolonged early (9%)
Intermediate (3%)
Late (16%)
Persistent (7%)
Never/infrequent (59%)
Probability of wheezing
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Atopy
6
18
30
42
54
69
81
Age (months)

Associations of wheezing phenotypes in the first 6 years of life with atopy, lung function and airway responsiveness in mid-childhood.

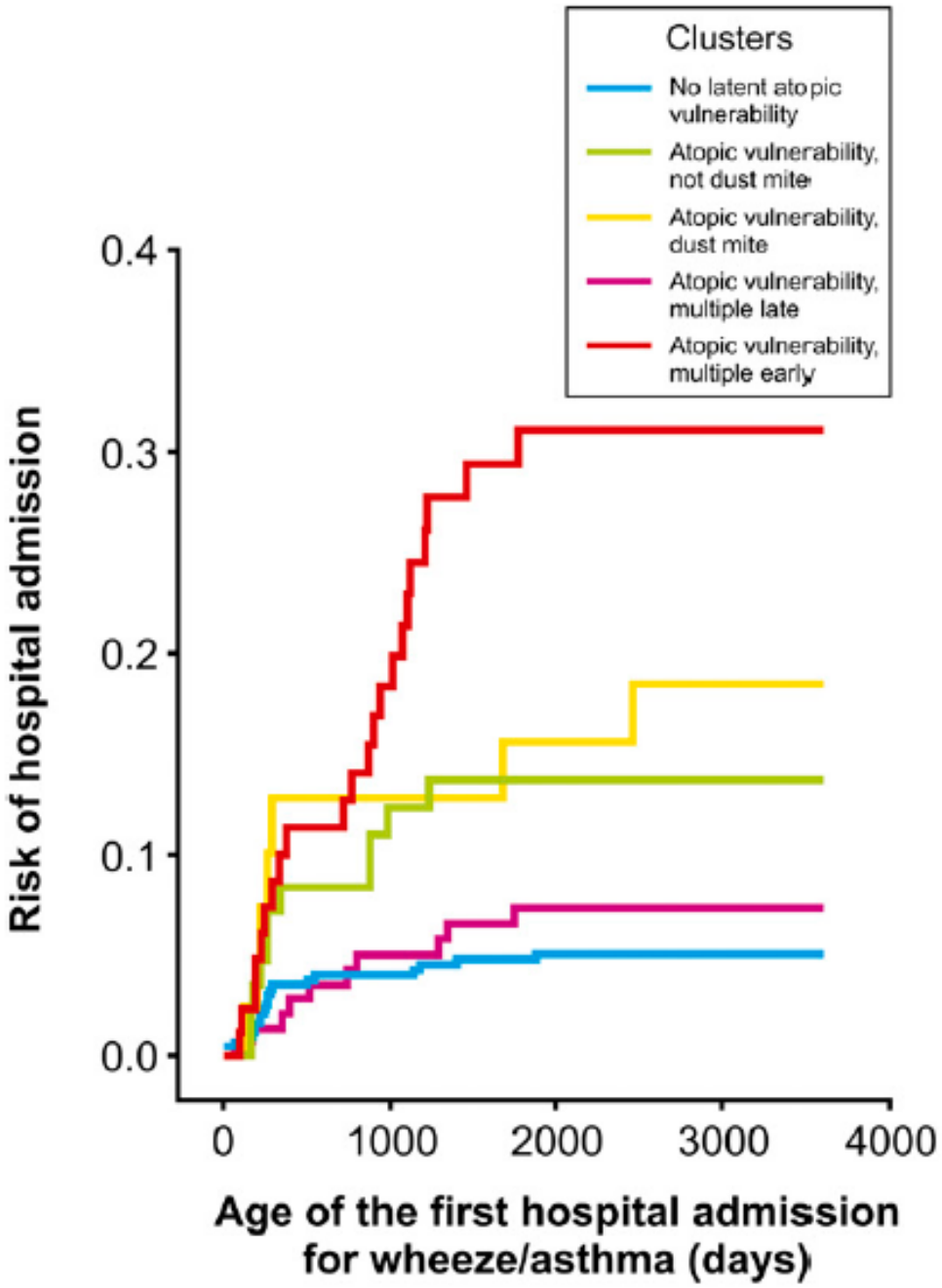
Henderson J, et al. Thorax 2008;63:974-80

Phenotype	Asthma	Atopy	FEV_1	FEF_{25-75}	AHR
Transient early	√	-	↓	↓	↑
Prolonged early	√ √	-	↓	↓↓	↑
Intermediate	√ √ √ √	√ √	↓↓	↓↓	↑↑
Late	√ √ √	√ √	↓	↓	↑↑
Persistent	√ √ √ √	√	↓↓	↓↓	↑↑

Beyond atopy. Multiple patterns of sensitization in relation to asthma in a birth cohort study.

Simpson A, et al. Am J Respir Crit Care Med 2010;181:1200-1206

- Manchester Asthma and Allergy Study (MAAS)
- Analysis of timing and type of sensitization to specific allergens in relation to phenotypes of asthma
- 5-class model of atopic vulnerability:
  - Multiple early (10.6%)
  - Multiple late (16.2%)
  - Dust mite (4.5%)
  - Non-dust mite (9.5%)
  - No latent vulnerability (59.2%)


Clusters
No latent atopic vulnerability
Atopic vulnerability, not dust mite
Atopic vulnerability, dust mite
Atopic vulnerability, multiple late
Atopic vulnerability, multiple early
Risk of hospital admission
0.4
0.3
0.2
0.1
0.0
0
1000
2000
3000
4000
Age of the first hospital admission for wheeze/asthma (days)

Multiple atopy phenotypes and their associations with asthma: similar findings from two birth cohorts.

