Integrating social and physical determinants into children's environmental health research: challenges of transdisciplinary research

Rosalind J. Wright, M.D., M.P.H.

Associate Professor of Medicine

Harvard Medical School

Respiratory, Environmental & Genetic Epidemiology Department &

Associate Professor Environmental Health

Harvard School of Public Health

Boston, MA

BRIGHAM AND WOMEN'S HOSPITAL

HARVARD MEDICAL SCHOOL

Making Social Toxins Mainstream in Children's Environmental Health

Wright RJ Curr Opin Pediatr 2009; 21(2):222-9

- While traditional disciplinary research has focused separately on how social and physical environmental factors affect children's health, evolving research underscores important integrated effects

- Given covariance across exposures and evidence that social stress and other environmental toxins (e.g., pollutants, tobacco smoke, chemicals) may influence common physiological pathways (e.g., oxidative stress, pro-inflammatory immune function, autonomic disruption), understanding synergistic effects may better inform children's environmental health vulnerabilities

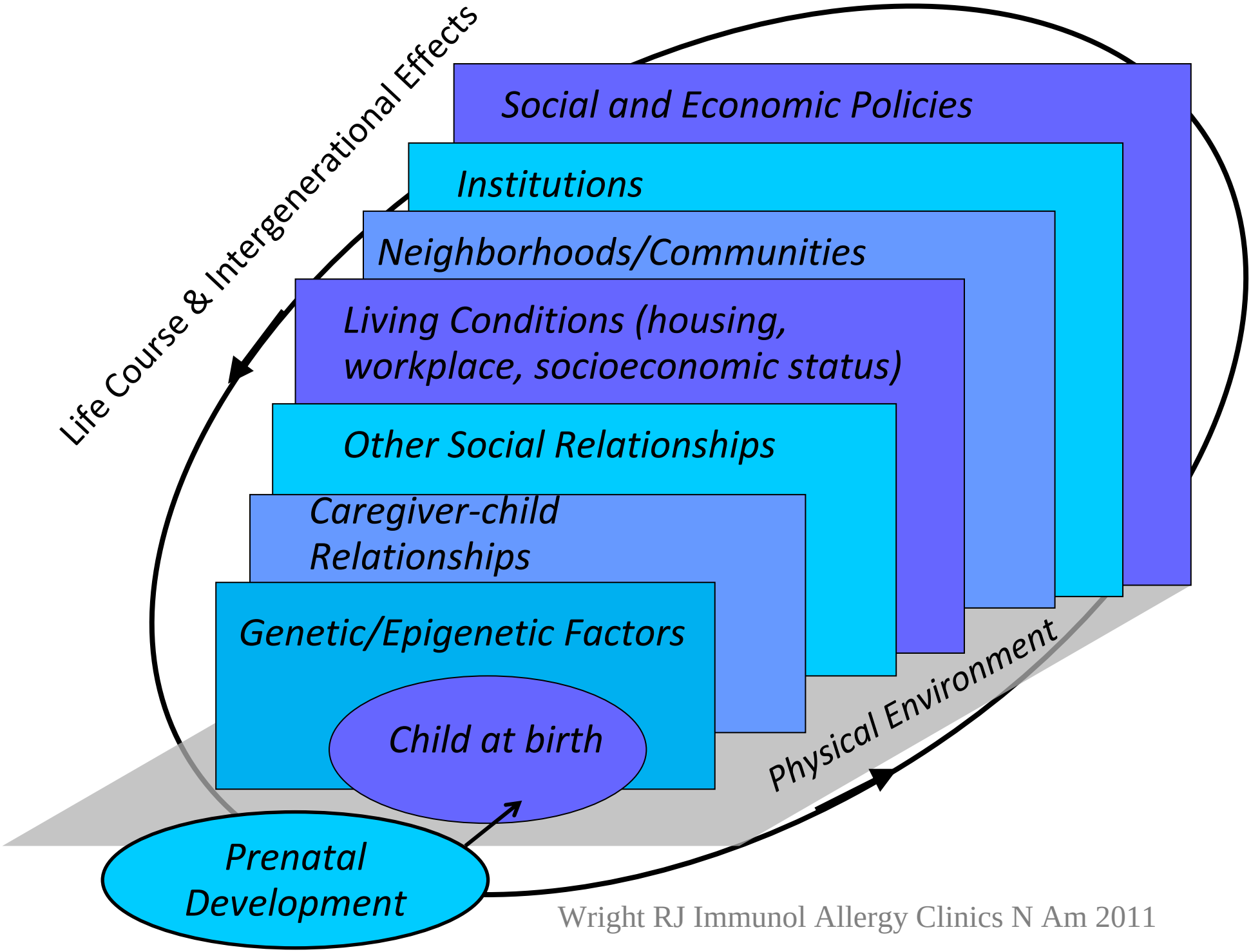
Life Course Approach

2006 Children's Framework

Temporal Stages of Life have distinct characteristics

- Anatomical
- Physiological
- Behavioral
- Functional

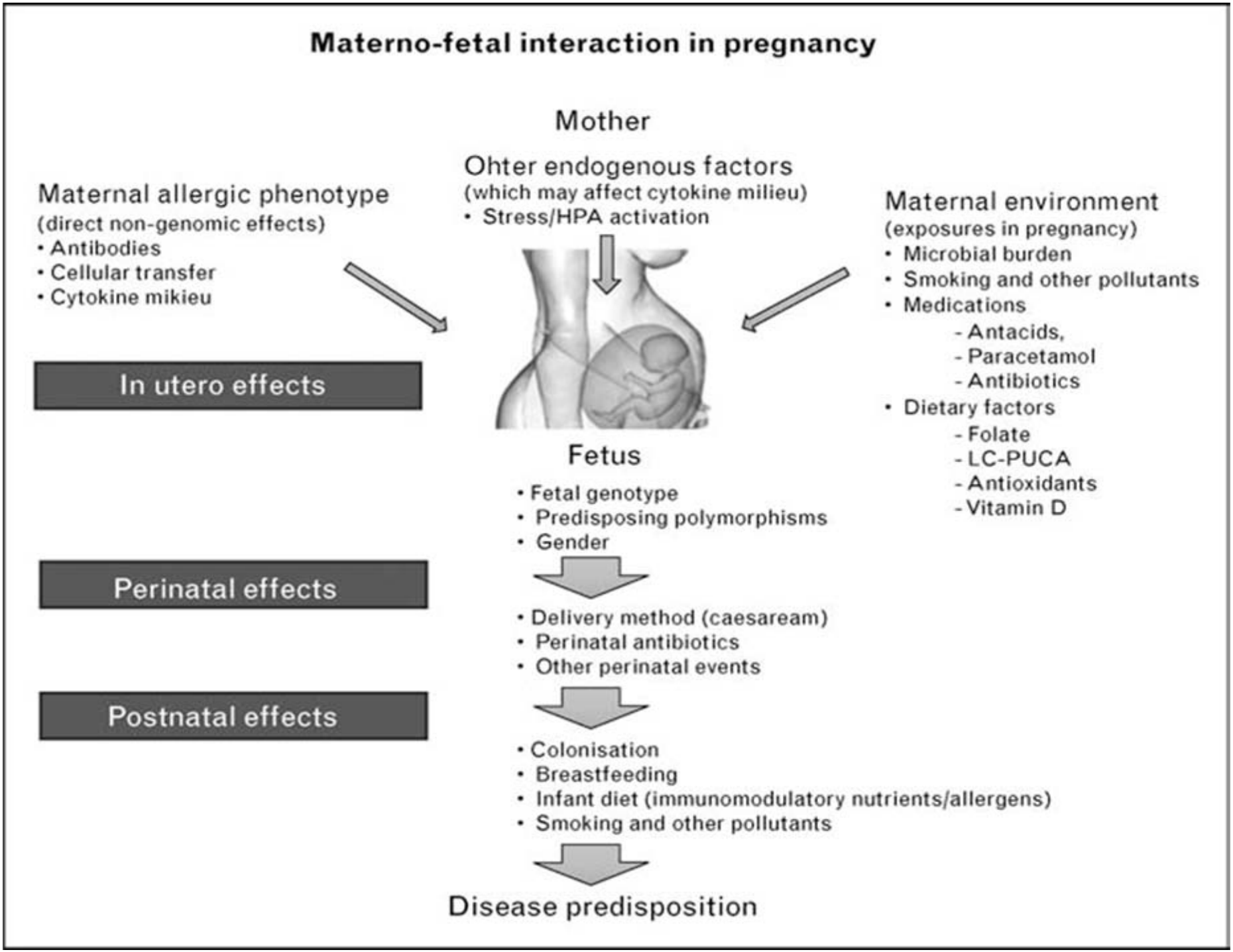
USEPA 2006 A Framework for Assessing Health Risks of Environmental Exposures to Children



