Outline of Presentation

• Asthma trends in the US and abroad: A look at prevalence, morbidity and mortality.

• Environmental determinants of increased prevalence and severity: research progress and challenges.
  – Two asthma outcomes (onset and exacerbation)
  – Examples from the air pollution literature

• Complex disease / complex designs.

• Gene-environment interactions
  – Examples from the air pollution literature

• Transdisciplinary designs.
Asthma Prevalence
US, 1980-2004

Child and Adult Asthma Prevalence
US, 1980-2004

Source: National Health Interview Survey; National Center for Health Statistics
Percentage* of Children Aged <18 Years with Current Asthma, by Race/Ethnicity and Sex — United States, 2001–2004

Source: National Health Interview Survey; CDC, National Center for Health Statistics

Current Asthma Prevalence by Poverty Status: US, 2004

Source: National Health Interview Survey; National Center for Health Statistics
International Changes in the Prevalence of Diagnosed Asthma


International Changes in the Prevalence of Atopy (Skin Prick Tests or Specific IgE)

American Lung Association Epidemiology and Statistics Unit, Research and Program Services. Trends in asthma morbidity and mortality 2006; Source: NCHS. National Hospital Discharge Survey
Change from ICD-9 to ICD-10

% of asthma visits with medication
- Inhaled corticosteroids
- Leukotriene modifiers
- Long-acting β2-agonists
- Cromones

Summary: Asthma Prevalence, Morbidity and Mortality

- Asthma prevalence has continued to increase possibly reaching a plateau recently, but morbidity and mortality has stabilized or decreased for most:
  - better case and self management / improvements in treatment – controller medications;
  - Patient education on triggers and use of medications.

- **Challenge:** prevention of asthma onset.

- Underlying etiologic and severity differences between genders, adults vs. children, race and SES are strongly suggested.

- **Challenge:** Target intervention based on susceptibility factors driving underlying differences.

Environmental Determinants of Increased Prevalence and Severity: Research Progress & Challenges

- Air pollution;
- Environmental tobacco smoke (ETS);
- Indoor allergens;
- Endotoxin;
- Infections, respiratory / nonrespiratory;
- Diet, physical activity and obesity;
- In utero environment and birth outcomes;
- Stress, maternal (in utero) and child;
- Socioeconomic disparities.

Two Asthma Study Outcomes

- **Asthma onset**
  - Cohort research designs
    - Prospective
    - Retrospective
  - Windows of vulnerability: in utero, early postnatal and later development,
  - Adult vs. pediatric / male vs. female / wheeze and cough phenotypes.

- **Acute-on-chronic responses** (lung function, symptoms, biomarkers of inflammation and oxidative stress, etc.)
  - Panel study
  - Clinical trial
  - Experimental study

- **Shared and different sets of etiologic factors and preventive strategies.**
  - e.g., endotoxin
Examples from the Air Pollution Literature

• Ambient Air Pollution
  – Time series studies

• Ambient, Outdoor Home and Personal Air Pollution
  – Cohort studies
  – Panel studies

• Environmental Tobacco Smoke
  – Cohort study

• Diet and Ozone
  – Panel study

Early Use of Available Data: Asthma Morbidity and Air Pollution

• Time series analyses of asthma hospital admissions and ED Visits.

• Led to early discoveries and incentives for larger studies worldwide and research on exposure-response relationships in individuals.
  – e.g., Bates and Sizto. *Environ Res.* 1987;43:317-31
    Summer SO$_4$ and O$_3$ were significantly correlated with asthma and other respiratory admissions in Southern Ontario.

• Led to tightening of air pollution regulation.
Limitations of Exposure Data for Asthma and Air Pollution Research

- Epidemiologic studies largely show associations between asthma and ambient “principal criteria air pollutants” regulated by EPA and measured at widely dispersed locations: PM$_{10}$, PM$_{2.5}$, O$_3$, NO$_2$, CO, SO$_2$

- To what extent are associations attributable to unmeasured personal exposure to toxic air pollutants (e.g., combustion-related organic compounds) and ultrafine PM?

- Limited progress in studying risks of asthma onset from outdoor air pollution exposure. Tackled first by Europeans.

![Graph showing Ultrafine vs. fine PM Spatial Distribution]

Traffic-related Air Pollution and Asthma Onset

• Numerous epidemiologic studies have shown associations between traffic near the home and asthma prevalence or morbidity, and atopy. Reviewed in:
  

• Exposure assessment has been crude in most studies—distance to traffic and traffic volume, not exposures directly estimated from monitored data.