Lazic N, et al. Allergy 2013;68:764-770

- Manchester (MAAS) and Isle of Wight cohorts
- Machine learning approach to cluster children based on skin prick tests and specific IgE
- Five-class solution best fit for both cohorts
- Children sensitized to a wide variety of allergens had
  - **more asthma**
  - **poorer lung function**
  - **greater airway reactivity**
  - **highest exhaled NO**
  - **most hospital admissions**

The Dunedin Multidisciplinary Health and Development Research Study

Dr. Malcolm Sears

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

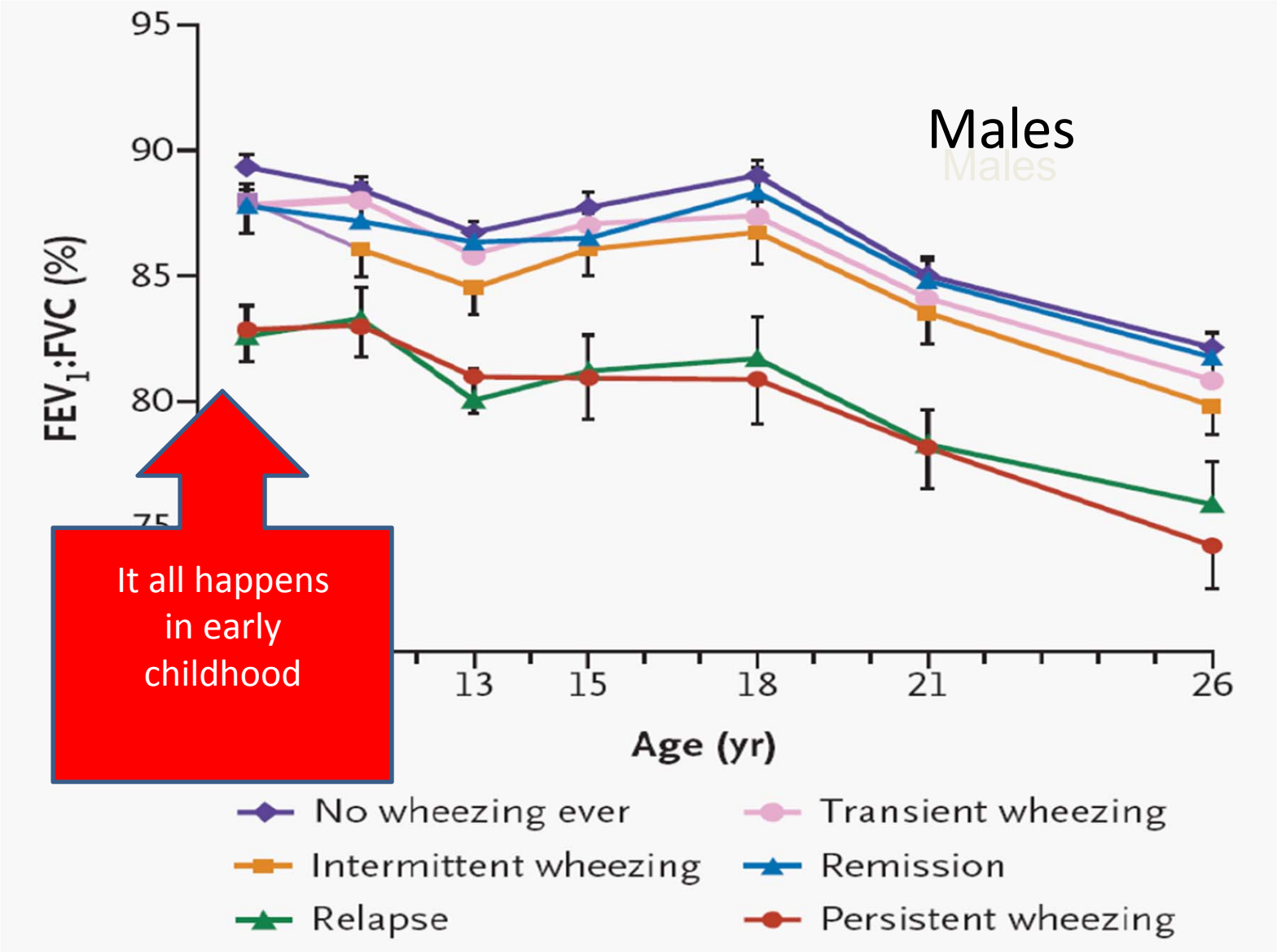
A Longitudinal, Population-Based, Cohort Study of Childhood Asthma Followed to Adulthood

Malcolm R. Sears, M.B., Justina M. Greene, Andrew R. Willan, Ph.D., Elizabeth M. Wiecek, M.D., D. Robin Taylor, M.D., Erin M. Flannery, Jan O. Cowan, G. Peter Herbison, M.Sc., Phil A. Silva, Ph.D., and Richie Poulton, Ph.D.

N Engl J Med 2003; 349: 1414-1422

Longitudinal lung function by asthma outcomes

Sears MR, et al. N Engl J Med 2003;349:1414-22



Institute of Human Development, Child and Youth Health *and* Partners

RFA announcement 2006:

"Indoor air exposures, genes and gene-environment interactions in the etiology of asthma and allergy in early childhood"

