The Origins of Asthma & Allergy: Lessons from Birth Cohorts

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&
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Disclosures

Christine C Johnson, PhD

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Outline

• Asthma statistics: descriptive epidemiology

• Evolution of “Hygiene Hypothesis” studied in birth cohorts over the last decades and other fun epidemiological tidbits
Epidemiology:
Chipping Away with Studies to Reveal
~The TRUE CAUSAL PATHWAY~
Prevalence of Pediatric Asthma <18 yrs
1970-2004

CDC: Surveillance for Asthma—United States 1960-1995;
National Surveillance for Asthma—United States 1980-2004
US Asthma Prevalence by Age and Sex
2001-2009, CDC
Worldwide Prevalence of Asthma

Study of 463,801 children 13-14 yrs in 58 countries

ISAAC, Lancet 1998
Asthma Hospital Discharges by Race, 5-18 Years of Age

Gupta RS et al. JACI 2006
Children from inner cities have increased asthma.

Kattan M, Pediatric Pulmonology, 1997
Birth Cohort Studies Very Useful in Asthma and Allergy Epidemiology

- Early exposures important
- Outcomes develop in first decade of life
- Outcomes are relatively common
Points regarding Birth Cohort Studies in Asthma Epidemiology

- Can recruit in pregnancy, birth or soon thereafter
- High risk versus general “unselected” study subjects
- Measure exposures before disease onset
- Can measure multiple exposures and multiple outcomes
- Fewer biases such as recall bias
- Expensive! Require strong recruitment and retention
- Hypotheses change over time....
Birth Cohorts: ~40 cohorts worldwide; ~25% US; ~25% high risk; n of ~250-16,000

Tucson Childhood Respiratory Study (TCRS)
Isle of Wight Birth Cohort

**Detroit Childhood Allergy Study (CAS)**
Wisconsin Childhood Origins of ASThma (COAST)
Boston Home Allergens and Asthma Study
Canadian Asthma Primary Prevention Study (CAPPS)
Cincinnati Childhood Allergy and Air Pollution Study (CCAAPS)
NYC Columbia Center for Environmental Health Cohort

**Detroit Wayne County Allergy & Asthma Longitudinal Study (WHEALS)**
Baltimore, Boston, NYC, St. Louis: Urban Environment and Childhood Asthma (URECA)
Canadian Health Infant Longitudinal Development Study (CHILD)
Germany Multi-Center Allergy Study (MAS)
Netherlands Prevention and Incidence of Asthma and Mite Allergy (PIAMA)
Bristol UK Avon Longitudinal Study of Parents and Children (ALSPAC)
UK Manchester Asthma & Allergy Study (MAAS)
Sydney Australia Childhood Asthma Prevention Study (CAPS)
Stockholm Children Allergy & Early Environmental Prospective Birth Cohort Study (BAMSE)
Perth Australia Childhood Asthma Study (CAS)
Copenhagen Studies on Asthma in Childhood (COPSAC)

NIAID Birth Cohort Workshop, 2012
Bousquet et al. JACI 2014
1980s: Major Theories on Increase in Asthma & Allergy Prevalence

Exposure to pollutants

• smog
• diesel exhaust particles
• proximity to traffic
• environmental contaminants, including environmental tobacco smoke

Tighter homes

• more allergen exposure
• increased moisture
• more time indoors
The Evolution of Ideas

**1980s:** Hypothesis: Is it an increase in early childhood exposure to outdoor/indoor pollution or allergens such as dust mites due to tighter homes, more time inside, etc?
Risk of Hay Fever Inversely Related to Number of Older Siblings

The Hygiene Hypothesis

Strachan et al. BMJ 1989
“Hygiene” Factors

- Decreased family size
- Increased standard of living
- Suburbanization
- Less exposure to animals
- More immunizations
- More antibiotics use
- Increased C-section rate
- Decreased breastfeeding
The Evolution of Ideas

1980s: Hypothesis: Is it an increase in early childhood exposure to outdoor/indoor pollution or allergens such as dust mites due to tighter homes, more time inside, etc?