  Alternative: use GIS to combine geographic data (subject locations vs. traffic & other pollutant sources) + spatially diverse and representative air monitor data.

  Reviewed in:
### Southern California Children’s Health Study (CHS)

Asthma-related outcomes & exposure to traffic & outdoor home NO₂ in 208 randomly sampled children ages 14-18 yr.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No</th>
<th>Measured NO₂ OR (95% CI) Per IQR</th>
<th>Distance to Freeway OR (95% CI)</th>
<th>CALINE4 Freeway NO₂ OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ever Asthma</td>
<td>31</td>
<td>1.83 (1.04–3.21)</td>
<td>1.89 (1.19–3.02)</td>
<td>2.22 (1.36–3.63)</td>
</tr>
<tr>
<td>Recent wheeze</td>
<td>43</td>
<td>1.72 (1.07–2.77)</td>
<td>1.59 (1.06–2.36)</td>
<td>1.70 (1.12–2.58)</td>
</tr>
<tr>
<td>Recent wheeze with exercise</td>
<td>25</td>
<td>2.01 (1.08–3.72)</td>
<td>2.57 (1.50–4.38)</td>
<td>2.56 (1.50–4.38)</td>
</tr>
<tr>
<td>Current asthma med use</td>
<td>26</td>
<td>2.19 (1.20–4.01)</td>
<td>2.04 (1.25–3.31)</td>
<td>1.92 (1.18–3.12)</td>
</tr>
</tbody>
</table>


### Early Life Exposure to Traffic-related Air Pollution and Asthma Onset

- French metro areas, 217 matched case-control pairs, ages 4-14 yr: MD-diagnosed asthma was associated with home and school traffic density during ages 0-3.
  - OR 2.28 (95% CI: 1.14 to 4.56) for third vs. first tertile, stronger with +SPT.
  - Zmirou *J Epidemiol Community Health* 2004;58:18-23

- A Dutch cohort study found possible increased risk of MD-diagnosed “asthma” incidence in 1-2 yr old children exposed to traffic-related air pollutants near the home: GIS-modeled NO₂ and PM₂.₅ black carbon (a marker of diesel exhaust).
  - Brauer M et al. *Am J Respir Crit Care Med* 2002;166:1092–8
### Asthma Prevalence in Children Ages 5-7 yr by Distance of Residence to a Major Road in Long-term Residents: Differences by Gender and Allergic Symptoms

<table>
<thead>
<tr>
<th>Major road distance</th>
<th>Boys (n = 945) OR (95% CI)</th>
<th>Girls (n = 901) OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 75 vs. &gt; 300 m</td>
<td>1.31 (0.75–2.29)</td>
<td><strong>2.13 (1.18–3.85)</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>No allergic symptoms (n = 942)</td>
</tr>
<tr>
<td>&lt; 75 vs. &gt; 300 m</td>
<td><strong>2.52 (1.07–5.93)</strong></td>
<td>1.29 (0.76–2.21)</td>
</tr>
</tbody>
</table>

McConnell et al. *Environ Health Perspect* 2006;114:766–772

**Prevalence of asthma in 1,330 children ages 5-7 yr by distance of residence to a major road in long-term residents, no family history of asthma.**

McConnell et al. *Environ Health Perspect* 2006;114:766–772
Panel Studies

- a longitudinal study with repeated measurements of health outcomes and exposures in individuals.
- **Design advantages:**
  - reduces the likelihood of recall bias & inaccuracy.
  - each subject serves as his/her own control over time.
  - determine within subject patterns of acute response
  - statistically efficient (increased signal to noise ratio) because:
    - multiple exposures and concentrations studied in each subject;
    - controls variability in exposure response relationships due to between subject characteristics
    - reduces variability of response without reducing magnitude of association = enhanced power & precision.

