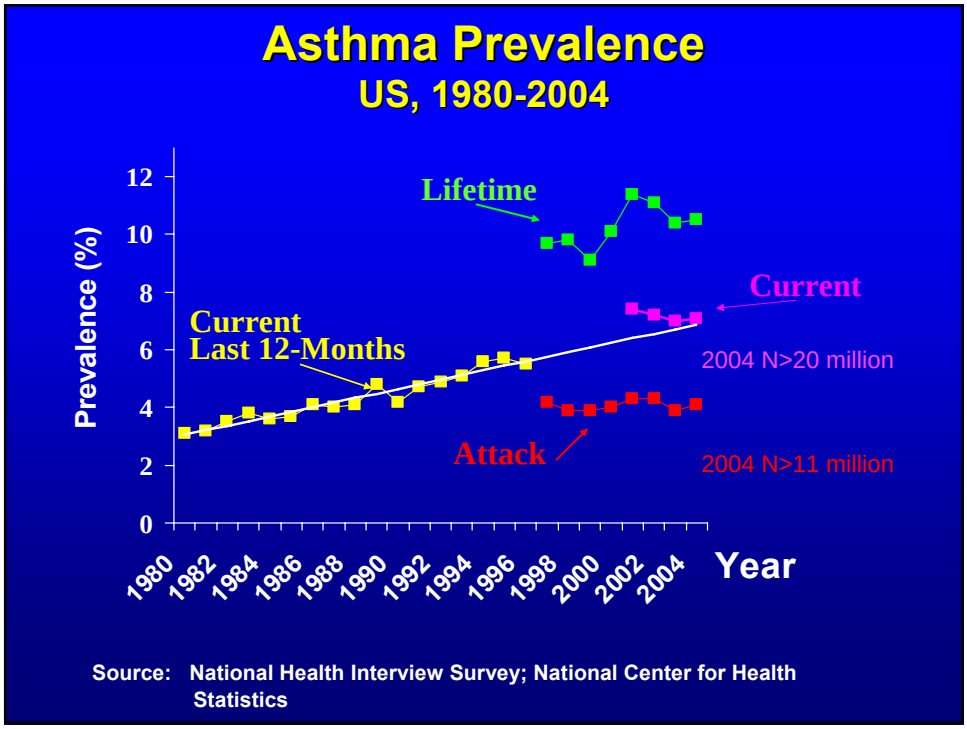
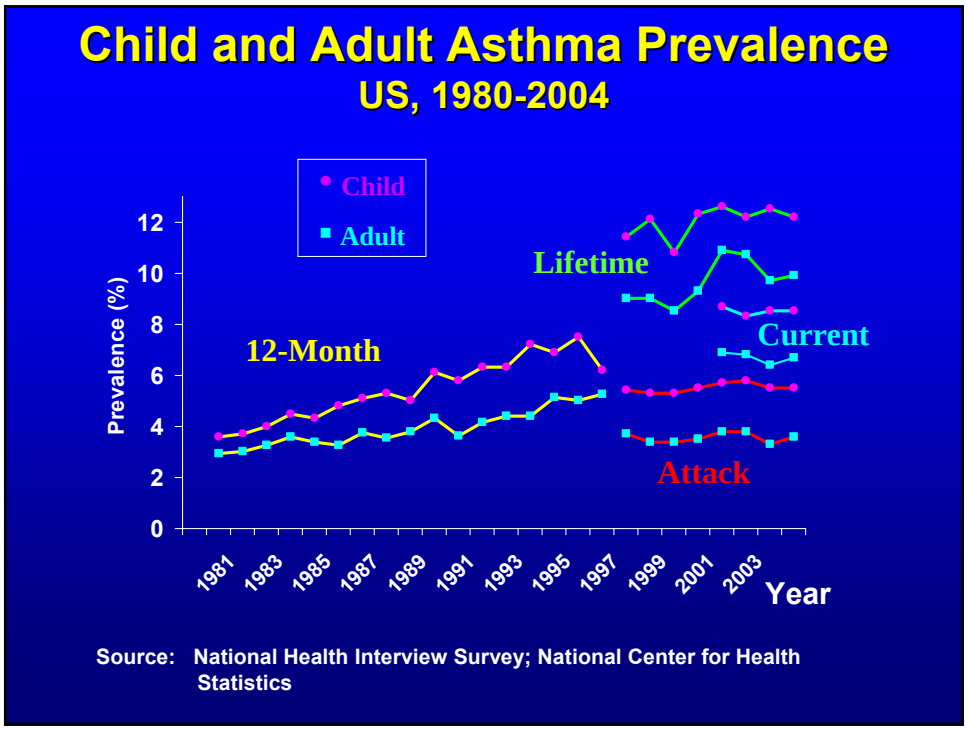
ASTHMA EPIDEMIOLOGY

Outline of Presentation

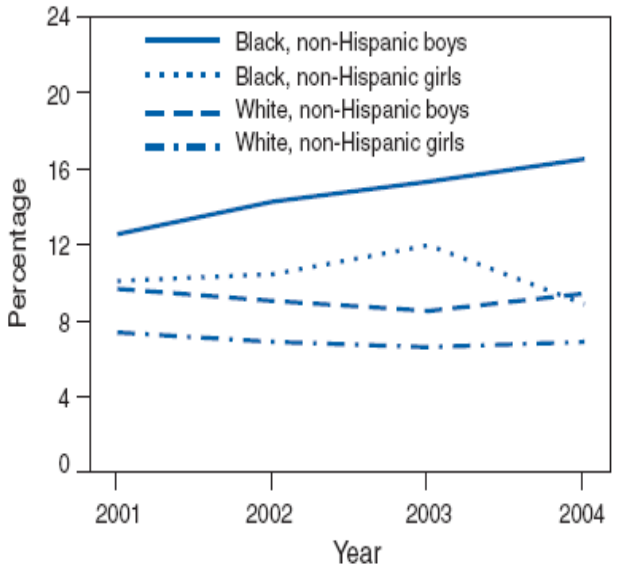
- Asthma trends in the US and abroad: A look at prevalence, morbidity and mortality.
- Environmental determinants of increased prevalence and severity: research progress and challenges.
  - Two asthma outcomes (onset and exacerbation)
  - Examples from the air pollution literature
- Complex disease / complex designs.
- Gene-environment interactions
  - Examples from the air pollution literature
- Transdisciplinary designs.


