



# Central role of Life stage on induction/ exacerbation of asthma.

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B • O • S • C HUMAN HEALTH PROGRAM REVIEW

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RESEARCH & DEVELOPMENT

## LTG 3 Poster 13

### Science Questions

Asthma does not impact all ages equally, it is twice as common among children than adults. In the U.S. nearly 5 million asthma sufferers are under age 18, making it the most common chronic childhood disease. While 44% of all asthma hospitalizations are for children, 60% of the annual 4,000 deaths due to asthma occur in the senior citizens. In addition, early life factors are predictive for chronic asthma in adulthood. Therefore ORD research has centered on the key questions of:

What life stage confers increased risk of asthma from environmental factors?

What are the host factors of susceptibility related to differences in life stage?



### Research Goals

The goal of life stage research in asthma is to provide a fundamental understanding of the environmental factors that can lead to increased risk to sensitive populations.

As such ORD research has coordinated its research on asthma across the intramural, extramural programs and its cooperative agreements to focus on the research goals of this program:

1. Identifying critical windows of exposure that establish formation of asthma
2. Identifying key environmental factors that drive life stage susceptibility to asthma
3. Understanding the key pathways in asthma by which environmental factors differentially affect different life stages.

### Findings and Conclusions

Asthma outcomes vary depending on exposure during life stage. In utero diesel exposure increases cellular inflammation in the offspring and alters levels of immuno-regulatory molecules important in the development of allergic asthma. Maternal smoking will not only increase the asthma risk of children but also that of grandchildren nearly two-fold. Prenatal exposure to airborne PAH and ETS can lead to increased respiratory symptoms and probable asthma by age 12 to 24 months.

Methylation and histone acetylation pattern changes induced by diesel suggests that epigenetic mechanisms may be responsible for its asthma trans-generational effects. Environmental exposures to herbicide and pesticides during the first year of life are associated with childhood asthma risk. Elevated Th2 status in one year old infants is associated with maternal agricultural work and may determine asthma and wheeze outcomes as they become toddlers.

Mouse allergen exposure in the home is strongly associated asthma-related outcomes in preschoolers. Children with asthma exposed to secondhand smoke are at increased risk of school absence. These are primarily respiratory-illness-related. Children in urban areas are at increased risk for elevated air-pollution exposure and asthma trigger levels in the home. Children residing in polluted communities show deficits in lung growth.

Different subtypes of asthma can be identified by gene expression and clinical and biological outcomes in school age children. Computational methods are being used to analyze, characterize, and quantify combined risk factors for asthma. Adolescent children have reduced defenses to oxidative stress. Controlled human exposures studies are comparing respiratory responses in older (<45 yrs) vs. young adults.

### Impact and Outcomes

Results used by California to support legislation limiting siting of new schools in near proximity to major roadways.

Results used by New York City to rule that bus fleet must convert their fuel sources to clean diesel.

Results used to support decision to install permanent EPA air monitors in Harlem.

Information used for criteria documents for ozone and particulate matter, the health assessment for diesel emissions, and the basis for the national ambient air quality standards for ozone.

Results will be used for hazard identification of components of diesel exhaust responsible for in utero alterations of immune function

Information and results used to develop protocols for the National Children's Study.

### Future Directions

•Determining the effect of exposure during gestation and during the first year of life to environmental factors such as allergens and air pollutants on the development of asthma.

•Determining the critical gestational age in which exposure alters asthma risk

•Identifying biomarkers in early life for evaluating interventions to reduce asthma

•Determining whether there are specific environmental factors that increase the risk of developing new asthma in older adults.

•Determining whether there are environmental risk factors specific to different subtypes of childhood asthma.

•Understanding how responses to microbes that may offer protection from asthma in early life may be modified by pollutants.

•Understanding epigenetic changes induced by pollutants that may result in long-term and trans-generational increased risk for asthma.

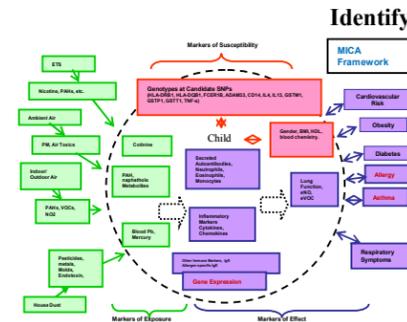
### Researchers Involved

Robert Devlin, Martha Sue Carraway, Ian Gilmour, Jane Gallagher, James Samet, Ann Williams (NHEERL) Rachel Miller, Frederica Perrera (Columbia University) Rob McConnell, (University of Southern California), (Patrick Breyse (Johns Hopkins University), Nina Holland, Brenda Eskenazi (University of California, Berkeley)