Power of Panel Studies to Detect Between-Subject Difference in Susceptibility

- Panel Studies of Asthma, Particulate Air Pollution & NO$_2$ (personal and ambient air pollutant exposures)
  - Asthma symptoms: episodes of interference with daily activity.
  - Forced expiratory volume in 1 sec (FEV$_1$).
  - Airway inflammation as represented by daily exhaled NO (eNO).
Asthma Symptoms in Children and Interactions Between Ambient Exposures and use of Anti-inflammatory Medication (7 on vs. 7 not on)

Delfino et al. Environ Health Perspect 1998;106:751-61

Asthma Symptoms in Children and Interactions Between Ambient Exposures and use of Anti-inflammatory Medication (10 on vs. 12 not on)

Percent Predicted FEV$_1$ in Relation to Personal PM: Interaction with Allergy to Indoor Allergens (HDM/Cat) (6 allergic vs. 6 non-allergic)

Delfino et al. Environ Health Perspect 2004;112:932-41
Relationship of exhaled NO in 45 children with asthma to air pollutant exposures over the previous 48 hours, Riverside and Whittier, CA

*Change in exhaled NO (ppb) per interquartile increase in pollutant (95% CI)

Delfino et al. Environ Health Perspect, 2006;114:1736-43

2-Day MA: Personal

PM$_{2.5}$ alone
PM$_{2.5}$ with EC
PM$_{2.5}$ with OC
PM$_{2.5}$ with NO$_2$

Expected change in $F_{Ex0}$

2-Day MA: Central Site
Exhaled NO is associated with personal PM$_{2.5}$ independent of EC, OC and NO$_2$, possibly due to bioaerosol components.

Associations of a biomarker (eNO) with ambient and personal EC and NO$_2$ suggests traffic-related emission components are causally related to airway inflammation.

Complex Disease / Complex Designs

- **Diagnostic phenotypes:**
  - Intermittent and reversible airway obstruction;
  - Airway hyperresponsiveness to contractile stimuli;
  - Airway inflammation:
    infiltration of inflammatory cells releasing cytokines, chemokines & chemical mediators.

- **Other asthma phenotypes:**
  Allergic vs. non-allergic;
  Early, persistent & late onset wheeze;*
  Eosinophilic vs. neutrophilic asthma**

- **Adult vs. pediatric / male vs. female**

- **Research strategy** Characterize phenotype-genotype-environment clusters

  ** Douwes et al. *Thorax* 2002;57:643-648
Why assess genetic susceptibility to environmental exposures in human studies?

• Exposure-response relationships may be missed;

• Clues to mechanisms and to key causal components in mixtures of exposures;

• Potential identification of susceptible subgroups for preventive interventions.
Accurate assessment of genes and clinical outcomes but not exposures?

• Most asthma genetic studies employ similar and highly accurate genotyping methods.

• Studies employ widely divergent and generally inaccurate methods of exposure assessment.

• Result:
  – Literature is inconsistent;
  – G x E may be missed, biased, or ignored;

Vineis 2004. *Int J Epidemiol* 33:945-46

GxE Measurement Error: Power vs. Precision

• Sample size for GxE depends on:
  – magnitude of interaction;
  – allele frequency;
  – strength of E-R relationship;
  – E and R measurement error.

• Greater accuracy and precision in measurements may be more cost effective than increasing sample size: *e.g., repeated measures of actual (not recalled) exposures and acute outcomes.*

Environmental epidemiology and key genetic polymorphisms

• promises to enhance detection of adverse effects in susceptible subgroups, but this is thwarted by:
  – Power issues with low prevalence of high risk polymorphism.
  – Complex toxicological mechanisms argue for > one gene to assess effect modification: genomic pathways.

• use depends on design and health outcome.

Interaction Between GSTM1 Polymorphism, O₃ and Dietary Antioxidants

• GSTM1: homozygous deletion polymorphism (null) abolishes glutathione transferase (GST) M1 activity in protecting cells against ROS
• Romieu 2004 Thorax 59:8-10. Randomized double blind trial of 158 asthmatic children in Mexico City given placebo or antiox vitamins E + C. 12 bi-weekly repeated measures of in-clinic lung function and ambient O₃

<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>% change (95% CI) in FEF₂₅₋₇₅ / 50 ppb O₃</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSTM1 null</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>29</td>
<td>-2.9 (−5.2 to −0.6)</td>
</tr>
<tr>
<td>Supplement</td>
<td>33</td>
<td>-0.2 (−2.3 to 1.9)</td>
</tr>
<tr>
<td>GSTM1 positive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>49</td>
<td>-0.6 (−2.1 to 0.9)</td>
</tr>
<tr>
<td>Supplement</td>
<td>47</td>
<td>0.3 (−1.6 to 2.2)</td>
</tr>
</tbody>
</table>
Interaction Between GSTM1 and *In Utero* ETS

- CHS: 2,950 schoolchildren enrolled in 4th, 7th, and 10th grade classrooms in 12 Southern CA communities.
- Parental reports of lifetime ETS Hx, wheezing and MD-diagnosed asthma at cohort entry.