Asthma Prevalence
US, 1980-2004
Prevalence (%)
0
2
4
6
8
10
12
1980
1982
1984
1986
1988
1990
1992
1994
1996
1998
2000
2002
2004
Year
Lifetime
Current
Current
Last 12-Months
2004 N>20 million
Attack
2004 N>11 million
Source: National Health Interview Survey; National Center for Health Statistics

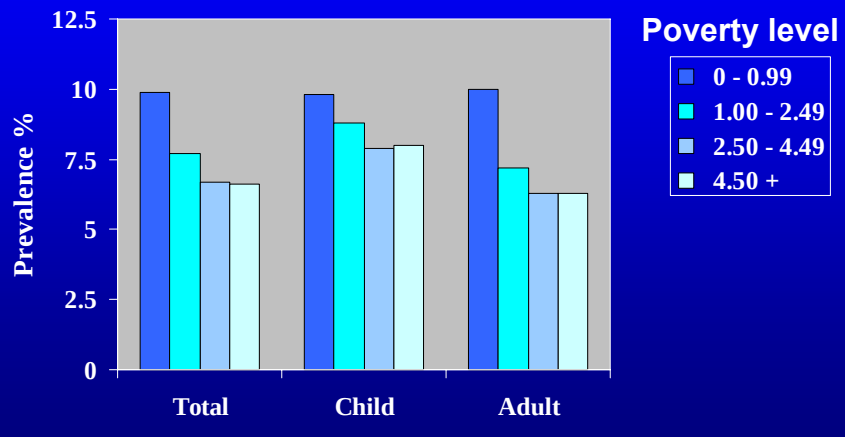

Child and Adult Asthma Prevalence
US, 1980-2004
Child
Adult
Prevalence (%)
0
2
4
6
8
10
12
1981
1983
1985
1987
1989
1991
1993
1995
1997
1999
2001
2003
Year
Lifetime
12-Month
Current
Attack
Source: National Health Interview Survey; National Center for Health Statistics

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

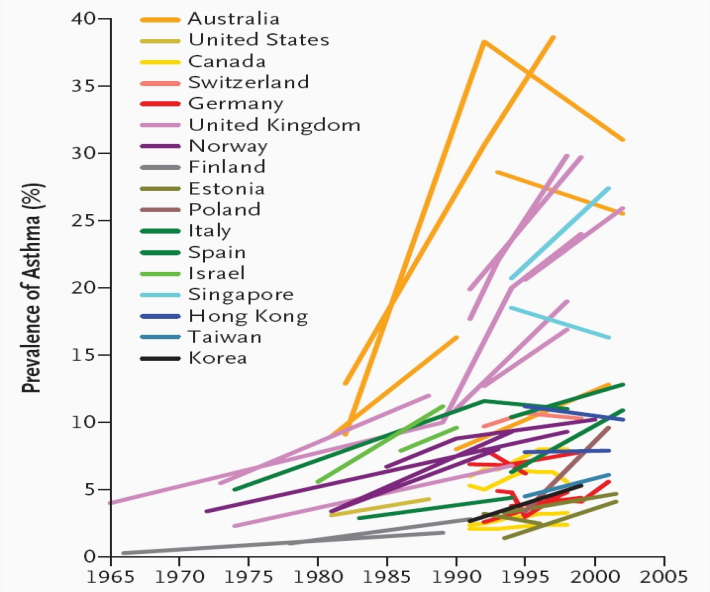


Current Asthma Prevalence by Poverty Status: US, 2004



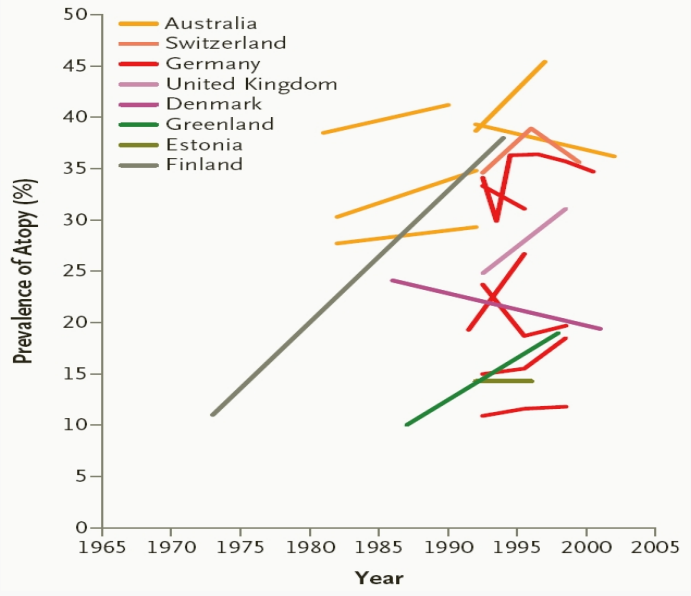
Source: National Health Interview Survey; National Center for Health Statistics

