Chemical & Psychological Stressors and Health

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Chronic Disease Challenge

50 yr old man, 40 pack year smoking history.

Diagnosis?

Prevention vs. Management
Lifecourse Framework: Importance of Early Life Events

Rapid Growth and Development During Early Childhood

20 fold increase in $\text{FEV}_{0.5}$ from birth to 9 years
Infant Wheezing Phenotypes

- Transient wheeze
- Non-atopic (viral induced) wheeze
- Atopic wheeze

- Stein RT et al Thorax 1997;52:946-52
Evolution of lung function in Infant Wheezing Phenotypes
Further evolution of Lung Function
Central Determinants in Development of the Respiratory System

Aberrant or excessive pro-inflammatory immune responses, both locally and systemically

Regulatory pathways involving collaboration of innate and acquired immune responses important

Factors outside immune system – neurohormonal phenotypes – may also influence underlying processes
Is toxic stress taking our breath away?
How does toxic stress get ‘into the body’ to impact respiratory health?
Stress Physiology is Organized Around Two Systems:
- Sympathetic-Adrenomedullary (SAM) System
- Hypothalamic-Pituitary-Adrenocortical (HPA) System

These systems are regulated in the brain Interaction with immune system functioning.
The stress reaction is neither good nor bad in itself.

- Depends on circumstances

- Stress is useful when it protects us in times of danger or helps us to adapt in times of change.

Optimal balance = health
Overview Model

External event/Stressor

Appraisal of demands and coping capabilities

Benign appraisal

Perceived stress

Physical toxins
- Tobacco smoke
- Ambient AP
- Allergens

Negative emotional responses

Atopic Disease
Airway responses
Lung growth

Wright et al, Thorax 1998
Wright et al, Cur Opin in All Clin Immunol 2005
Wright RJ, Biol Psychol 2010
Social & Physical Toxins
Impact Fetal Programming -
Similar Magnitude of Effect

Materno-fetal interaction in pregnancy

Mother
- Other endogenous factors
  - Stress/HPA activation
- Maternal environment
  - Medications
    - Antacids
    - Paracetamol
    - Antibiotics
  - Dietary factors
    - Folate
    - LC-PUFA
    - Antioxidants
    - Vitamin D

Fetus
- Fetal genotype
- Predisposing polymorphisms
- Gender
- Delivery method (cesarean)
- Perinatal antibiotics
- Other perinatal events
- Colonisation
- Breastfeeding
- Infant diet (immunomodulatory nutrients/allergens)
- Smoking and other pollutants
- Disease predisposition

In utero effects
- Maternal allergic phenotype
  - Direct non-genomic effects
  - Antibodies
  - Cellular transfer
  - Cytokine milieu

Perinatal effects

Postnatal effects

Pregnancy cohort studies
Asthma Coalition on Community, Environment & Social Stress (ACCESS)

- Stress
- Allergens
- Air Pollution
- Tobacco Smoke
- Diet

Childhood Asthma Risk
Lung Function Development

NIEHS, NHLBI, NIMH, NIMHD, Leaves of Grass Foundation
955 pregnant women recruited Aug 2002 – Sept 2009

Enrolled through prenatal clinics at BWH & BMC and affiliated CHCs & WIC centers

50% Hispanic, 35% AA, 15% Caucasian

Primarily lower-SES
Motivation for ACCESS Cohort Design

Gottlieb et al., 1995


ACCESS Participants
Central Theories

- **Co-occur**
  
  Exposure 1 present usually Exposure 2 present

- **Proxies**
  
  Exposure 1 & 2 co-vary → effect of Exposure 2

- **Interactions**
  
  - Additive
    
    Exposure 1 + Exposure 2 = effect Exposure 1+2
  
  - Synergistic
    
    Exposure 1 + Exposure 2= effect > Exposure 1+2
Independent impact of psychological stressors?
Cumulative Stress Domains

- Financial strain
- Racism/discrimination
- Relationships
- Community/interpersonal violence
- Other negative life events (housing, landlords, fear of eviction, etc.)
Pre- and Postnatal Maternal Stress and Child Repeated Wheeze: Adjusted GAMs