### Methods/Approach

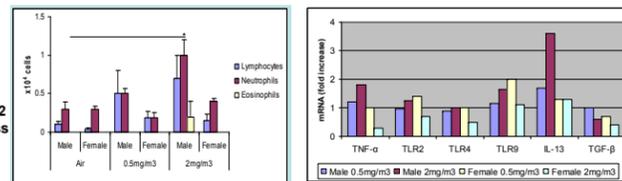
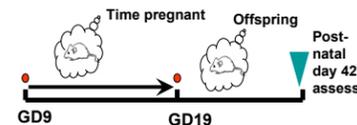
Life Stage	Age Group	Characteristics Relevant to Out and In-utero Exposure	Characteristics Relevant to In-utero Exposure	Anatomy and Physiology Characteristics	Life Stage	Age Group	Characteristics Relevant to Out and In-utero Exposure	Characteristics Relevant to In-utero Exposure	Anatomy and Physiology Characteristics
Prenatal	Maternal	• Prenatal smoking • Prenatal diet • Prenatal stress	• Fetal growth and weight gain • Increased proportion of body fat • Increased respiratory activity • Deficiencies in lung angiogenesis • Deficiencies in lung angiogenesis • Deficiencies in lung angiogenesis	• Fetal growth and weight gain • Increased proportion of body fat • Increased respiratory activity • Deficiencies in lung angiogenesis • Deficiencies in lung angiogenesis • Deficiencies in lung angiogenesis	12 to <24 months	Infant/Child	• Prenatal smoking • Prenatal diet • Prenatal stress	• Fetal growth and weight gain • Increased proportion of body fat • Increased respiratory activity • Deficiencies in lung angiogenesis • Deficiencies in lung angiogenesis • Deficiencies in lung angiogenesis	• Fetal growth and weight gain • Increased proportion of body fat • Increased respiratory activity • Deficiencies in lung angiogenesis • Deficiencies in lung angiogenesis • Deficiencies in lung angiogenesis
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Adolescent	Adolescent	• Prenatal smoking • Prenatal diet • Prenatal stress	• Fetal growth and weight gain • Increased proportion of body fat • Increased respiratory activity • Deficiencies in lung angiogenesis • Deficiencies in lung angiogenesis • Deficiencies in lung angiogenesis	• Fetal growth and weight gain • Increased proportion of body fat • Increased respiratory activity • Deficiencies in lung angiogenesis • Deficiencies in lung angiogenesis • Deficiencies in lung angiogenesis	6 to <11 years	Adult	• Prenatal smoking • Prenatal diet • Prenatal stress	• Fetal growth and weight gain • Increased proportion of body fat • Increased respiratory activity • Deficiencies in lung angiogenesis • Deficiencies in lung angiogenesis • Deficiencies in lung angiogenesis	• Fetal growth and weight gain • Increased proportion of body fat • Increased respiratory activity • Deficiencies in lung angiogenesis • Deficiencies in lung angiogenesis • Deficiencies in lung angiogenesis
	Adult	• Prenatal smoking • Prenatal diet • Prenatal stress	• Fetal growth and weight gain • Increased proportion of body fat • Increased respiratory activity • Deficiencies in lung angiogenesis • Deficiencies in lung angiogenesis • Deficiencies in lung angiogenesis	• Fetal growth and weight gain • Increased proportion of body fat • Increased respiratory activity • Deficiencies in lung angiogenesis • Deficiencies in lung angiogenesis • Deficiencies in lung angiogenesis	12 to <24 months	Adult	• Prenatal smoking • Prenatal diet • Prenatal stress	• Fetal growth and weight gain • Increased proportion of body fat • Increased respiratory activity • Deficiencies in lung angiogenesis • Deficiencies in lung angiogenesis • Deficiencies in lung angiogenesis	• Fetal growth and weight gain • Increased proportion of body fat • Increased respiratory activity • Deficiencies in lung angiogenesis • Deficiencies in lung angiogenesis • Deficiencies in lung angiogenesis

Life stages for ORD research is based on the categorization by the EPA Risk Assessment Forum and the Children's Environmental Health Research highlight document with the addition of two groups: adolescents and older adults



Exposure	Controls		Any asthma ORF (95% CI)	
	No.	No.	No.	ORF (95% CI)
Herbicide exposure	Never	387	257	1.0
	Ever	25	22	1.20 (0.58-2.47)
	In 1st year and later	5	11	4.58 (1.36-15.43)
Pesticide exposure	Never	367	239	1.0
	Ever	45	40	1.61 (0.93-2.79)
	In 1st year and later	23	23	2.39 (1.17-4.89)
Herbicide and/or pesticide exposure	Never	360	232	1.0
	Ever	52	47	1.53 (0.91-2.57)
	In 1st year and later	22	25	2.53 (1.25-5.09)
Not in 1st year	Never	20	11	0.58 (0.24-1.39)
	Ever	22	17	1.00 (0.46-2.19)