International Changes in the Prevalence of Diagnosed Asthma



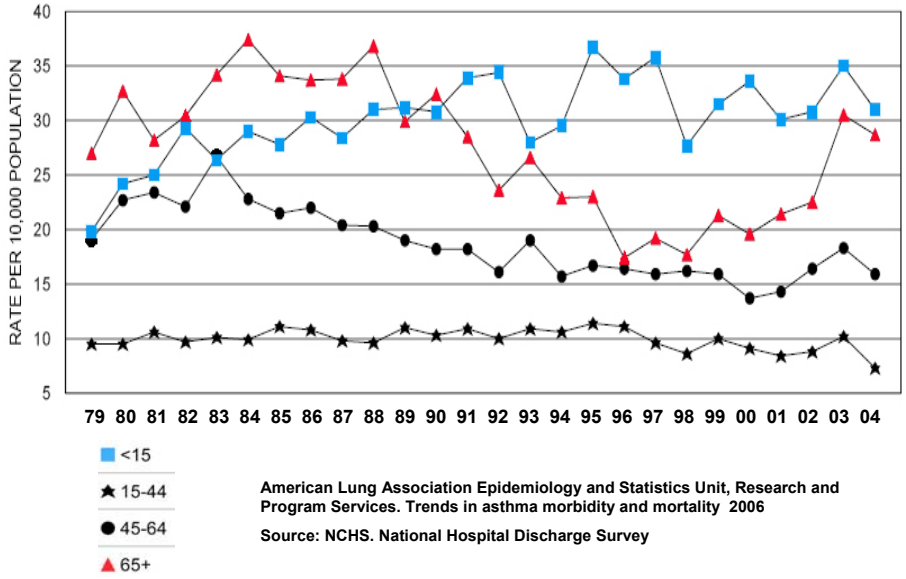
Eder et al. *N Engl J Med*. 2006;355:2226-35

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



Eder et al. *N Engl J Med*. 2006;355:2226-35

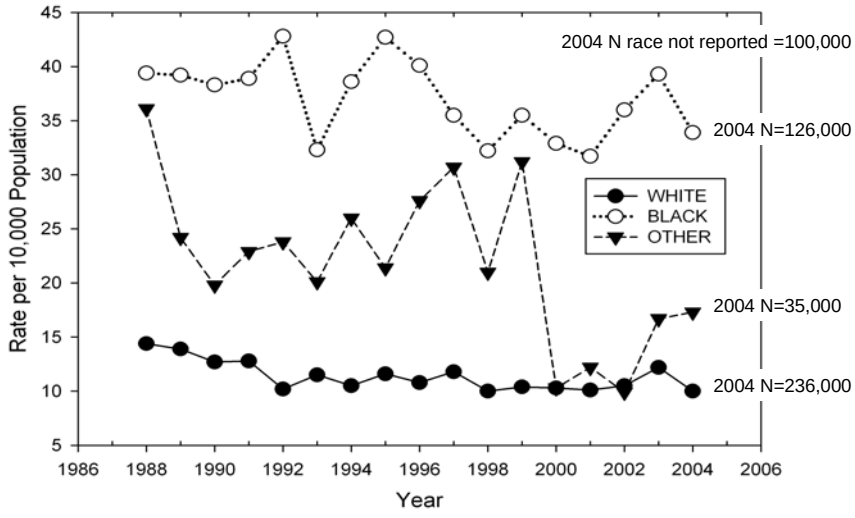
US Trends in Asthma Hospital Discharge Rates/10,000 by Age 1979-2004



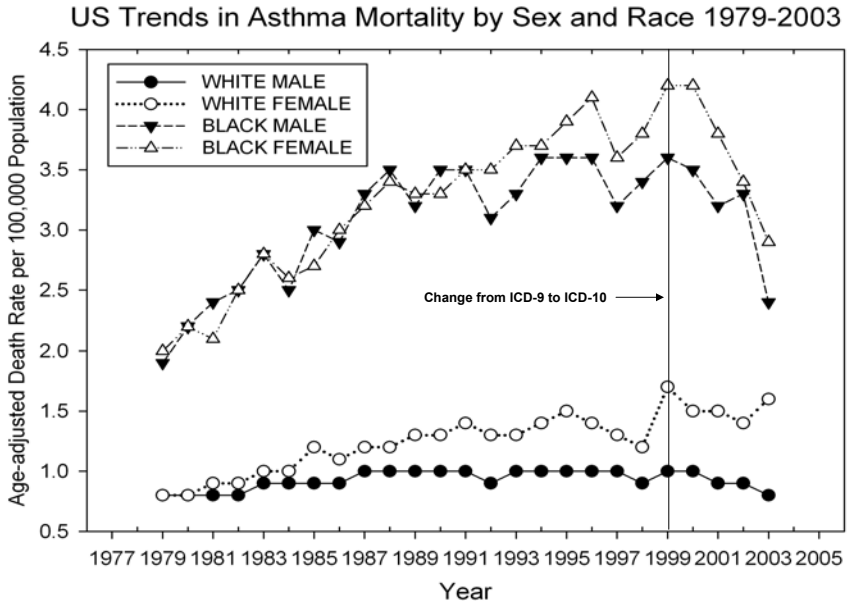
American Lung Association Epidemiology and Statistics Unit, Research and Program Services. Trends in asthma morbidity and mortality 2006