1990s: Hypothesis: Maybe other environmental factors contributing besides allergens, perhaps early respiratory infections or early immune stimulation?
Prevalence of Allergic Conditions in Children by Residency of Mothers during Pregnancy (Bavarian ALEX Study, n=901)

Farming, Bavarian Style
Dogs and cats in the house are bad for allergies, right?
Dogs, Cats and Atopic Diseases

• Overwhelming clinical experience of allergic rhinoconjunctivitis, asthma and urticaria related to dog and cat exposure

• Many studies showing increased symptoms in sensitized persons living with dogs and cats
So, clinicians had assumed that exposure to cats & dogs also causes the DEVELOPMENT of atopic disorders---
Pets Inversely Associated with Allergic Sensitivity at age 6 yrs

Ownby, Johnson, Peterson JAMA 2002
Day Care and Asthma, Tuscon Children’s Respiratory Study (n=875)

Pet in House during Pregnancy Associated with Decreased Total IgE from Birth through 2 yrs

![Graph showing the relationship between total IgE and age of child, with a comparison between no prenatal pet and prenatal pet groups.](Havstad_JACI_2011)
The Evolution of Ideas

1980s: Hypothesis: Is it an increase in early childhood exposure to pollutants and allergens such as dust mites due to tighter homes, more time inside, etc?

1990s: Hypothesis: Maybe other environmental factors contributing besides allergens, perhaps respiratory diseases?

Early 2000s: Hypothesis: ...could it be something associated with pets and livestock and daycare such as “good bacteria”? Very early in life important?
Drinking Water, Microbes, and Atopy

- 563 children, 7-16 years, living in Finnish- and Russian- Karelia

- Skin prick tested with 14 common allergens and foods

- Finnish children more often sensitized – 48% vs 16%

- Greater bacterial contamination of drinking water in Russian Karelia.

Von Hertzen et al. Allergy 2007
SUMMARY

Pets ↓ IgE/allergies/asthma

Farming ↓ IgE/allergies/asthma

Unpasteurized milk ↓ IgE/allergies/asthma

Day Care ↓ IgE/allergies/asthma

Contaminated Water ↓ IgE/allergies/asthma

Antibiotic Use, C-sections ↑ IgE/allergies/asthma

?
Evolution of the HYGIENE HYPOTHESIS

1989: DECREASED INFECTIONS?

2000: DECREASED BACTERIA EXPOSURE?

2007: CULTURE INDEPENDENT TECHNOLOGY

THE MICROBIAL DYSBIOSIS HYPOTHESIS
The Evolution of Ideas

1980s: Hypothesis: Is it an increase in early childhood exposure to allergens such as dust mites due to tighter homes, more time inside, etc?

1990s: Hypothesis: Maybe other environmental factors contributing besides allergens?

Early 2000s: Hypothesis: Something in the environment related to pets is associated with allergies...could it be something associated with lower “Hygiene” such as “good bacteria”?

Late 2000s: Hypothesis: Is it the microbial balance/patterns in the mother and child’s environment & child’s gut and/or skin and lung that impacts immune development and atopic disorders/asthma?
MAAP Causal Model

- Household Characteristics
- Microbial Community Composition In Home
- Prenatal Immune Status
- Baby's Genotype, Season, SES, Delivery Mode, URI's, Antibiotics, Diet, Activity, Pets, Other Children, Pollutants, Stress
- Early Immune Response & Development
- Persistent Immune Response Phenotype
- Allergic Asthma
Questions...

• What environmental and social characteristics are related to the environmental microbiota?

• What social and environmental characteristics are related to the infant gut microbiota?

• How does the infant gut microbiota relate to atopic conditions?
Wayne County Health, Environment, Allergy & Asthma Longitudinal Study (WHEALS) Birth Cohort

- Pregnant mothers recruited 2003-2007, from Henry Ford Health System OB clinics in metropolitan Detroit Michigan USA (urban/suburban)

- Racially and SES diversity (50% minority)

- Population-based (n=1258)

- Conducted interviews with mothers at prenatal and approximately 1 month (neonate) and 6 month (infant) home visits

- Dust and Stool samples collected at home visits; used Illumina MiSeq Sequencing platform -tag sequencing of the 16S rRNA gene (v4 region) to identify bacteria present (Operational Taxonomic Units or OTUs) N=298
The Indoor Microbiota: What does the dust tell us?
Are Babies exposed to House Dust?

- Hand-to-mouth activity in all children
- Well studied by toxicologists
- Average dust ingestion is 30–100 mg/day (20 – 70 million bacteria) for children 6 months – 11 yrs of age.