<table>
<thead>
<tr>
<th></th>
<th>ETS (−), GSTM1 (+)</th>
<th>ETS (−), GSTM1 (−)</th>
<th>ETS (+), GSTM1 (+)</th>
<th>ETS (+), GSTM1 (−)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ever asthma</strong></td>
<td>Ref group</td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Active asthma*</td>
<td>Ref group</td>
<td>1.0 (0.8, 1.2)</td>
<td>0.9 (0.6, 1.4)</td>
<td>1.4 (0.9, 2.1)</td>
</tr>
<tr>
<td>Meds for asthma*</td>
<td>Ref group</td>
<td>0.8 (0.6, 1.1)</td>
<td>0.8 (0.5, 1.3)</td>
<td><strong>1.7 (1.1, 2.8)</strong></td>
</tr>
<tr>
<td>Early onset asthma*</td>
<td>Ref group</td>
<td>0.9 (0.7, 1.2)</td>
<td>0.7 (0.4, 1.2)</td>
<td><strong>1.6 (1.1, 2.8)</strong></td>
</tr>
<tr>
<td>Persistent asthma*</td>
<td>Ref group</td>
<td>1.0 (0.8, 1.2)</td>
<td>0.9 (0.6, 1.4)</td>
<td><strong>1.6 (1.1, 2.4)</strong></td>
</tr>
</tbody>
</table>

* significant GxE interaction


Pollutant Toxicity and Gene Expression

- Link gene expression to toxic exposures
- Challenges:
  - Is expression relevant to harmful or protective mechanisms?
  - Can similar expression patterns used as “signatures” for toxic mechanisms be linked to a class of compounds?
  - Acute vs. chronic (within- vs. between-subject) exposure gene expression
  - Human exposure-dose-response is complex
- One part of the solution: use *phenotypic anchoring*: biological or clinical endpoints are linked to gene expression & chemical exposure → clues to toxicological pathways.

Neonatal immune and metabolic phenotypes

Maternal genes

Maternal lifestyle (smoking, diet, alcohol, etc) atopy (IgE) and infection (antibiotics)

In Utero Environment

Neonatal immune and metabolic phenotypes

Fetal Genes

Air pollution Environmental tobacco smoke Allergens / endotoxin

Asthma and Allergy Phenotypes

Allergens / endotoxin

Diet / Physical activity other lifestyle & SES factors

Child’s Genes

Lower respiratory infections


Transdisciplinarity

Definition:

- It involves academic researchers from different unrelated disciplines (interdisciplinary team) as well as non-academic participants.

- Together they develop a shared conceptual framework that integrates and extends discipline-specific theories, concepts, and methods to address a common research problem or to execute a plan where there are solutions to the problem (with non-academic participants).

Approaches to Interdisciplinary Research

- **R01s** ...individual scientist develops an interdisciplinary approach to a particular research question by assembling a collaborative research team;

- **Centers** multiple researchers trained in different fields combine efforts as members of a collaborative team focusing on a particular topic;

- **Large-scale research initiatives**: e.g.
  - NIH Transdisciplinary Tobacco Use Research Centers
  - Robert Wood Johnson Foundation’s (RWJF) Active Living, Obesity, and Nutrition Program.
  - National Children’s Study

- **NIH Roadmap Initiative**:
  - Interdisciplinary Research Implementation Group
  - Public Private Partnerships Implementation Group

Interdisciplinary Needs

- **Bring down disciplinary barriers, e.g., air pollution and asthma research**:  
  - **Multidisciplinary crosstalk** → new ideas, coherent results, and biological plausibility of inferences.
  - **Interdisciplinary e.g.**: same subject in an epidemiologic study with well characterized phenotype, genotype and exposure, then enters a clinical trial or experimental exposure phase.  
    → Susceptibility in real life clarified experimentally
  - Epidemiologists, exposure assessment experts, pulmonologists, allergists, atmospheric chemists, environmental engineers, geneticists, biochemists …
Interdisciplinary Needs for Asthma Research

• Preparing for ‘omics research in subjects with asthma:
  – Clinical & epidemiologic studies - limited funds to do it all.
  – Archive biospecimens using valid methods
    • Standardization through targeted small grant initiatives? NIH Roadmap Implementation Groups?
    • genomics, proteomics, metabolomics, cell cytometry, etc. on targeted subsamples: responder phenotype, exposure extremes
  – Biostatistical model development & availability for complex interactions of many G x many E for many Y.

• Developing and using improved air pollution and bioaerosol measurement and exposure modeling methods.