Source: NCHS. National Hospital Discharge Survey

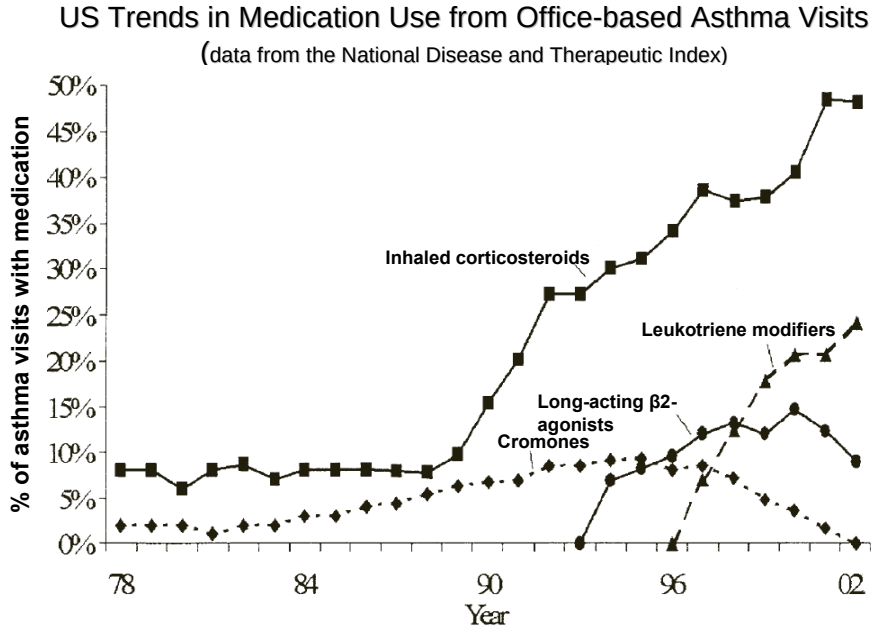
US Trends in Asthma Hospitalization by Race, 1979-2004



American Lung Association Epidemiology and Statistics Unit, Research and Program Services. Trends in asthma morbidity and mortality 2006; Source: NCHS. National Hospital Discharge Survey

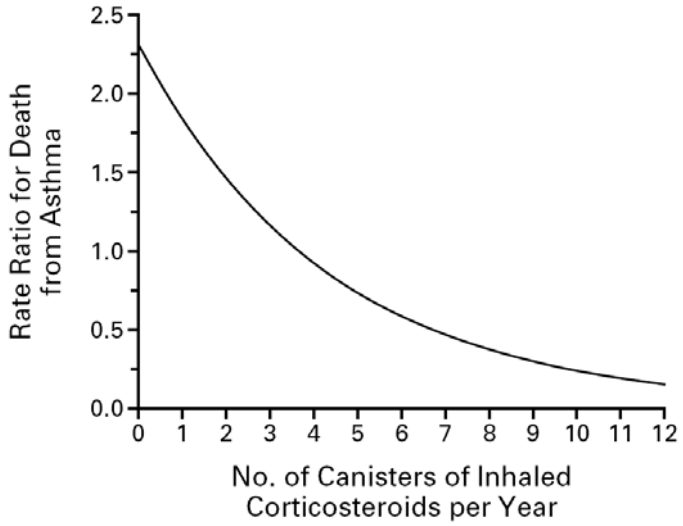


American Lung Association Epidemiology and Statistics Unit, Research and Program Services. Trends in asthma morbidity and mortality 2006; Source: NCHS. National Hospital Discharge Survey



Stafford et al. *J Allergy Clin Immunol*. 2003;111:729-35

Rate ratio of asthma deaths by number of canisters



Suissa et al. *N Engl J Med*. 2000;343:332-6.

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

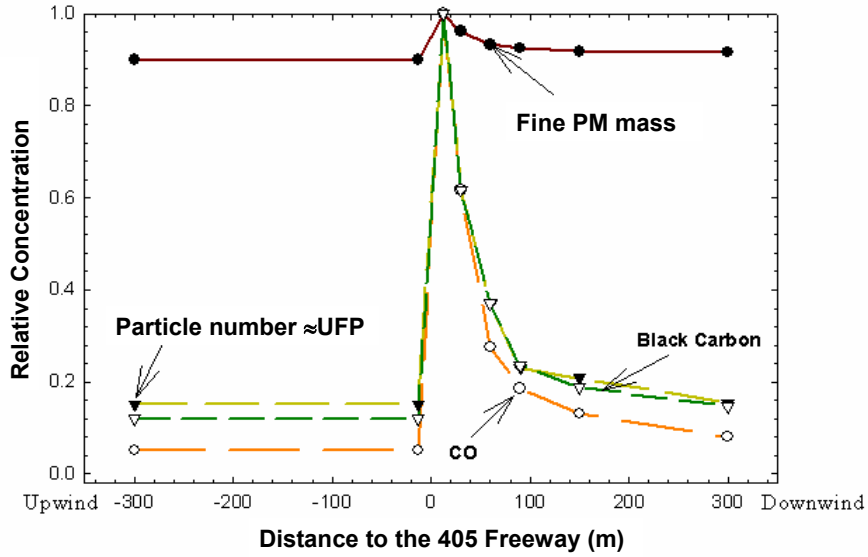
Early Use of Available Data: Asthma Morbidity and Air Pollution

- 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.