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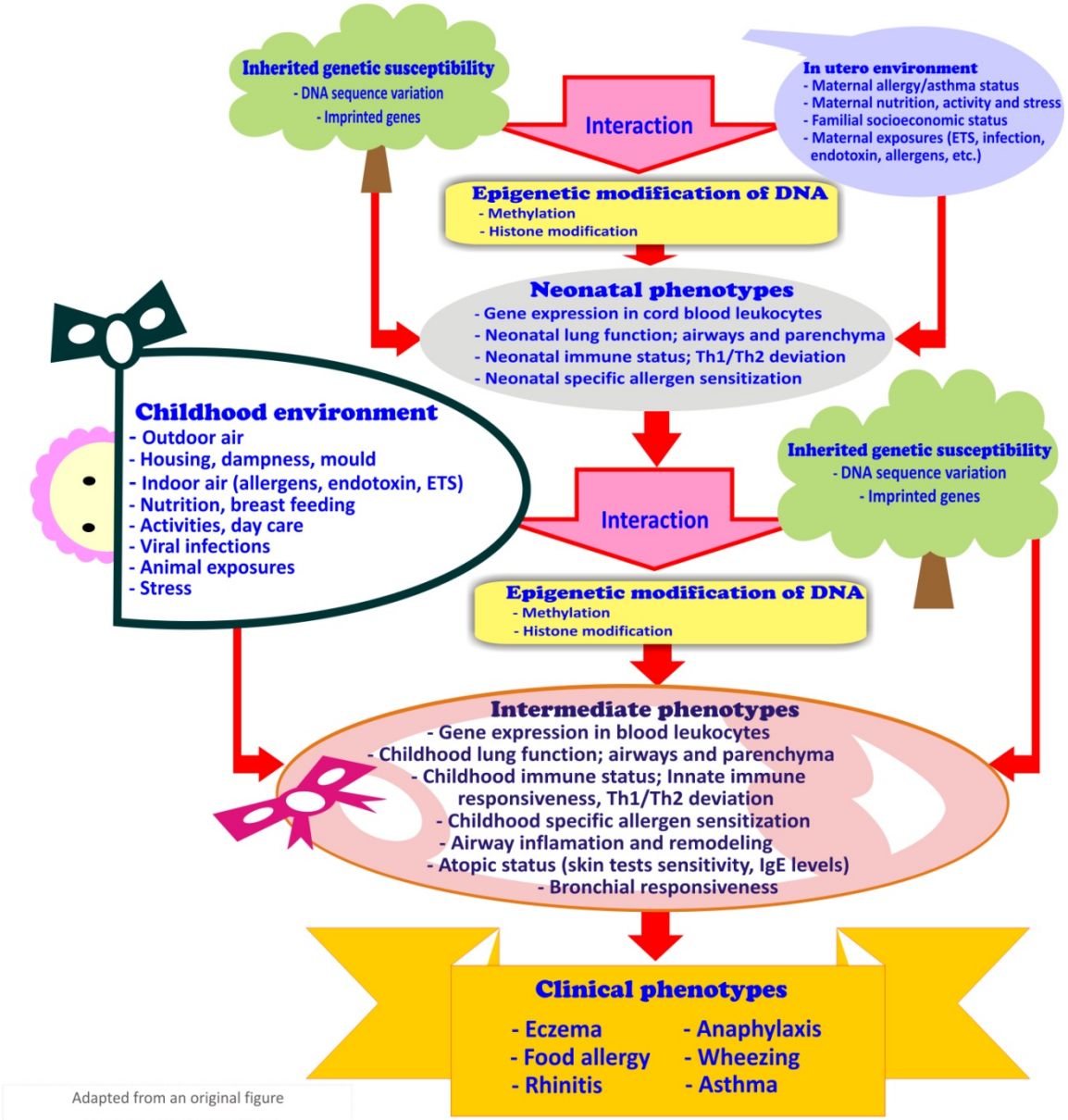
The origins of allergy and asthma



Adapted from an original figure
developed by Dr. Peter Paré
as part of the CIHR grant application.

Disciplines involved in developing the Canadian Healthy Infant Longitudinal Development (CHILD) study

- Epidemiology
- Neonatology
- Pediatrics
- Population health
- Environmental assessment
- Environmental hygiene
- Nutrition
- Infectious disease
- Genetics
- Obstetrics
- Geographic Information Systems
- Endocrinology/metabolism
- Mind-body
- Physiology
- Immunology
- Allergy
- Air quality
- Toxicology
- Sociology
- Molecular biology
- Psychology
- Neuroimmunology
- Biostatistics
- Ethics and legal
- Respirology
- Occupational health

Canadian Healthy Infant Longitudinal Development **(CHILD)** investigators

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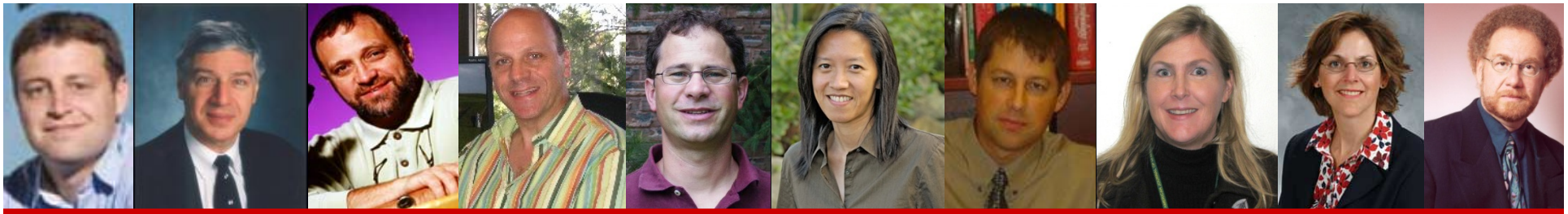


Ryan Allen | Allan Becker | Dean Befus | Michael Brauer | Jeff Brook | Edith Chen | Michael Cyr | Denise Daley | Sharon Dell | Judah Denburg

Susan Elliott | Hartmut Grasemann | Kent HayGlass | Rick Hegele | Linn Holness | Michael Kobor | Tobias Kollman | Anita Kozyrksyj | Catherine Laprise | Mark Larche

Wendy Lou | Joe Macri | Piush Mandhane | Greg Miller | Redwan Moqbel | Theo Moraes | Peter Pare | Clare Ramsey | Bruce Ritchie | Felix Ratjen | Andy Sandford

James Scott | Jeremy Scott | Malcolm Sears | Fran Silverman | PJ Subbarao | Tim Takaro | Patrick Tang | Scott Tebbutt | Teresa To | Stuart Turvey

Current recruitment sites for CHILD

Canadian Healthy Infant Longitudinal Development (CHILD)

Malcolm Sears

Director

Padmaja Subbarao

Toronto

Co-Director & Site Leader

Allan Becker

Winnipeg

Piush Mandhane

Edmonton

Stuart Turvey

Vancouver

Site Leaders

Courtesy of Meghan Azad

Recruitment of a general population cohort

Inclusion criteria

- Pregnant women aged >18 years (19in Vancouver)
- Residential proximity (<50km) to participating delivery hospital
- Able to read, write and speak English
- Willing to donate cord blood
- Planning to deliver at a designated recruitment centre participating hospital
- Infant born at or after 35 weeks