U.S. EPA. Child Specific Exposure Factors Handbook 2008
Bacterial Communities* in House Dust from Dog vs No-Pet Households

*measured by PhyloChip

Fujimura KE, JACI 2010;126:410-412
The Infant’s Microbiota: What Do the Stools Tell Us?
Bacterial Family Relative Abundance by Sample Time in WHEALS Children

Relative Abundance %

Neonatal  Infant

Family
- Bacteroidaceae
- Bilobobacteriaceae
- Enterobacteriaceae
- Lachnospiraceae
- Other
- Veillonellaceae
Univariate gut microbiota compositional analyses

Displays factors significantly associated with composition (p value < 0.05)
Baby Stool Univariate Compositional Differences: by Mode of Delivery

- 1 month stools
- p-value < 0.001
- $R^2 = 1.9\%$
Baby Stool Univariate Compositional Differences: by Pet Keeping at 1 month

- 1 month stools
- p-value = 0.026
- $R^2 = 1.0\%$
Bacteria Families by Breastfeeding

Not Currently Breastfeeding at 1 Month

Currently Breastfeeding at 1 Month

1 Month

Relative Abundance (%)

0% 25% 50% 75% 100%

0% 25% 50% 75% 100%

100% 75% 50% 25% 0%

6 Month

Family
- Bifidobacteriaceae
- Bacteroidaceae
- Enterobacteriaceae
- Lachnospiraceae
- Veillonellaceae
- Other
Composition Differs by Breastfeeding

Both p-values < 0.001
OTU Pattern at 1 Month for Breastfed and Non-Breastfed Infants

Breastfed Only
N=8,919 (27%)
- 8%
- 20%
- 12%
- 7%
- 4%
- 49%

Both
N=9,864 (30%)
- 8%
- 10%
- 10%
- 13%
- 5%
- 54%

Non-Breastfed Only
N=14,269 (43%)
- 6%
- 9%
- 6%
- 21%
- 2%
- 56%

Bacteroidaceae
Bifidobacteriaceae
Enterobacteriaceae
Lachnospiraceae
Veillonellaceae
Other
Does the Infant’s Microbiota relate to Disease Outcomes?
First Year Gut Microbiota Stratifies into Four Distinct Enterotypes

Dirichlet Mixture Model to statistically define infant sub-populations based on microbiota composition

4.5% of the variation explained (p<0.001)
Prevalence of Sensitization at 2 yrs (allergen sIgE >0.35) for 10 Allergens within each Latent Class

Havstad et al. JACI 2014

Predominantly Multi-sensitized group (PM group)
Neonates with Co-Dominant Enterotype had Higher Risk of Developing Multi-Sensitization at age 2yrs*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>NEONATES</th>
<th>Risk Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>E to B</td>
<td>C to B</td>
<td>C to E</td>
</tr>
<tr>
<td>Multiple sensitization</td>
<td>1.43</td>
<td>2.94</td>
<td>2.06</td>
</tr>
<tr>
<td></td>
<td>(0.73-2.81)</td>
<td>(1.42-6.09)</td>
<td>(1.01-4.19)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome</th>
<th>INFANTS</th>
<th>Risk Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B to L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple sensitization</td>
<td>1.02</td>
<td></td>
<td>0.94</td>
</tr>
<tr>
<td></td>
<td>(0.59-1.75)</td>
<td></td>
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</tr>
</tbody>
</table>

**Key**

E = Enterobacteriaceae  B = Bifidobacteriaceae  C = Co-Dominant  L = Lachnospiraceae

*Havstad et al. JACI 2014*
Breastfeeding and Allergic-Like Response to Pets

• In WHEALS, breastfed babies were less likely to have an allergic-like response to pets at age 4
  • OR (95% CI) = 0.58 (0.36, 0.94)
  • p-value = 0.028
Bacterial Compositional Differences by Allergic-Like Response to Pets

**Neonatal Visit:**
- $p$-value $= 0.023$

**Infant Visit:**
- $p$-value $= 0.60$
Identifying Potentially Mediating OTUs
Identifying Potentially Mediating OTUs

77 (71%) Significant OTUs

51 (66%) OTUs
Breastfeeding may protect against colonization of specific Lachnospiraceae bacteria at 1 month of age
  ▫ Associated with increased risk of allergic-like response to pets at age 4

Lachnospiraceae: common adult gut colonizers
  ▫ Newborns (1%) → Infants (10%) → Adults (17%)
  ▫ In terms of gut microbiome, does breastfeeding prevent a premature shift to adulthood?
Distribution of Early House Dust Allergen & Bacterial Exposures by Disease Outcomes at 3 yrs, URECA Birth Cohort