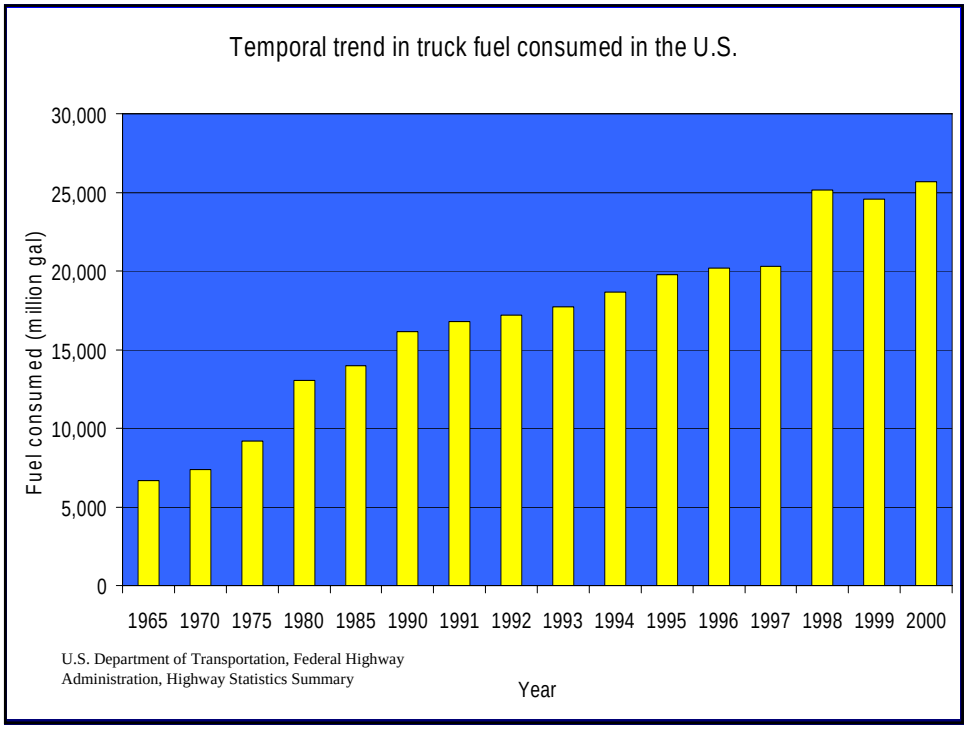
Limitations of Exposure Data for Asthma and Air Pollution Research

- 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.

Ultrafine vs. fine PM Spatial Distribution



Zhu et al. *J Air Waste Manage Assoc* 2002;52:1032-1042.



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:
  - Delfino RJ. *Environ Health Perspect*, 2002; 110(Suppl 4):573-89.
  - Heinrich and Wichmann. *Curr Opin Allergy Clin Immunol*, 2004;4:341-8
  - Sarnat and Holguin 2007 *Curr Opin Pulm Med* 2007;13:63-6
- 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:
    Jerrett et al. *J Expo Analysis and Environ Epidemiol* 2005;15:185–204.

Southern California Children's Health Study (CHS)

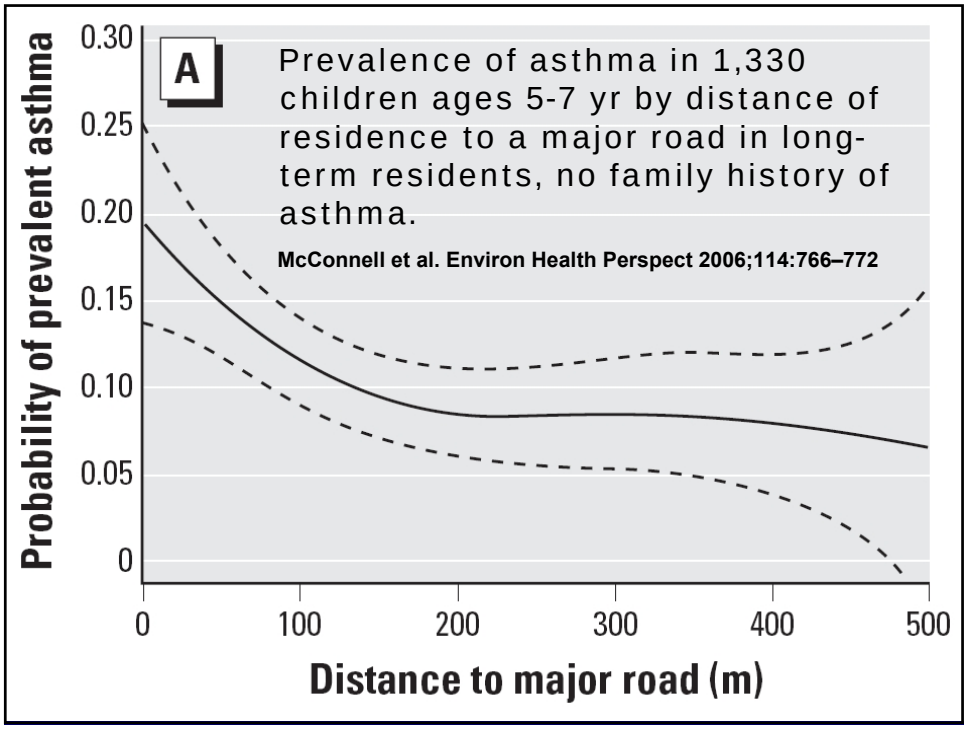
Asthma-related outcomes & exposure to traffic & outdoor home NO_2 in 208 randomly sampled children ages 14-18 yr.

Outcome	No	Measured NO_2 OR (95% CI) Per IQR	Distance to Freeway OR (95% CI)	CALINE4 Freeway NO_2 OR (95% CI)
Ever Asthma	31	1.83 (1.04–3.21)	1.89 (1.19–3.02)	2.22 (1.36–3.63)
Recent wheeze	43	1.72 (1.07–2.77)	1.59 (1.06–2.36)	1.70 (1.12–2.58)
Recent wheeze with exercise	25	2.01 (1.08–3.72)	2.57 (1.50–4.38)	2.56 (1.50–4.38)
Current asthma med use	26	2.19 (1.20–4.01)	2.04 (1.25–3.31)	1.92 (1.18–3.12)

Gauderman et al. *Epidemiology* 2005;16:737-43

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 NO_2 and $PM_{2.5}$ 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