Exclusion criteria

- Children born with major congenital abnormalities or respiratory distress syndrome
- Expectation of moving away from a recruitment centre within 1 year of recruitment
- Children of multiple births
- Children resulting from in-vitro fertilization
- Children who will not spend at least 80% of nights in the index home

Key components of the CHILD study

- Assess the home environment
  - by questionnaire in pregnancy, and each year to 5 years
  - by direct home inspection and dust sampling at 3 months
- Collect and store blood at birth (cord), 1 and 5 years
- Document viral/other infections in first year of life
- Examine immune / inflammatory responses to pathogens and allergens; markers of innate immune function
- Measure lung function in infancy, and at 1, 3 and 5 years
- Obtain family history by questionnaires, skin tests, lung function, and obtain parental DNA
- Assess the psychosocial / stress environment during pregnancy and annual follow-up

Potential environmental factors

- Indoor
  - Indoor allergens
  - Mold and damp
  - Volatile organic compounds
  - Impact of renovations
  - Environmental tobacco smoke
  - Brominated flame retardants
  - Perfluorinated compounds
  - Phthalates
  - Phenols
- Outdoor
  - Diesel exhaust particle(DEP)
  - Traffic-related air pollutants (TRAP)
  - Other particulate matter
  - Smog
  - Outdoor allergens

Potential childhood exposures

- Country of birth and residence
- Mode of delivery
- Exposure to vaginal microbiome
- Breast-feeding
- Home environment, home microbiome exposure
- Daycare
- Viral and other infections
- Medications
  - Antibiotics
  - Acid suppressive drugs
  - Vitamin D

Potential personal factors

- Sex
- Obesity
- Maternal diet in pregnancy
- Infant diet
- Infant growth
- Stress
- Genetics
- Epigenetics

Key variables obtained by questionnaires

HOME	MOTHER	FATHER	CHILD
Current residence	Maternal demographics	Paternal demographics	Mode of delivery
Previous residences (12 mo)	Maternal health	Paternal health	Medications around birth
Changes of residence	Maternal medications	Paternal medications	Sleeping arrangements
Type and age of home	Maternal smoking	Paternal smoking	Activities outside home
Characteristics of home	Maternal respiratory symptoms	Paternal respiratory symptoms	Colds and infections
Attached garage	Maternal diagnosed asthma	Paternal diagnosed asthma	Coughing episodes
Heating and cooling systems	Maternal allergies	Paternal allergies	Wheezing episodes
Humidifiers	Maternal occupation	Paternal occupation	Medications
Basement/crawl space	Health of other children	Hobbies and activities in home	Food allergy
Water leaks and mold	Health during pregnancy		Atopic dermatitis / eczema
Swimming pool, spa	Diet before and in pregnancy		Doctor visits
Renovations	Vitamins and supplements		Hospital/ER visits
Furniture	Prenatal/postnatal maternal stress		Breastfeeding
Cooking systems	Socioeconomic status		Introduction of milk, solids
Cleaning habits	Depression module		Vaccinations
Chemicals used in home	Labor and delivery		Time/activity/locations
Smoking in the home	Post-partum health		Travel times and exposures
Characteristics of bedroom	Post-partum stress		Daycare arrangements
Animals in home (pets)	Breastfeeding		
Insects and pests in home	Parenting stress		

Assessment of 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	✓	✓			✓

Infant lung function and viral infections

Toronto sub-cohort

Infant Pulmonary Function

Infant pulmonary function testing at 3, 12 and 18 months (lung volumes, airflow, exhaled NO)

Viral Studies

Parents call in when child has cold symptoms

Viral swabs taken if the cold is of sufficient severity

Assessment of psychosocial risk factors

All mothers in CHILD study will complete a short form of psychosocial / stress assessment

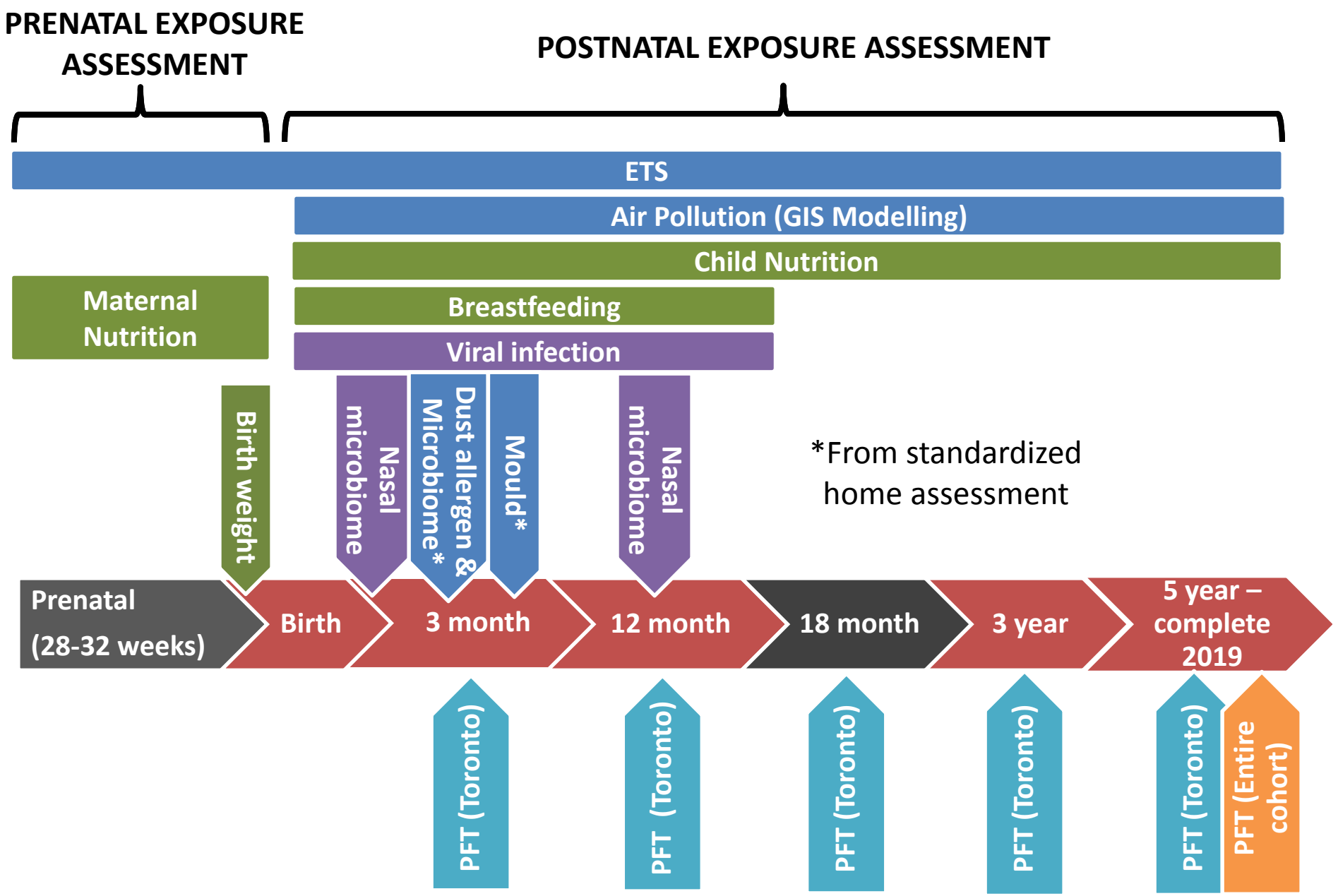
Vancouver mothers will participate in a structured interview for more detailed assessment