Prenatal-Postnatal Stress and Asthma by age 6 years

OR of Asthma

Prenatal-Postnatal Stress

Low-Low  High-Low  Low-High  High-High
Pre/Postnatal Stress and Lung Function

**Prenatal-Postnatal PM2.5 and FEV1**

- Difference in FEV1 (L)
  - Low-Low
  - High-Low
  - Low-High
  - High-High

**Prenatal-Postnatal PM2.5 and FVC**

- Difference in FVC (L)
  - Low-Low
  - High-Low
  - Low-High
  - High-High
Stress-elicited Imbalance in Prenatal Key Regulatory Systems
Maternal prenatal cortisol trajectory associated with early asthma risk in children

Higher prenatal maternal stress alters child’s immune response at birth

Wright RJ et al., AJRCCM 2010; 182:25-33.
Important

Nature of Stressor?  Timing?
Maternal interpersonal trauma and cord blood IgE levels in an inner-city cohort: A life-course perspective

Michelle Judith Sternthal, PhD, Michelle Bosquet Enlow, PhD, Sheldon Cohen, PhD, Marina Jacobson Canner, MA, John Staudenmayer, PhD, Kathy Tsang, MHA, and Rosalind J. Wright, MD, MPH

Note: All probabilities are based on adjusted, log transformed cord blood IgE scores. Trend significant at p<.01. High IgE= .77 IU/mL & above.

Sternthal et al., JACI 2009; 124:954-60
Lifecourse Framework: Importance of Early Life Events
# Air Pollution, Community Violence, and Wheeze

*Chiu Y-HM et al., JACI 2013*

## Table: Prenatal maternal exposure to air pollution and community violence in relation to repeated wheeze in children: Logistic Regression Models

<table>
<thead>
<tr>
<th>Variables</th>
<th>Unadjusted Model</th>
<th>Multivariable-adjusted Model</th>
<th>Model 1</th>
<th>Model 2</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95%CI</td>
<td>OR</td>
<td>95%CI</td>
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<tr>
<td><strong>BC &amp; ECV Model</strong></td>
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<tr>
<td>Prenatal BC exposure</td>
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<td>Low (≤median, 0.38 μg/m³)</td>
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<td>High (&gt;median)</td>
<td>1.61</td>
<td>0.98</td>
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<tr>
<td>Prenatal community violence</td>
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<tr>
<td>Low</td>
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<tr>
<td>Medium</td>
<td>1.44</td>
<td>0.79</td>
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<tr>
<td>High</td>
<td>2.08</td>
<td>1.25</td>
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<td>1.95</td>
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<td><strong>PM2.5 &amp; ECV Model</strong></td>
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<td>Prenatal PM2.5 exposure</td>
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<td>Low (≤median, 11.2 μg/m³)</td>
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<td>Prenatal community violence</td>
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<td>Low</td>
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<td></td>
<td>2.02</td>
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<td></td>
<td>1.41</td>
<td>0.75</td>
<td>2.68</td>
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<td>2.15</td>
<td>1.24</td>
<td>3.71</td>
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</tbody>
</table>

*Model 1 included air pollution and community violence. Model 2 additionally adjusted for child’s gender, season of birth, maternal race, education level, atopy, and prenatal cockroach allergen exposure.*
Interactions?

Psychological stressors enhance effects of chemical/physical toxins
Overview Model

External event/Stressor

Benign appraisal

Perceived stress

Negative emotional responses

Physical toxins
- Tobacco smoke
- Ambient AP
- Allergens

Autonomic Functioning
- Increased
- Decreased

HPA Axis Functioning

Immune Function

Oxidant-Antioxidant Balance

Atopic Disease
Airway responses
Lung growth

Wright et al, Thorax 1998
Wright et al, Cur Opin in All Clin Immunol 2005
Wright RJ, Biol Psychol 2010 [Epub ahead of print]
Prenatal stress and dust mite predicts cord blood IgE

Results for Multiplicative Interaction

Chiu Y-HM et al., JACI 2013

**Prenatal ETV and Repeated Wheeze, stratified by BC level**

- Medium ETV vs. Low ETV
- High ETV vs. Low ETV

**Prenatal ETV and Repeated Wheeze, stratified by PM$_{2.5}$ level**

- Medium ETV vs. Low ETV
- High ETV vs. Low ETV
How mother’s prenatal psychological stress impacts fetal brain development?