Major road distance	Boys (n = 945) OR (95% CI)	Girls (n = 901) OR (95% CI)
< 75 vs. > 300 m	1.31 (0.75–2.29)	**2.13 (1.18–3.85)**
	No allergic symptoms (n = 942)	Allergic symptoms (n = 723)
< 75 vs. > 300 m	**2.52 (1.07–5.93)**	1.29 (0.76–2.21)

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

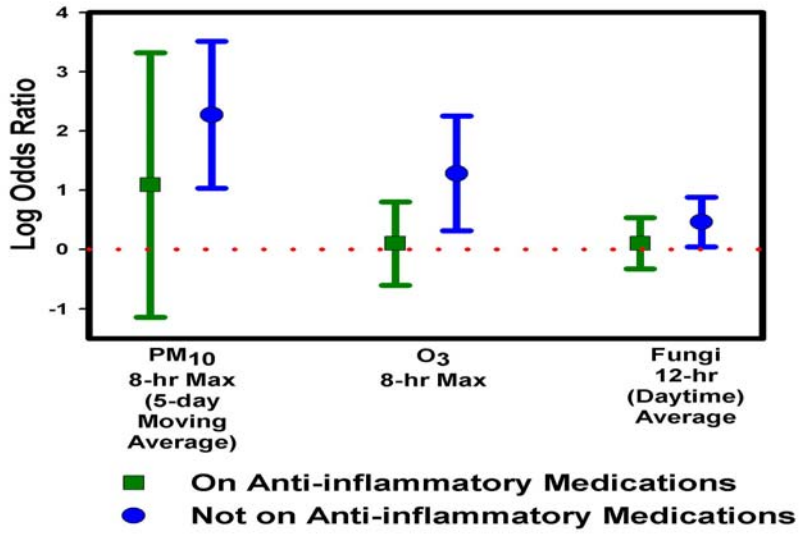
Panel Studies

- 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

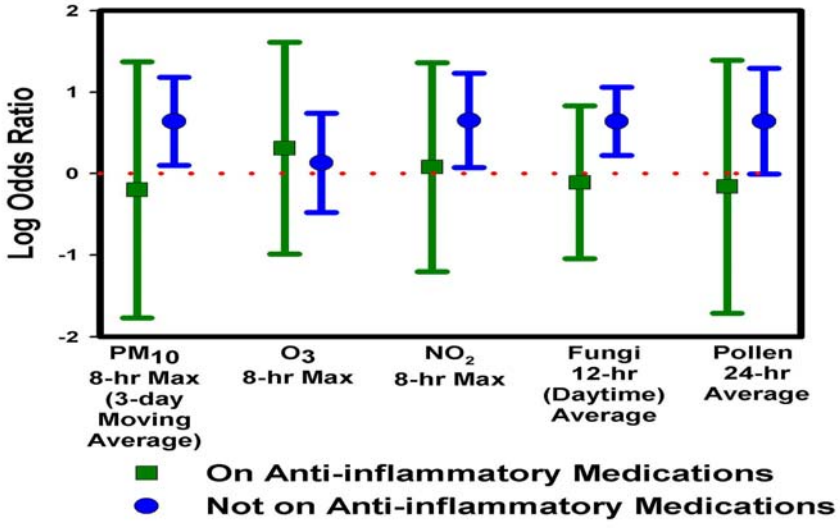
- Panel Studies of Asthma, Particulate Air Pollution & NO_2 (personal and ambient air pollutant exposures)
  - Asthma symptoms: episodes of interference with daily activity.
  - Forced expiratory volume in 1 sec (FEV_1).
  - Airway inflammation as represented by daily exhaled NO (eNO).

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

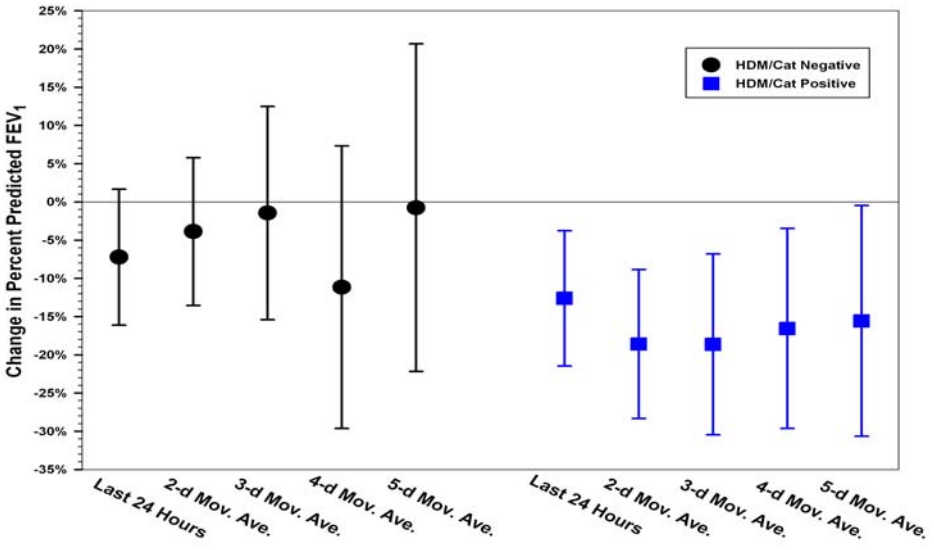
Asthma Symptoms in Children and Interactions Between Ambient Exposures and use of Anti-inflammatory Medication (10 on vs. 12 not on)