Timing: Prenatal at recruitment and ~36 weeks gestational age; postnatal at 6 months, 12 months, then annually

Content: Questionnaire: social support, marital quality, SES; Interview: family, work stress, maternal depression

CHILD – a 6-year study of 3,542 children

In-utero	- **recruitment:** maternal, paternal studies; clinical, stress, nutrition and environment questionnaires
Delivery	- **delivery:** outcomes, cord blood, meconium
3 months	- **home visit:** health questionnaires, home inspection, dust sampling, breast-milk, urine, nasal swab, stool, infant lung function, stress (sub-cohorts)
6 months	- questionnaire follow-up
1 year	- **clinic:** skin tests, blood, lung function, infections, urine, nasal swab, stool; maternal studies
1 ½ years	- questionnaire follow-up
2 years	- questionnaire follow-up
2 ½ years	- questionnaire follow-up
3 years	- **clinic:** questionnaires, clinical assessment, skin tests, lung function, urine
4 years	- questionnaire follow-up
5 years	- **clinic:** questionnaires, clinical assessment, skin tests, lung function, blood, physician assessment


PRENATAL EXPOSURE ASSESSMENT
POSTNATAL EXPOSURE ASSESSMENT
ETS
Air Pollution (GIS Modelling)
Child Nutrition
Maternal Nutrition
Breastfeeding
Viral infection
Birth weight
Nasal microbiome
Dust allergen & Microbiome*
Mould*
Nasal microbiome
*From standardized home assessment
Prenatal (28-32 weeks)
Birth
3 month
12 month
18 month
3 year
5 year – complete 2019
PFT (Toronto)
PFT (Toronto)
PFT (Toronto)
PFT (Toronto)
PFT (Toronto)
PFT (Entire cohort)

CHILD Outcomes

- The study is powered on the primary outcome of diagnosed asthma at 5 years
  - Intermediate outcomes of food and inhalant sensitization, atopic dermatitis, food allergy and recurrent wheeze are assessed throughout

The CHILD cohort at birth

Birth outcomes			
Cesarean section (%)	25.6	Male sex (%)	52.4
Cord blood obtained (%)	75.1	Discharged with mother (%)	97.0
Birth weight (n=3192)	3448 gm, SD 482	Hospital stay > 7 days (%)	1.3
Birth length (n=2306)	51.4 cm, SD 2.5	Given antibiotics (%)	5.4
Head circumference (n=2294)	34.6 cm, SD 1.5		

The CHILD cohort at 1 year

Outcomes reported through the first year			
	0 to 3 months	3 to 6 months	6 to 12 months
1 or more colds (%)	42.9	52.3	81.5
Any wheeze (%)	7.1	6.7	9.9
Reported food allergy (%)	4.2	3.2	8.2
Skin allergy – eczema/atopic dermatitis (%)	8.1	12.1	14.8
ER visits for respiratory illness (%)	2.4	2.9	6.4
Hospital admission for resp illness (%)	0.6	1.1	1.7
Exclusive breast feeding (%)	58.5	13.9	0

The CHILD cohort at 1 year

Skin allergy tests at one year (≥2mm wheal)			
Any positive skin test (%)	14.7	Any food allergen sensitization (%)	11.5
Any inhalant allergen sensitization (%)	4.7	Peanut sensitization (%)	5.0