### Identifying trans-generational asthma effects of in utero exposure to air pollutants



The effect of diesel exposure during gestation on subsequent immune status of newborn were assessed in a murine model. Animals were exposed to either 0.5mg/m<sup>3</sup> and 2 mg/m<sup>3</sup> or air for 4 h/day over 10 days. Neutrophil and lymphocyte cell populations were increased in the lungs of male offspring in both diesel concentration groups. Allergic and inflammatory cytokines (IL-13, TNFα) increased in male offspring from mothers exposed to diesel.

#### Epidemiology Studies

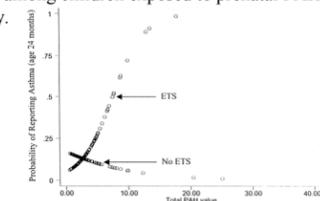
Table 4—Multivariable Analysis of the Joint Associations of Maternal and Child's In Utero Exposure to Maternal Smoking With Child's Asthma Risk, OR, and 95% CI\*

In Utero Exposure to Maternal Smoking		No.†	OR	95% CI
Mother	Child			
Unexposed	Unexposed	118/151	1.0	
	Exposed	27/58	1.3	0.5-2.1
Exposed	Unexposed	165/34	1.5	1.0-3.3
	Exposed	102/36	2.6	1.6-4.5

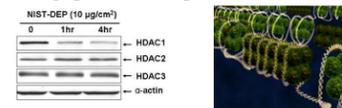
\*Models are adjusted for race/ethnicity, gestational age, and SHS exposure.  
†Number of counter-matched control subjects/case patients.

The S. California Children's Health Study studied the effect of maternal smoking on increased asthma risk in children and grandchildren.

In New York, 303 pregnant women, believed to be at high risk for exposure to both PAH and ETS were recruited. 48-h personal PAH exposure measurements were collected and their children monitored prospectively. By 24 months, difficulty breathing and probable asthma were reported more frequently among children exposed to prenatal PAH and ETS postnatally.



#### Epigenetic changes



In vivo allergen and diesel exposure are associated with hypomethylation of IL-4 and hypermethylation of IFN-γ promoters. In vitro expression of a pro-inflammatory cytokine (COX-2) induced by DEP exposure involves chromatin modification and acetylation in bronchial epithelial cells.

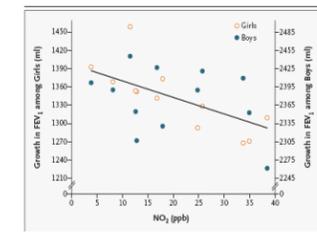
## Susceptible Populations

The Detroit Children's Health Study (see poster 3-11) has been used to recruit 205 non-asthmatic and asthmatic children aged 9-13 years into the Mechanistic Indicators of Childhood Asthma (MICA) study. By collecting clinical, genetic and biological samples we can identify and classify novel subtypes of childhood asthma. Parents of 92 children have also completed a participant-based collection of indoor and outdoor air samples for the children's homes (MICA-Air) that focuses on passively measured NO<sub>2</sub> and volatile organic compounds.

Characteristic	Th1	Th2
Health outcomes (at 2 years of age)		
Doctor-diagnosed asthma		
Yes	3.0 (2.6-3.4)	1.0 (0.7-1.2)*
No	2.9 (2.3-3.7)	0.7 (0.6-0.7)
Mother's work status		
Did agricultural fieldwork	3.4 (2.7-4.1)	0.9 (0.7-1.0)**
Did other agricultural work	3.1 (2.2-4.2)	0.7 (0.4-1.0)
Did nonagricultural work/did not work	2.7 (2.4-3.2)	0.6 (0.6-0.7)

The CHAMACOS study in Monterey County, CA looked at the relationships between several environmental exposures during the first 12 months of life and levels of Th1 and Th2 cytokines in 239 24-month-old children living in an agricultural community.

Nasal cells from adolescents (11-14yrs) respond to diesel particles by making an increased inflammatory but decreased antioxidant response



The S. California Children's health study (see poster 3-11) has studied lung function growth in a prospective study of children and seen deficits in growth of FEV-1 in communities with high NO<sub>2</sub> and associated pollutants. A nested case-control study using a counter-matched sampling design to select subjects has been used to identify early-life environmental factors for asthma.