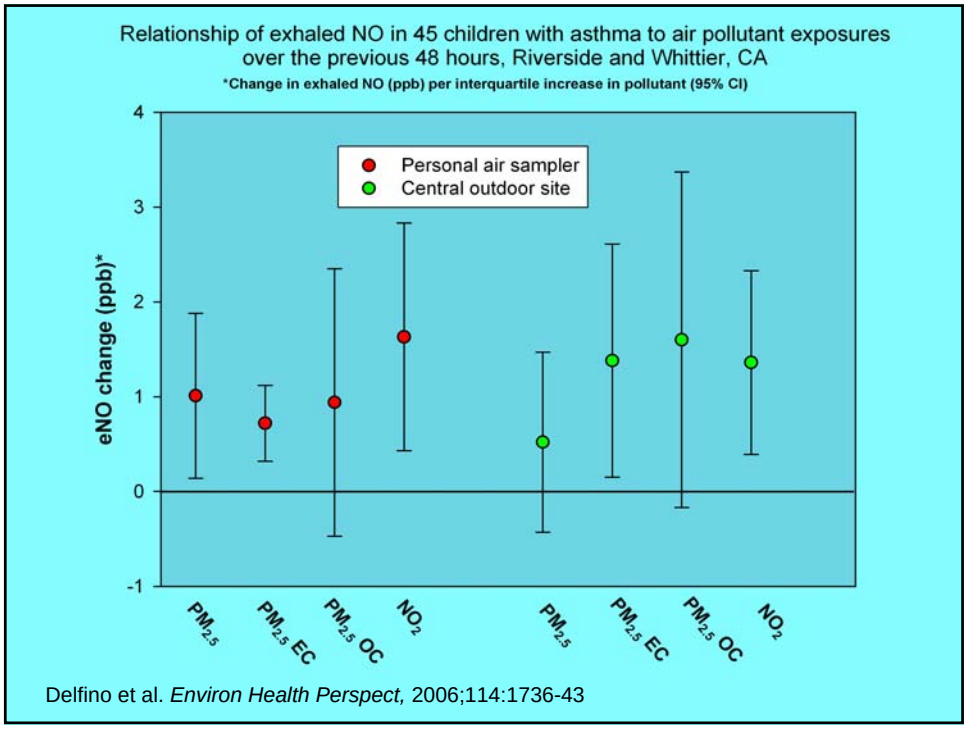
Delfino et al. *Environ Health Perspect* 2002;110:A607-A617

Personal Real-time Particle Sensor

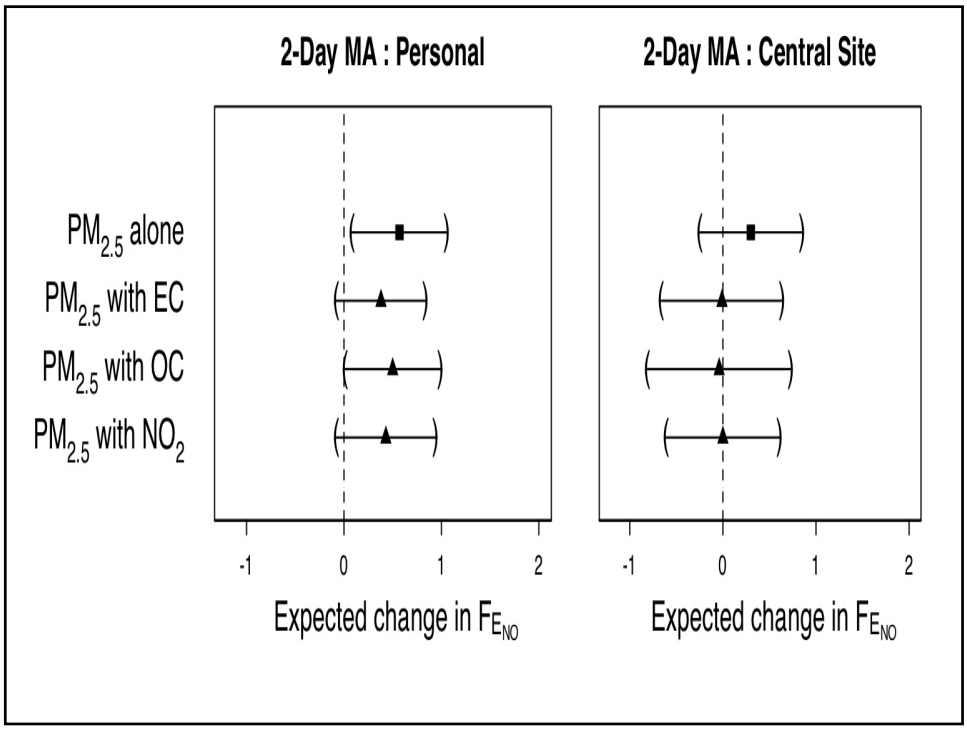
Percent Predicted FEV_1 in Relation to Personal PM: Interaction with Allergy to Indoor Allergens (HDM/Cat) (6 allergic vs. 6 non-allergic)



Delfino et al. *Environ Health Perspect* 2004;112:932-41



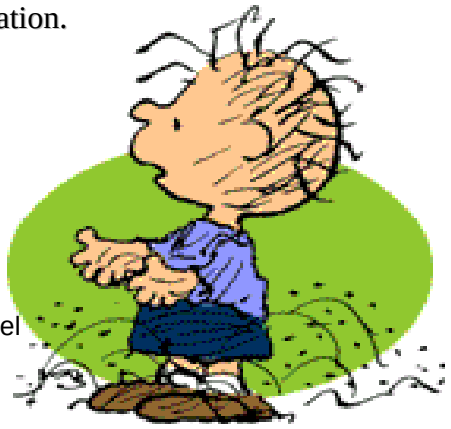
Delfino et al. *Environ Health Perspect,* 2006;114:1736-43



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.

