Maternal Stress & Childhood Asthma: Risk & Resilience

Rosalind J. Wright, MD, MPH
Horace W. Goldsmith Professor
Dean for Translational Biomedical Sciences
Department of Pediatrics &
Environmental Medicine & Public Health
Icahn School of Medicine at Mount Sinai
Disparities


Source: Gottlieb et al., 1995
The Wealthier are Healthier
Early life experiences can influence later-life health & disease –

**Lifecourse Framework**

Toxic exposures

Low birth weight

Obesity, hypertension, CNS, cardiovascular/pulmonary disease, diabetes

How environmental exposures in early life influence health and development in childhood and across the human life span.
Early life experiences can influence later-life health & disease – 
Lifecourse Framework

Toxic exposures
Low birth weight

Obesity, hypertension, CNS, cardiovascular/pulmonary disease, diabetes

How environmental exposures in early life influence health and development in childhood and across the human life span.
Multiple Factors Interact to Influence Health & Disease

Contributors/Opportunities
- Nutrients
- Chemicals
- Pollutants
- Smoking

Pathways
- Healthy Aging
- Resilience
- Growth and Development

Outcomes
- Vulnerability
- Disease
- Dementia

Built Environment
- Society
- Individual/Family
- Community
Coined by James Garbarino (1970s)
- Violence (gangs, war)
- Poverty
- Economic hardships
- Racism/discrimination

Social toxins are as detrimental IF NOT MORE SO as chemical/physical toxins to children’s development

Chemical and non-chemical social stressors can have synergistic effects

Stress physiology organized around 2 key systems – SAM & HPA
Interact with immune function & oxidant balance
Microbes

Smoke

Air pollution

Autonomic Function

HPA Axis Function

Immune Function

Oxidant-Antioxidant Balance

Downregulation of TLRs

Inhibition of cytokine production

Circulation

TLRs

Increased TLR expression

Cytokines

Maternal bone marrow

‘Programmed’ DCs and monocytes

Fetus

Placenta

Lungs
Asthma Coalition on Community, Environment & Social Stress (ACCESS)

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

Childhood Asthma Risk
Lung Function Development
Neurodevelopment

NIEHS, NHLBI, NIMH, NIMHD, Leaves of Grass Foundation
Motivation

Asthma Hospitalizations by Zip Code
1994-1997

Gottlieb et al., 1995

ACCESS Participants

Asthma Patients & Town Boundaries
Important

Nature of Stressor?

Timing?

Sex/Gender?
Independent impact of psychological stressors?
When external challenges overwhelm one’s ability to cope there can be adverse emotional and physiological responses that then influence health.
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

Exposure-response relationship between pre- & postnatal NLEs and wheeze

Rosa MJ, et al., Annals of Allergy, Asthma & Immunology, 2016
Also see: Lee A, et al., J Allergy Clinical Immunology 2016
Cumulative Stress (NLEs) and Asthma Onset

* Adjusted for child’s gender, season of birth, maternal race, education level, atopy, prenatal BC and cockroach allergen.
Meta-analysis: prenatal maternal stress and respiratory morbidity in childhood