Lynch, JACI 2014
Many Studies Suggest that Atopic Disorders Are Less Common Among Children with Early Exposure to Mammals: Farm Animals & Pets

~Implying a higher prevalence in “inner cities” BUT:
Is there an urban:rural difference in asthma prevalence?
Lung Health Survey

• Conducted in high schools located in inner city Detroit Michigan (in 2007) and four Counties in rural Georgia USA (in 2010)

• N=7297 students in Detroit and 2523 students in Georgia
Urban Detroit, USA
Growing up on a Farm Bavarian Style
Rural Georgia Homes and Farms
## Zip Code Characteristics of Lung Health Survey Subjects’ High Schools, 2013

<table>
<thead>
<tr>
<th>Location</th>
<th>Population Density (people/sq mile)</th>
<th>% Eligible for free/reduced cost lunch</th>
<th>% Poverty in zip code</th>
<th>% Black Students</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Georgia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 Rural Counties, 2010</td>
<td>45.1</td>
<td>73.3%</td>
<td>22.8%</td>
<td>67.4%</td>
</tr>
<tr>
<td><strong>Michigan</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban Detroit, 2007</td>
<td>5627.8</td>
<td>74.2%</td>
<td>23.0%</td>
<td>98.9%</td>
</tr>
</tbody>
</table>

Ownby DR et al. *JACI* 2015
### Adolescent Current Asthma
#### 2013 BRFSS Compared to Lung Health Surveys

<table>
<thead>
<tr>
<th>State</th>
<th>Sample #</th>
<th>Prevalence %</th>
<th>95% CI</th>
<th>Prevalence #</th>
</tr>
</thead>
<tbody>
<tr>
<td>Georgia</td>
<td>1864</td>
<td>10.8%</td>
<td>9.1 - 12.7</td>
<td>259,917</td>
</tr>
<tr>
<td>Michigan</td>
<td>2715</td>
<td>10.9%</td>
<td>9.5 – 12.5</td>
<td>238,422</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>State</th>
<th>Sample #</th>
<th>Current Diagnosed Asthma Prevalence %</th>
<th>Current UnDiagnosed, %</th>
<th>Prevalence %, Diagnosed and Undiagnosed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Georgia, rural</td>
<td>2523</td>
<td>13.7%</td>
<td>7.3%</td>
<td>13.7 + 7.3 = 21.0</td>
</tr>
<tr>
<td>Michigan, Detroit</td>
<td>7297</td>
<td>15.0%</td>
<td>7.8%</td>
<td>15.0 + 7.8 = 22.8</td>
</tr>
</tbody>
</table>

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Behavioral Risk Factor Surveillance System (BRFSS)
www.cdc.gov/asthma/asthma_stats/default.html
Ownby DR et al. J Allergy Clin Immunol 2015
Impoverished US Cities and Rural Towns: Microbial Deserts?
# African American Families Less Likely to have Dogs

<table>
<thead>
<tr>
<th>Maternal race</th>
<th>Dog-keeping at prenatal interview</th>
<th>Unadjusted OR (95% CI)</th>
<th>Multivariable aOR (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes n (%)</td>
<td>No n (%)</td>
<td></td>
</tr>
<tr>
<td>White (n=290)</td>
<td>132 (45.5%)</td>
<td>158 (54.5%)</td>
<td>3.16 (2.37, 4.22)</td>
</tr>
<tr>
<td>Black (n=775)</td>
<td>162 (20.9%)</td>
<td>613 (79.1%)</td>
<td>Referent</td>
</tr>
</tbody>
</table>

† Adjusted for the following covariates: (1) maternal age, (2) City residence (Detroit), (3) maternal education, (4) household income, (5) marital status, (6) number of siblings, (7) mother smoked prepregnancy, (8) kept other non-dog pet, and (9) ever intentionally not kept pets because someone living in their home is highly allergic to animals.

Ezell et al. Ethn Dis 2014
Other Theories on Increase in Asthma: Perhaps by effect on Gut Microbiomes?

- Less time outside
- Less exercise
- More refined or “Westernized” foods
  - less fruit and vegetable intake
  - less fish intake
- Obesity
Current Hypothesis

The risk of development of allergy and asthma is mainly influenced by the gut microbes to which a child is exposed in the first year of life and the composition of these microbes are determined by maternal and environmental factors.
We thank the families and children who have participated in the WHEALS birth cohort and other P01 and HFHS birth cohort studies.

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QUESTIONS?