Wright RJ Immunol Allergy Clinics N Am 2011

Background

- Stress is central to studying the health effects of social adversity *(Wright RJ, Prenatal maternal stress and early caregiving experiences: implications for childhood asthma risk. Pediatric Perinatal Epi 2007; 21:8-14)*
- Starting *in utero*, social environmental factors may permanently organize key physiological systems (HPA axis, ANS functioning, immune system) toward trajectories of enhanced disease risk *(Phillips DIW, Programming of the stress response: a fundamental mechanism underlying the long-term effects of the fetal environment. J Int Med 2007; 262:453-60)*
- HPA axis and autonomic functioning [sympathetic-adrenal-medullary (SAM) system] particularly susceptible to early-life programming due to stress and other environmental toxins
- Child may inherit a biological vulnerability to disrupted stress regulatory systems altering their reactivity to subsequent challenges
  - Psychosocial
  - Physical

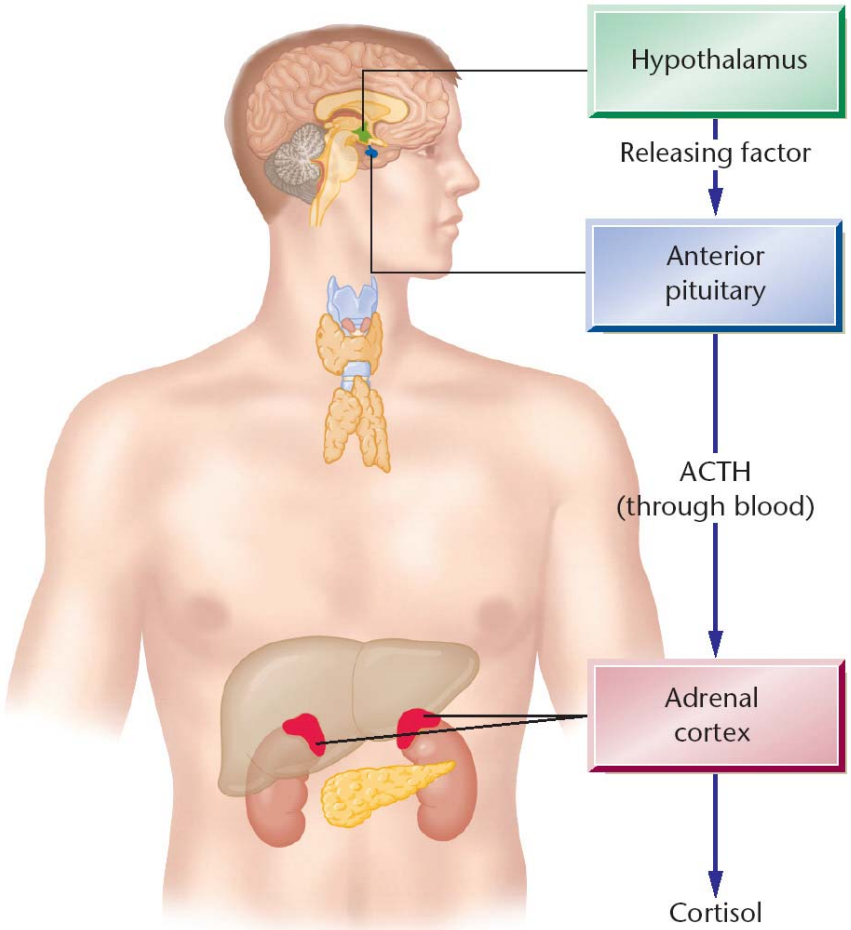


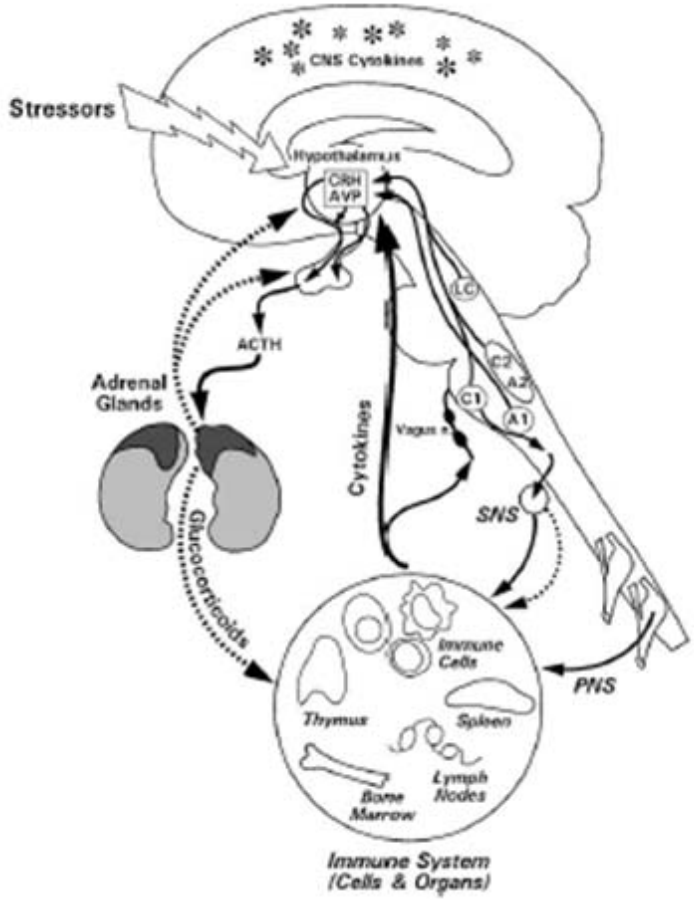
Prescott & Clifton, Cur Opin All Clin Immunol 2009; 9:417-26

Background

- Animal models as well as human studies link an adverse intrauterine environment and/or prenatal stress with disrupted HPA axis functioning (e.g., cortisol disruption) as well as alterations of ANS balance (e.g., sympathovagal balance) in offspring.
- In experimental rat models, prenatal stress is associated with exaggerated cardiovascular reactivity to restraint stress.
- In animals, stress effects can be mimicked by stimulating cortisol production in pregnancy.
- Animal and human studies link exposure of a pregnant female to repeated stress or to synthetic glucocorticoids (GCs), which cross the placenta, to reduced offspring BW and HTN, metabolic disturbances (e.g., hyperglycemia), and anxiety-related behaviors throughout life.
- In humans, the administration of synthetic GCs to women at high risk for preterm delivery affects infant neurodevelopment.
- Alteration or programming of the ANS may also be influenced by prenatal administration of exogenous steroids.
- In humans, lower birth weight and reduced gestational age, surrogates of adverse intrauterine conditions, have been associated with:
  - increased blood pressure reactivity in later life
  - enhanced autonomic and HPA responses to stress
  - In animals, stress effects can be mimicked by stimulating cortisol production in pregnancy