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Stress</th>
<th></th>
<th>No Stress</th>
<th></th>
<th>Weight %</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High quality#</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHIU [32]</td>
<td>49</td>
<td>275</td>
<td>31</td>
<td>378</td>
<td>7.5</td>
<td>2.43 [1.50–3.92]</td>
</tr>
<tr>
<td>COOKSON [33]</td>
<td>232</td>
<td>1546</td>
<td>503</td>
<td>4264</td>
<td>32.0</td>
<td>1.32 [1.12–1.56]</td>
</tr>
<tr>
<td>GUXENS [35]</td>
<td>23</td>
<td>212</td>
<td>178</td>
<td>3126</td>
<td>8.1</td>
<td>2.02 [1.27–3.19]</td>
</tr>
<tr>
<td>Subtotal</td>
<td></td>
<td>2033</td>
<td>7768</td>
<td></td>
<td>47.6</td>
<td>1.77 [1.18–2.67]</td>
</tr>
<tr>
<td>Total events</td>
<td>304</td>
<td>712</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate quality‖</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALTON [30]</td>
<td>5</td>
<td>33</td>
<td>56</td>
<td>758</td>
<td>1.9</td>
<td>2.24 [0.83–6.02]</td>
</tr>
<tr>
<td>BEIJERS [31]</td>
<td>31</td>
<td>116</td>
<td>10</td>
<td>51</td>
<td>2.9</td>
<td>1.50 [0.67–3.34]</td>
</tr>
<tr>
<td>DE MARCO [34]</td>
<td>30</td>
<td>330</td>
<td>196</td>
<td>3370</td>
<td>10.1</td>
<td>1.62 [1.08–2.42]</td>
</tr>
<tr>
<td>KHASHAN [27]</td>
<td>45</td>
<td>1467</td>
<td>67375</td>
<td>3191566</td>
<td>16.2</td>
<td>1.47 [1.09–1.97]</td>
</tr>
<tr>
<td>LEFEVRE [36]</td>
<td>24</td>
<td>34</td>
<td>114</td>
<td>213</td>
<td>3.0</td>
<td>2.08 [0.95–4.57]</td>
</tr>
<tr>
<td>REYES [37]</td>
<td>57</td>
<td>81</td>
<td>107</td>
<td>198</td>
<td>5.8</td>
<td>2.02 [1.16–3.51]</td>
</tr>
<tr>
<td>WOOD [38]</td>
<td>108</td>
<td>203</td>
<td>146</td>
<td>312</td>
<td>12.4</td>
<td>1.29 [0.91–1.84]</td>
</tr>
<tr>
<td>Subtotal</td>
<td></td>
<td>2264</td>
<td>3196468</td>
<td></td>
<td>52.4</td>
<td>1.54 [1.30–1.84]</td>
</tr>
<tr>
<td>Total events</td>
<td>300</td>
<td>68004</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>4297</td>
<td>3204236</td>
<td>100.0</td>
<td></td>
<td></td>
<td>1.56 [1.36–1.80]</td>
</tr>
<tr>
<td>Total events†</td>
<td>604</td>
<td>68716</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

©2016 by European Respiratory Society

Prenatal-Postnatal Stress and FEV1

Prenatal-Postnatal Stress and FVC

Lee A, et al., *Ann Allergy Asthma Immunol*, accepted
Early life toxic stress is **literally** taking our breath away?

**Lifelong consequences**
Life course vs. current
Cumulative lifetime trauma in mothers can be transmitted to their children.
War-related Trauma
Rasch scores on the logit scale for those reporting any war-related stressors

R J Wright et al. J Epidemiol Community Health 2010;64:630-635
# Participant Characteristics (N=3185)

<table>
<thead>
<tr>
<th>Variables</th>
<th>N</th>
<th>New Asthma [n (%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>3185</td>
<td>449 (14.1)</td>
</tr>
<tr>
<td><strong>WRSS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No reported stressors</td>
<td>1431</td>
<td>172 (12.0)</td>
</tr>
<tr>
<td>Low</td>
<td>876</td>
<td>122 (13.9)</td>
</tr>
<tr>
<td>High</td>
<td>878</td>
<td>155 (17.7)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1703</td>
<td>200 (11.7)</td>
</tr>
<tr>
<td>Male</td>
<td>1482</td>
<td>249 (16.8)</td>
</tr>
<tr>
<td><strong>Age at invasion</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-3</td>
<td>937</td>
<td>140 (14.9)</td>
</tr>
<tr>
<td>4-7</td>
<td>1134</td>
<td>147 (13.0)</td>
</tr>
<tr>
<td>8-11</td>
<td>1114</td>
<td>162 (14.5)</td>
</tr>
<tr>
<td><strong>Smoking status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoked</td>
<td>2427</td>
<td>323 (13.3)</td>
</tr>
<tr>
<td>Former smoker</td>
<td>117</td>
<td>20 (17.1)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>641</td>
<td>106 (16.5)</td>
</tr>
<tr>
<td><strong>Obesity (BMI≥30kg/m²)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>2593</td>
<td>325 (12.5)</td>
</tr>
<tr>
<td>Yes</td>
<td>592</td>
<td>124 (20.9)</td>
</tr>
<tr>
<td><strong>Paternal asthma</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>2442</td>
<td>298 (12.2)</td>
</tr>
<tr>
<td>Yes</td>
<td>743</td>
<td>151 (20.3)</td>
</tr>
<tr>
<td><strong>Fear for loss of life</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1984</td>
<td>264 (13.3)</td>
</tr>
<tr>
<td>Yes</td>
<td>1201</td>
<td>185 (15.4)</td>
</tr>
</tbody>
</table>
Distribution of war-related stressor score (WRSS) in n=1657 who reported any stressors

