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

<table>
<thead>
<tr>
<th>Previous descriptions</th>
<th>Recent methodologies</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Extrinsic vs. intrinsic</td>
<td>• Cluster analysis</td>
</tr>
<tr>
<td>• Transient vs. persistent</td>
<td>• Latent class analysis</td>
</tr>
<tr>
<td>• Mild vs. severe</td>
<td>• Latent class growth analysis</td>
</tr>
<tr>
<td>• Childhood vs. adult onset</td>
<td>• Multiple factor analysis</td>
</tr>
<tr>
<td>• Seasonal vs. perennial</td>
<td>• Unsupervised statistical learning techniques</td>
</tr>
<tr>
<td>• Eosinophilic vs. neutrophilic</td>
<td>• Trajectories</td>
</tr>
<tr>
<td>• Occupational asthma</td>
<td></td>
</tr>
<tr>
<td>• Exercise induced asthma</td>
<td></td>
</tr>
<tr>
<td>• Aspirin-sensitive asthma</td>
<td></td>
</tr>
</tbody>
</table>
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.


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


<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Asthma</th>
<th>Atopy</th>
<th>FEV₁</th>
<th>FEF₂₅-₇₅</th>
<th>AHR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transient early</td>
<td>✓</td>
<td>-</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Prolonged early</td>
<td>✓ ✓</td>
<td>-</td>
<td>↓</td>
<td>↓↓</td>
<td>↑</td>
</tr>
<tr>
<td>Intermediate</td>
<td>✓ ✓ ✓ ✓</td>
<td>✓ ✓</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↑↑</td>
</tr>
<tr>
<td>Late</td>
<td>✓ ✓ ✓</td>
<td>✓ ✓</td>
<td>↓</td>
<td>↓</td>
<td>↑↑</td>
</tr>
<tr>
<td>Persistent</td>
<td>✓ ✓ ✓ ✓</td>
<td>✓</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↑↑</td>
</tr>
</tbody>
</table>
Beyond atopy. Multiple patterns of sensitization in relation to asthma in a birth cohort study.

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

• 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

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


Longitudinal lung function by asthma outcomes

It all happens in early childhood
Innovation from cell to society

RFA announcement 2006:

“Indoor air exposures, genes and gene-environment interactions in the etiology of asthma and allergy in early childhood”
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
Current recruitment sites for CHILD

National Coordinating Centre
Canadian Healthy Infant Longitudinal Development (CHILD)

Malcolm Sears
Director
Toronto
Co-Director & Site Leader

Padmaja Subbarao

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 (19 in 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

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

**Note:** The table lists variables that were obtained through questionnaires in the context of a study on various aspects related to home, mother, father, and child. Each variable is categorized under a specific label (HOME, MOTHER, FATHER, CHILD) and represents a type of data collection method or subject matter.
Assessment of the physical environment

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Questionnaires</th>
<th>house dust</th>
<th>Home Assessment (3 mo)</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 dampress</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>
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**

- Maternal Nutrition
- Birth weight
- Birth
- Prenatal (28-32 weeks)

**POSTNATAL EXPOSURE ASSESSMENT**

- ETS
- Air Pollution (GIS Modelling)
- Child Nutrition
- Breastfeeding
- Viral infection
- Birth weight
- Birth
- PFT (Toronto)
- 3 month
- 12 month
- 18 month
- 3 year
- 5 year – complete 2019

**Nasal microbiome**

**Dust allergen & Mould**

*From standardized home assessment
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

<table>
<thead>
<tr>
<th>Birth outcomes</th>
<th>25.6</th>
<th>Male sex (%)</th>
<th>52.4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cesarean section (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cord blood obtained (%)</td>
<td>75.1</td>
<td>Discharged with mother (%)</td>
<td>97.0</td>
</tr>
<tr>
<td>Birth weight (n=3192)</td>
<td>3448 gm, SD 482</td>
<td>Hospital stay &gt; 7 days (%)</td>
<td>1.3</td>
</tr>
<tr>
<td>Birth length (n=2306)</td>
<td>51.4 cm, SD 2.5</td>
<td>Given antibiotics (%)</td>
<td>5.4</td>
</tr>
<tr>
<td>Head circumference (n=2294)</td>
<td>34.6 cm, SD 1.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The CHILD cohort at 1 year

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

<table>
<thead>
<tr>
<th>Skin allergy tests at one year (≥2mm wheal)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Any positive skin test (%)</td>
<td>14.7</td>
<td>Any food allergen sensitization (%)</td>
<td>11.5</td>
</tr>
<tr>
<td>Any inhalant allergen sensitization (%)</td>
<td>4.7</td>
<td>Peanut sensitization (%)</td>
<td>5.0</td>
</tr>
</tbody>
</table>
**Traffic-Related Air Pollution**

- NO$_2$ exposure was very different in the 4 cities

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

- Adjusted OR of atopy per 10μg/m³ of NO₂

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

Mice born to parents harboring VLRF successfully 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 inoculated 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.
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