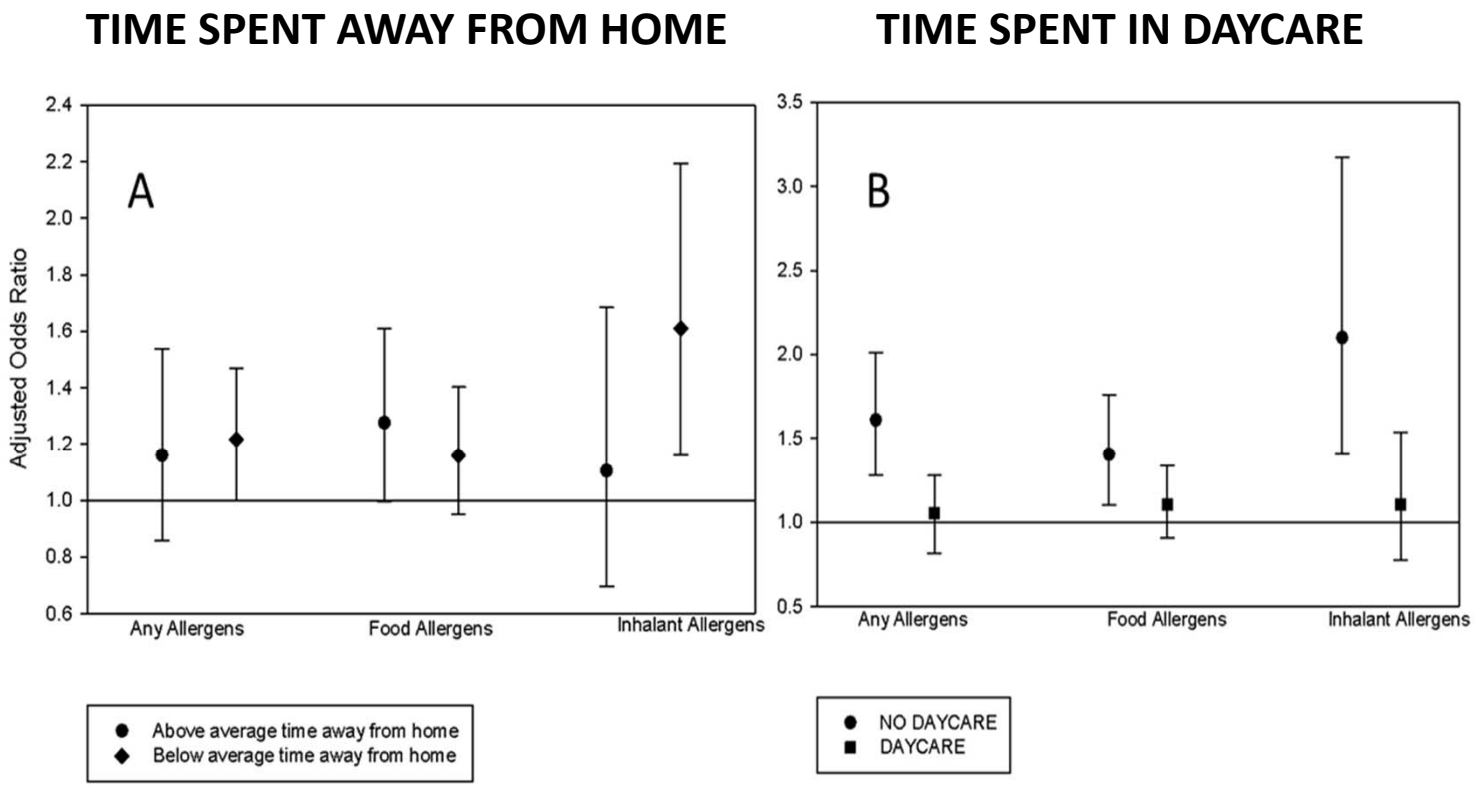
Traffic-Related Air Pollution

- NO_2 exposure was very different in the 4 cities

		PREGNANCY		FIRST YEAR	
		Based on address at enrollment	Temporally adjusted using all addresses	Based on address at birth	Temporally adjusted using all addresses
Edmonton (N=554)	AM (SD)	26.3 (8.5)	24.1 (8.8)	26.1 (8.6)	24.0 (8.8)
	Median	27.3	24.4	27.2	24.8
	Range	10.3 - 45.8	6.9 - 50.7	10.3 - 50.2	7.6 - 49.3
Toronto (N=496)	AM (SD)	37.2 (9.3)	28.1 (7.9)	36.9 (9.3)	28.2 (7.7)
	Median	36.1	26.7	35.3	25.2
	Range	17.7 - 78.8	12.7– 60.9	17.6 – 78.6	12.0 – 59.4
Vancouver (N=543)	AM (SD)	36.2 (8.3)	23.6 (6.4)	35.9 (8.4)	23.8(6.1)
	Median	35.2	22.5	35.1	29.5
	Range	11.8 - 58.9	7.2 - 47.3	11.8 - 58.8	7.3 – 47.2
Winnipeg (N=580)	AM (SD)	16.5 (5.7)	9.4 (4.0)	16.4 (5.7)	9.9 (3.6)
	Median	16	9	15.9	7.5
	Range	3.9 - 30.3	1.2 - 29	2.3 - 28.9	1.1 - 17.3

Sbihi *Environ Health Perspect* 2015

Traffic-Related Air Pollution



- Adjusted OR of atopy per 10ug/m^3 of NO_2

Sbihi *Environ Health Perspect* 2015

Impact of the microbiota on immune development and disease

Brett Finlay, Stuart Turvey, et al, Vancouver

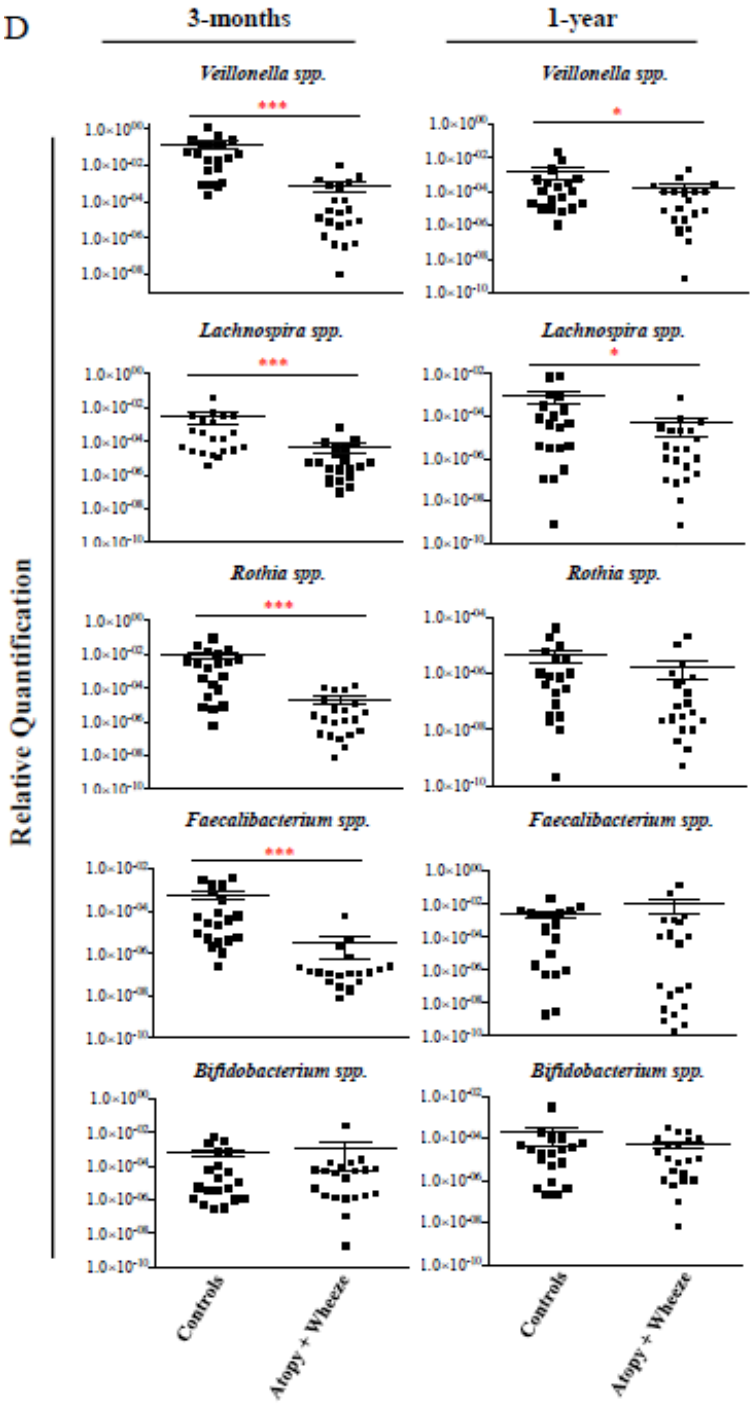
- **Hypothesis:** Intestinal microbiota affects immune development, including atopy and asthma, and that specific microbial populations play protective or harmful roles in these processes.
- **Three major objectives:**
  - Murine models (especially asthma) to study role of subsets of microbiota
  - Microbiota characterized in CHILD human birth cohort study and role in atopic phenotypes in allergic diseases
  - Correlations established between murine and human studies