Products of fossil fuel combustion

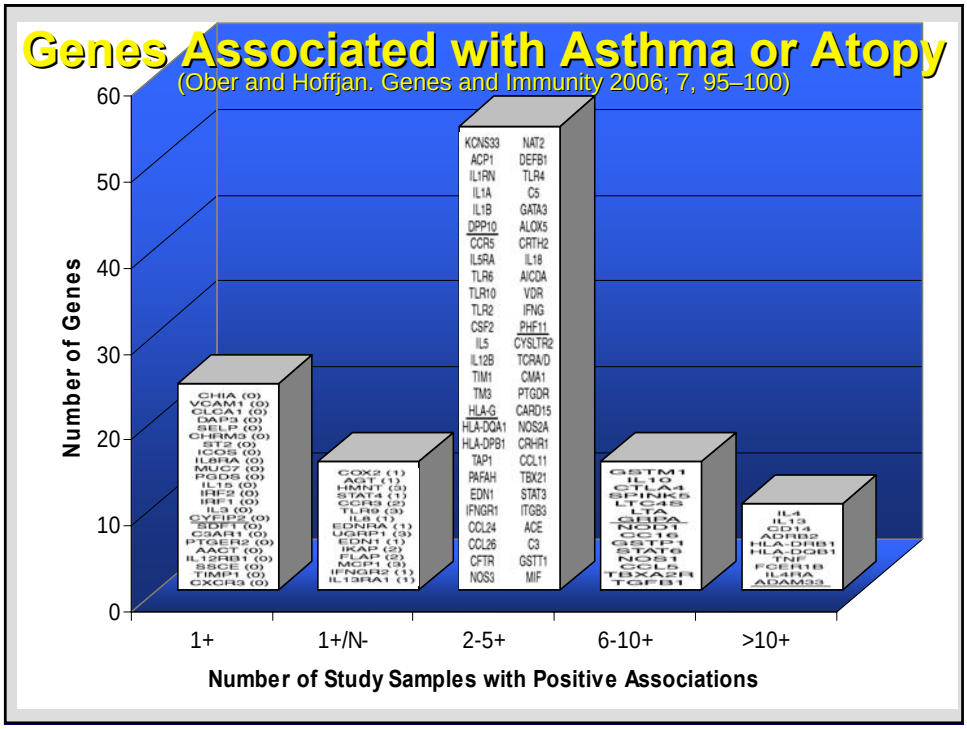


Bioaerosols

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

* Morgan et al. *Am J Respir Crit Care Med* 2005;172:1253-58
** 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.

Wong et al. 2003 *Int J Epidemiol* 32:51-57.

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, O_3 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 O_3

Group	No.	% change (95% CI) in FEF_{25-75} / 50 ppb O_3
GSTM1 null		
Placebo	29	–2.9 (–5.2 to –0.6)
Supplement	33	–0.2 (–2.3 to 1.9)
GSTM1 positive		
Placebo	49	–0.6 (–2.1 to 0.9)
Supplement	47	0.3 (–1.6 to 2.2)

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.

	ETS (–), GSTM1 (+)	ETS (–), GSTM1 (–)	ETS (+), GSTM1 (+)	ETS (+), GSTM1 (–)
		OR (95% CI)	OR (95% CI)	OR (95% CI)
Ever asthma	Ref group	1.0 (0.8, 1.2)	0.9 (0.6, 1.4)	1.4 (0.9, 2.1)
Active asthma*	Ref group	0.8 (0.6, 1.1)	0.8 (0.5, 1.3)	**1.7 (1.1, 2.8)**
Meds for asthma*	Ref group	0.9 (0.7, 1.2)	0.7 (0.4, 1.2)	**1.8 (1.1, 2.8)**
Early onset asthma*	Ref group	0.9 (0.7, 1.2)	0.9 (0.7, 1.4)	**1.6 (1.0, 2.5)**
Persistent asthma*	Ref group	1.0 (0.8, 1.2)	0.9 (0.6, 1.4)	**1.6 (1.1, 2.4)**

* significant GxE interaction

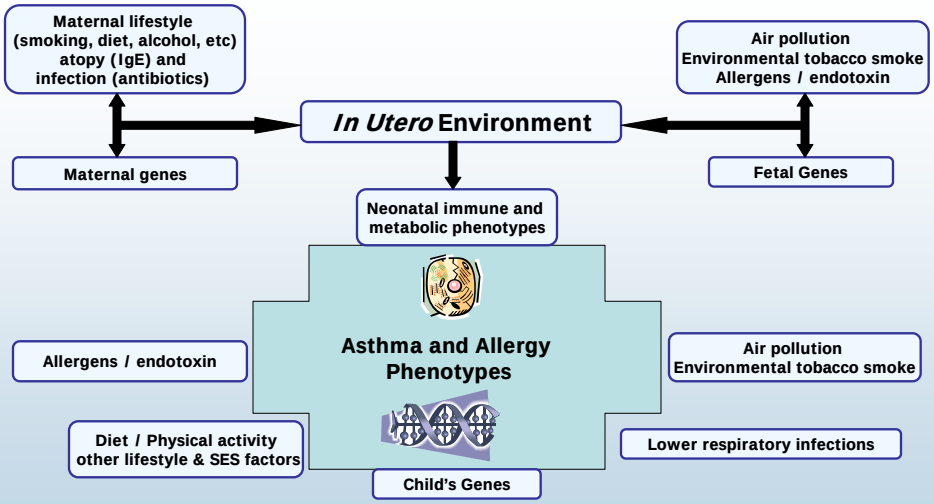
Gilliland 2002 *Am J Respir Crit Care Med* 166: 457-63.

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.

Environ Health Perspect. Toxicogenomics, 2003, Vol 111.

Causal Pathways to Asthma and Atopy in Childhood



Adapted from Tantisira and Weiss. Respir Res 2001;2:324-7.

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).

Rosenfield PL. Soc Sci Med. 1992;35:1343-57

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.