- Modified multi-item Harvard Trauma Questionnaire (Mollica R 1992)
- Events witnessed and experienced during the invasion/occupation based on parent-report and self-report
- WRSS, a latent variable, was created by Rasch modeling including both witnessed and direct victimization items.
- Categorized as no exposure, low and high exposures (based on median split).
### WRSS and incident asthma in N=3185 participants: multivariable-adjusted logistic regression

<table>
<thead>
<tr>
<th>Variables</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WRSS</strong></td>
<td></td>
</tr>
<tr>
<td>No reported stressors</td>
<td>Ref, --</td>
</tr>
<tr>
<td>Low</td>
<td>1.22 (0.94-1.59)</td>
</tr>
<tr>
<td>High</td>
<td>1.68 (1.29-2.18)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>Ref, --</td>
</tr>
<tr>
<td>Male</td>
<td>1.52 (1.19-1.94)</td>
</tr>
<tr>
<td><strong>Age at invasion (yrs)</strong></td>
<td></td>
</tr>
<tr>
<td>8-11</td>
<td>Ref, --</td>
</tr>
<tr>
<td>4-7</td>
<td>0.96 (0.75-1.23)</td>
</tr>
<tr>
<td>0-3</td>
<td>1.27 (0.96-1.68)</td>
</tr>
<tr>
<td><strong>Smoking status</strong></td>
<td></td>
</tr>
<tr>
<td>Never smoked</td>
<td>Ref, --</td>
</tr>
<tr>
<td>Former smoker</td>
<td>1.03 (0.61-1.74)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>0.93 (0.70-1.25)</td>
</tr>
<tr>
<td><strong>Obesity (BMI≥30kg/m²)</strong></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>Ref, --</td>
</tr>
<tr>
<td>Yes</td>
<td>1.82 (1.44-2.30)</td>
</tr>
<tr>
<td><strong>Parental asthma</strong></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>Ref, --</td>
</tr>
<tr>
<td>Yes</td>
<td>2.08 (1.60-2.70)</td>
</tr>
</tbody>
</table>
Effect modification by fear for loss of life
Interactions?

Stress enhances effects of chemical/physical toxins
Methods: Modeling of daily PM$_{2.5}$

- Daily exposure to PM$_{2.5}$ estimated for each cohort participant during pregnancy (i.e., individual-level exposure estimates)

- Novel spatio-temporal model that incorporates Moderate Resolution Imaging Spectroradiometer (MODIS) satellite-derived Aerosol Optical Depth (AOD) measurements at a 1 × 1 km spatial resolution

Slide courtesy of: Allan Just and Itai Kloog
Identifying perinatal windows of vulnerability to PM2.5 in children’s asthma risk

Wilson A, et al., Biostatistics 2017 [Published online]

Also see: Hsu HH, et al Am J Respir Crit Care Med 2015
Gang-related Trauma
Community Violence
Caretaker Exposure to Violence

- Afraid Children May Be Hurt in Neighborhood: 38%
- Afraid to Let Child Play Outside: 34%
- Fight w/Weapon: 28%
- Violent Argument: 33%
- Gang Fight: 15%
- Sexual Assault/Rape: 9%
- Robbery/Mugging: 21%

Experienced in last six months:
Results for GAMs with penalized splines: Prenatal ECV and Prenatal PM$_{2.5}$

* Covariates included prenatal ECV, prenatal BC, child’s gender, season of birth, maternal race, education level, atopy, and prenatal cockroach allergen exposure.
Mechanisms
Cortisol in Health and Disease

Decreased

Increased
Microbes, Smoke, and Air pollution can lead to Autonomic Function and Immune Function disturbances. Oxidant–Antioxidant Balance is also affected. Stressors can trigger TLRs, leading to increased TLR expression and subsequent cytokine production. This can downregulate TLRs in the placenta, inhibit cytokine production, and affect the fetus and maternal bone marrow. Ultrasound images are used to monitor fetal development. HPA Axis Function, Immune Function, and Autonomic Function are interconnected, highlighting the complexity of these biological processes.
Maternal prenatal cortisol trajectory associated with early asthma risk in children