Arrietta *Science Translational Medicine* 2015

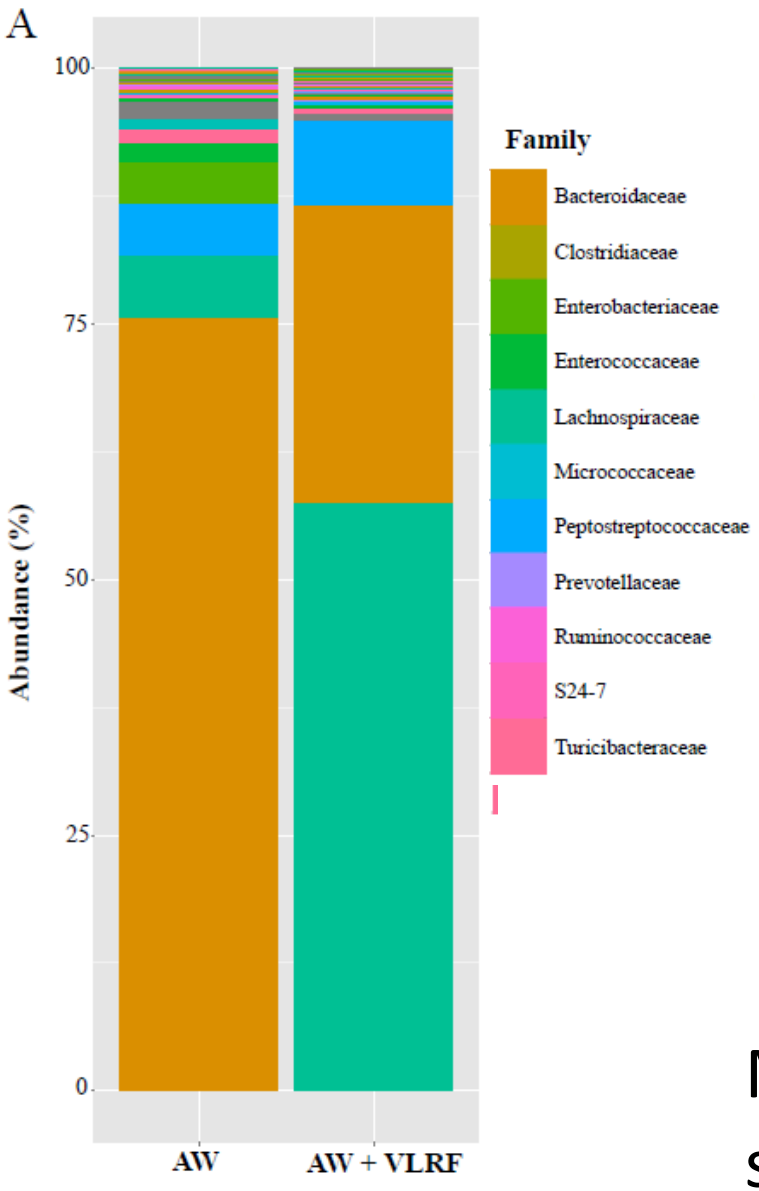
Comparison of the human gut microbiota between the extreme phenotypes showed significant differences at 3 months but not apparent at one year;