Psychological Stress → Systemic Inflammation

→ Oxidative Stress
→ Proinflammatory Cytokines
→ Antiinflammatory Cytokines

mother → placenta → fetus

microglia

↑ Oxidative Stress
↑ Proinflammatory Cytokines
↓ Antiinflammatory Cytokines

Disrupted Neurodevelopment

Altered Neuroprogression
Prenatal Stress (NLEs) and Early Temperament: African American Mother-Child Pairs

![Graph showing the relationship between maternal NLEs and child temperament]

- **Orienting/Regulation**
  - Lower (-1 SD)
  - Higher (+1 SD)

- **Extraversion**
  - Lower (-1 SD)
  - Higher (+1 SD)

- High n3:n6 ratio vs. Low n3:n6 ratio
  - **p_int = 0.002**

- High Vitamin E vs. Low Vitamin E
  - **p_ext = 0.008**
Summary

- Socially toxic environments are **NOT** simply a marker of a more toxic physical environment
- Social contexts and consequent stress may be as detrimental to children’s health as chemical toxins
  - Social pollutants/toxins
- Psychological stress disrupts biological systems overlapping with those altered by physical pollutants/toxins
- Psychosocial stress may impact host resistance such that physical toxins (e.g., indoor allergens, traffic-related air pollution) may have adverse effects, even at relatively lower doses
- Interventions to reduce stress and/or stress effects (e.g., antioxidant intake) may also reduce toxicity of chemical/physical toxins
“It is easier to build strong children than to repair broken men.”

Frederick Douglas
Co-investigators
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Brent Coull (HSPH)
Diane Gold (HSPH)
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Robert Wright (MSSM)
Michelle Bosquet-Enlow (HMS)
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Michelle Sternthal
Kelly Brunst
Hannah Schreier

Funding
NIEHS
NHLBI
NIMHD
NIMH
Leaves of Grass Foundation
Linking experiences of discrimination, ethnic identity and prenatal smoking in minority women

Stress may increase exposure to tobacco smoke in pregnancy

<table>
<thead>
<tr>
<th>Experiences of Discrimination *</th>
<th>Hispanic (n=412)</th>
<th>Black (n=265)</th>
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<tr>
<td>1 or 2 situations</td>
<td>1.00</td>
<td>1.00</td>
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<tr>
<td>None</td>
<td>2.45 (0.90, 6.70)</td>
<td>1.05 (0.42, 2.62)</td>
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<tr>
<td>3 +</td>
<td>2.08 (0.60, 7.14)</td>
<td><strong>3.36 (1.23, 9.19)</strong></td>
</tr>
</tbody>
</table>

During early childhood the human stress system is under strong social regulation.

Sensitive, responsive, supportive care “buffers” or protects young children from experiencing elevated stress hormone levels.

As quality of care decreases, young children become highly stress vulnerable.
Stress may increase risk for maternal depression

<table>
<thead>
<tr>
<th>ABUSE EXPERIENCE</th>
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<tr>
<td>Never (referent group)</td>
<td>1.27</td>
<td>(0.94, 1.73)</td>
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<td>Child/Teem</td>
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<td>(1.35, 2.64)</td>
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<td>Adult Pre-pregnancy</td>
<td>1.73</td>
<td>(1.00, 3.02)</td>
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<td>Pregnancy</td>
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## Stress x Environment Interactions

<table>
<thead>
<tr>
<th>LITERATURE</th>
<th>STUDY TYPE (N)</th>
<th>SUBJECTS</th>
<th>EXPOSURE/OUTCOME</th>
<th>RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shankardass K et al., PNAS 2009</td>
<td>Children’s Health Study Prospective school-aged cohort N=2,497</td>
<td>Child (5-9 yrs followed for 3 years)</td>
<td>Prenatal maternal NLEs Dust mite mother’s bedroom Maternal Atopy Cord Blood Total IgE</td>
<td>See figure</td>
</tr>
</tbody>
</table>

### Effect of TRAP on incident asthma across parental stress quartiles

![Graph showing the effect of TRAP on incident asthma across parental stress quartiles](image)

Adjusted for child age, gender, race/ethnicity and community random effects