Immune Imbalance
Prenatal Maternal Stress and Cord Blood Innate and Adaptive Cytokine Responses in an Inner-City Cohort


Increasing stress → Increasing stress → Increasing stress

Wright RJ et al., AJRCCM 2010

Urban Environment and Childhood Asthma Study (URECA)—New York, Boston, Baltimore, and St. Louis
Building Resilience
During early childhood human stress response systems are under strong social regulation. Sensitive, responsive, supportive care “buffers” young children from disruption of these stress response systems. As quality of care decreases, young children become more stress vulnerable.
PRogramming of Intergenerational Stress Mechanisms (PRISM) Study

• Pregnancy cohort to study long term health consequences of stress starting in pregnancy and maternal caregiving on child development
• Dual site study – Boston & NY
• N ~ 800 to date
• NHLBI, NICHD, NIEHS, ECHO

“The same soul governs the two bodies and the desires and fears and sorrows are common....”

Leonardo da Vinci
Caregiving Sensitivity

Lab Stressor

- Negative Affect
  - Activity
- HPA Axis
- ANS
  - SNS
  - PNS
Reaction to Still-Face
6-Month Assessment

Still-Face Paradigm-Repeated

Still-Face 1
(Stressor)
≤ 2 min

Play
(Baseline)
2 min

Reunion 1
(Recovery)
2 min

Still-Face 2
(Stressor)
≤ 2 min

Reunion 2
(Recovery)
2 min
6-Month Assessment
Infant Stress Reactivity Parameters

- **Negative Affect**
  - Fussing
  - Crying
  - Hard Crying

- **BioRadio System**
  - Heart Rate (HR)
  - T-Wave Amplitude (TWA)
    - SNS
  - Respiratory Sinus Arrhythmia (RSA)
    - PNS

- **HPA Axis**
  - Cortisol (saliva via cotton rolls)
    - prior to SFP-R
    - immediately after SFP-R
    - every 20 minutes x 3
6-Month Assessment

Maternal Sensitivity

Video coding using a 9-point scale (Ainsworth, 1969)

Sensitive
- accurately reads infant’s cues
- responds promptly, appropriately
- facilitates smooth interactions

Insensitive
- inaccurately interprets infant’s cues
- delays or does not respond
- ends interactions abruptly while infant engaged
- intrusive, hostile, withdrawn
Maternal Sensitivity and Infant Autonomic Response

More distressed

Sensitive

Insenstive

Greater sympathetic (adrenalin) response

Maternal Sensitivity and Infant Neuroendocrine Response

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)**

• Concomitant psychosocial stress enhances effects of physical/chemical toxins such that they have adverse effects, even at lower doses

• Need intervention studies building resilience –
  – promoting positive maternal health preconception and prenatally
  – sensitive caregiving
  – dietary enhancements
Lifecourse strategy for lung development

Chronic ND risk

Mother & infant

Childhood

Adulthood

No intervention
Late intervention less impactful
Late intervention

Early intervention improves functional capacity & responses to new challenges

Early intervention
Most impactful

Life course

Fixed genetic contributions to risk is small

Plasticity

Inadequate response to new challenges

Hanson M, Godfrey K et al. Prog Biophys Molec Biol 2011; 106: 272-280
Looking ahead…..

“It is easier to build strong children than to repair broken men.”

Frederick Douglas
Co-investigators

Robert Wright (ISMMS)
Krisitn Bernard (SB)
Michelle Bosquet-Enlow (HMS)
Joel Schwartz (HSPH)
Brent Coull (HSPH)
John Staudenmayer (UMass)
Thomas Ritz (SMU)
Chris Gennings (ISMMS)
Srinathi Kannan (SIU)

Postdoctoral Students/Trainees

Yueh-Hsiu Mathilda Chiu
Michelle Sternthal
Kelly Brunst
Hannah Schreier
Shakira Franco Suglia
Junenette Peters
Alison Lee
Perry Sheffield
Lianna Lipton
Katrina Devick
Maria Rosa

Funding

NIEHS
NHLBI
NIMHD
NIMH
NICHD
Leaves of Grass Foundation
ECHO