atopy + wheeze
atopy only
wheeze only
controls

Slide courtesy of
Stuart Turvey, UBC

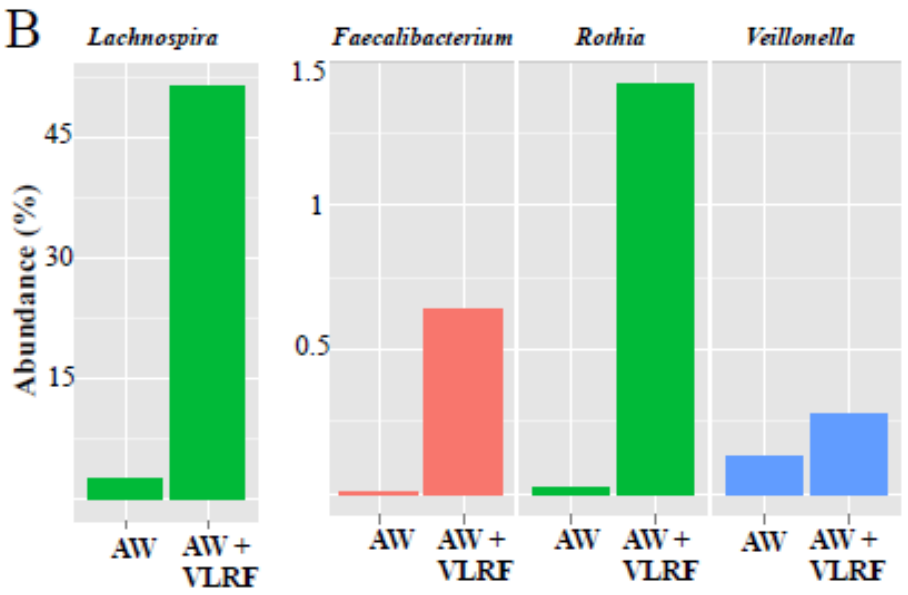


Arrietta *Science Translational Medicine* 2015



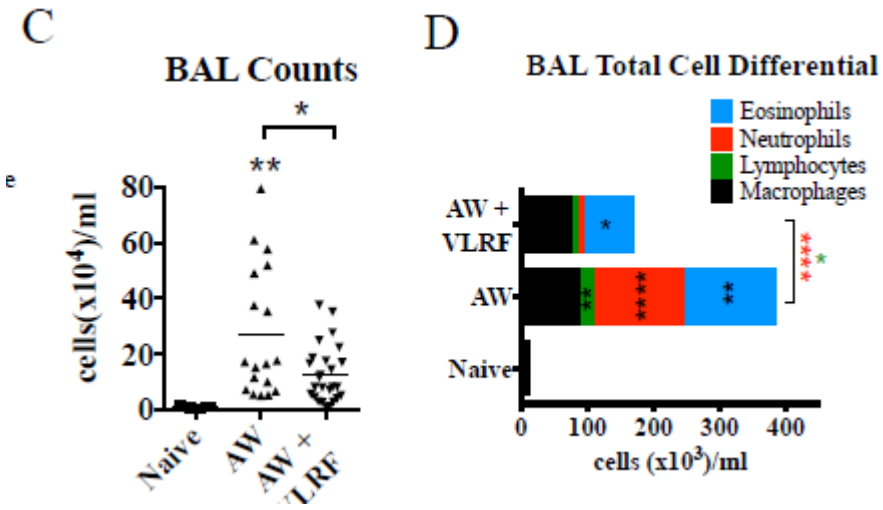
Arrietta *Science Translational Medicine* 2015

Germ-free mice were innoculated with feces from an AW subject at 3 months or same stool supplemented with VLRF.

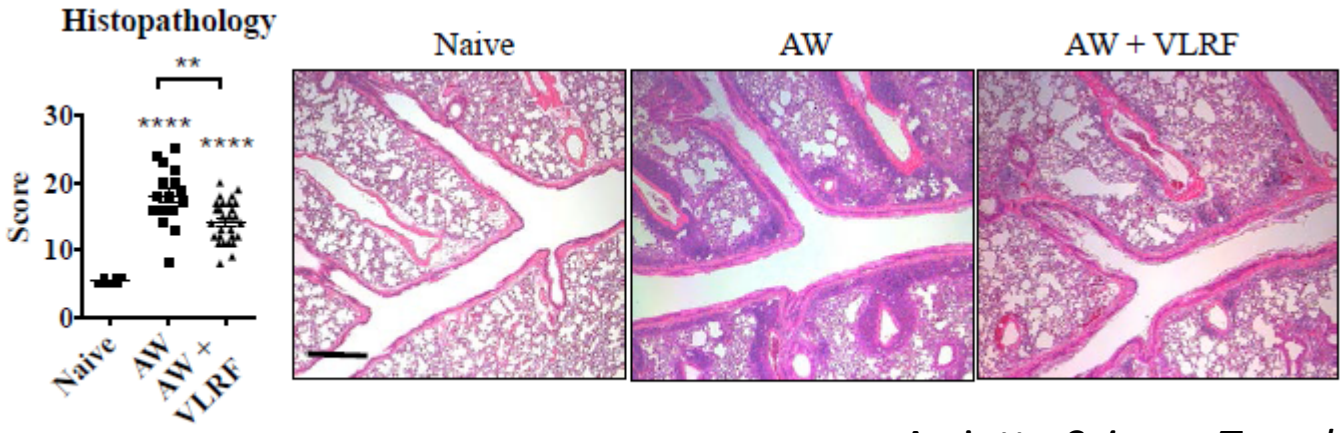


Mice born to parents harboring VLRF succesfully adopted these strains, colonizing Lachnospira at higher abundance than other 3 species.

Mice were then immunized using an ovalbumin sensitization protocol to induce airway inflammation at 7-8 weeks.
Mice innoculated with AW microbiota exhibited an enhanced lung inflammatory response and supplementation with VLRF decreased total lung cell infiltrate.



Histopathological scoring confirmed that VLRF reduced airway inflammation and concentrations of key lung proinflammatory cytokines



Arrietta *Science Translational Medicine* 2015

Strategic Focus of CHILD Research

- To understand key relationships and interactions among the many genetic determinants and environmental exposures associated with the development of asthma, and use this understanding to prevent it and improve its treatment.
- Multiple asthma/allergy hypotheses related to:

Innate immunity	Genetic risk, epigenetic effects
Microbiome	Nutrition
Infant lung function	Viral infections
Psychosocial effects, stress	Environmental exposures

- **Data collection has been expanded to provide for the study of development of other chronic non-communicable diseases including metabolic (obesity, diabetes) and cardiac disorders.**

AllerGen

The Canadian Healthy Infant Longitudinal Development Study

A platform for many current and future longitudinal studies in asthma, allergy, other chronic diseases of childhood and adulthood

Courtesy of Meghan Azad

CHILD Study Funding

CIHR IRSC

AllerGen
Allergy, Genes and Environment Network
Le réseau des allergies, des gènes et de l'environnement

Health Canada Santé Canada

Environment Canada Environnement Canada

CMHC SCHL

**Private donors –
Don & Debbie Morrison**

childhood asthma FOUNDATION