Neuroendocrine - Immune Interactions

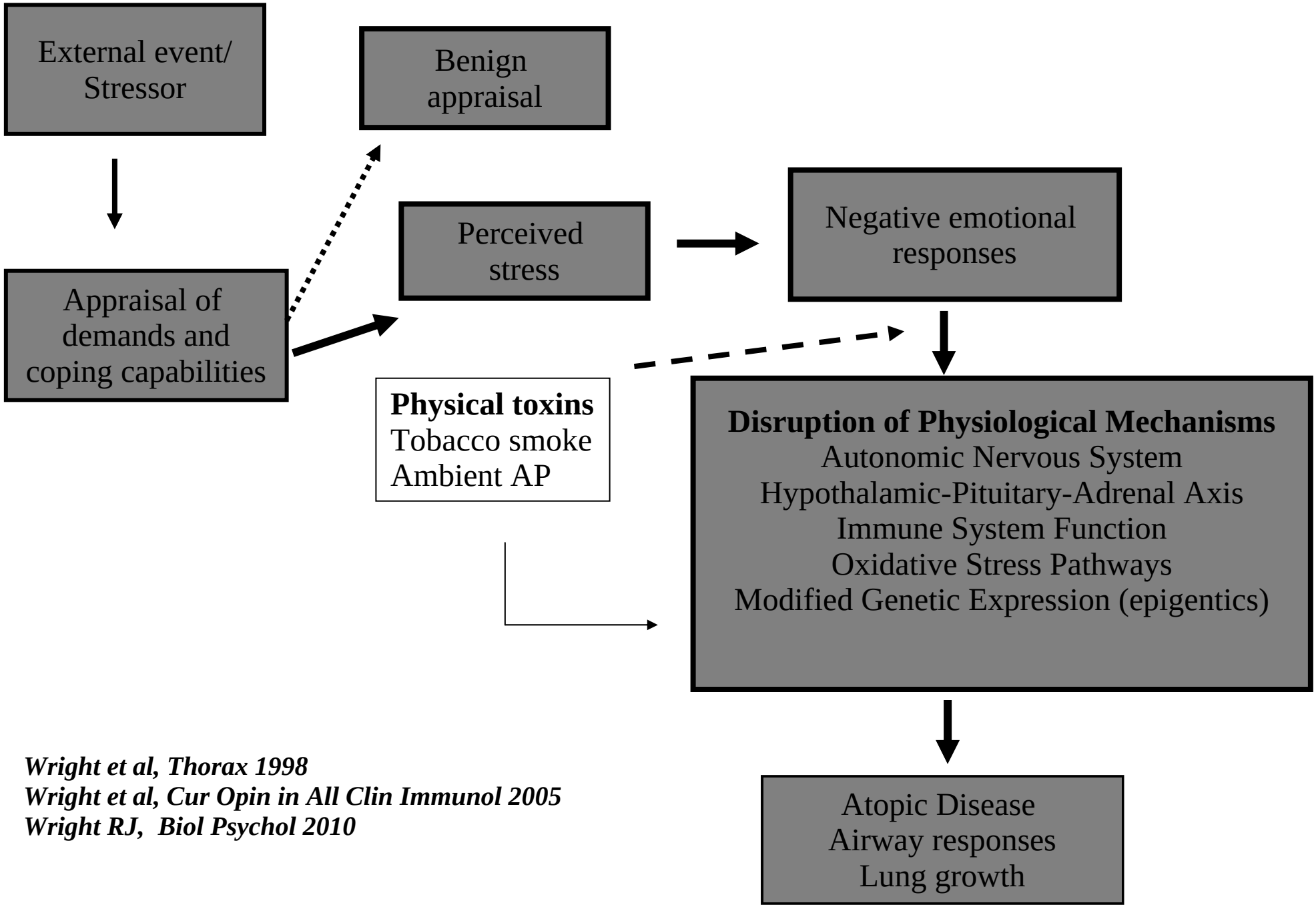




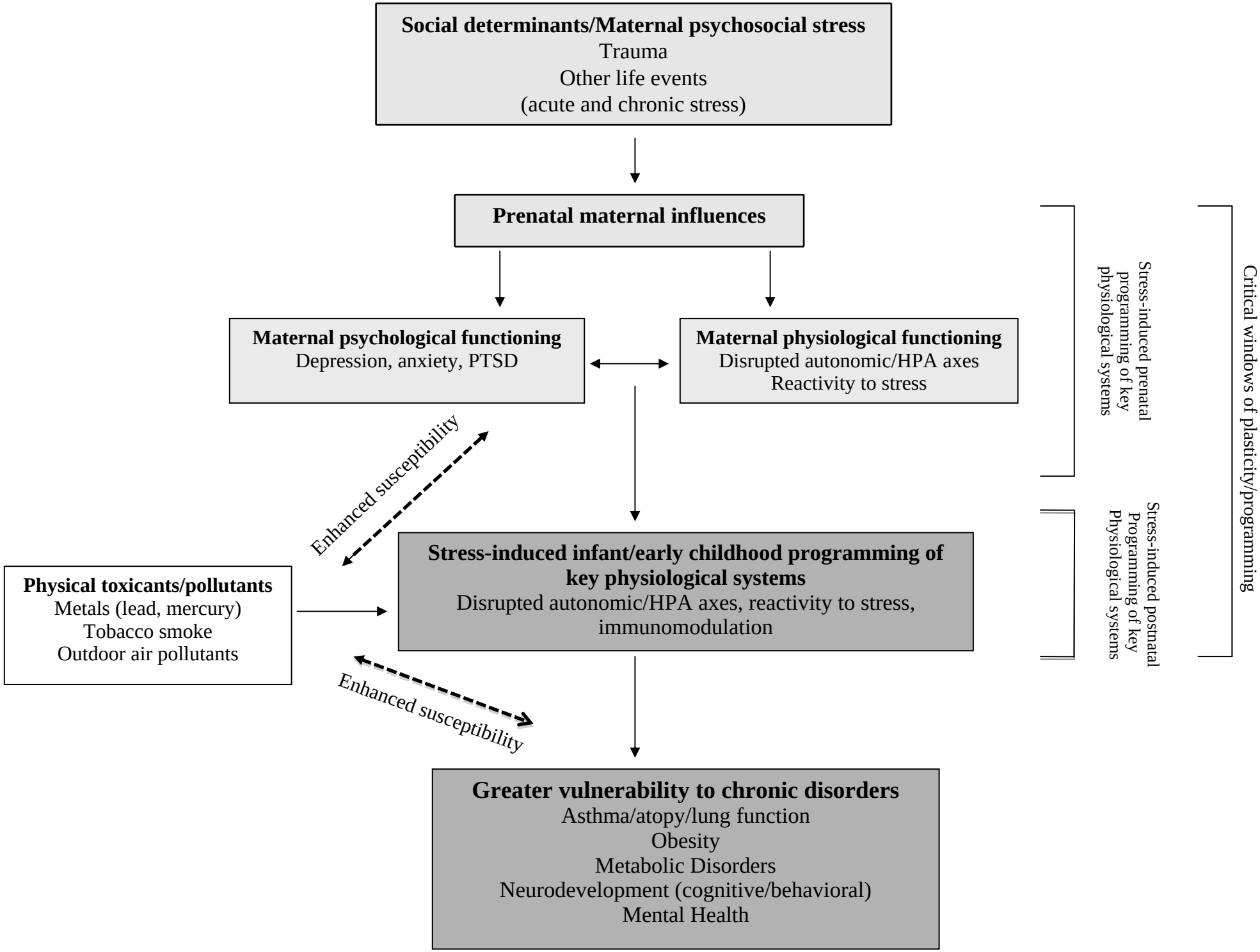
- Sympathetic-Adrenomedullary (SAM) System
- Hypothalamic-Pituitary-Adrenocortical (HPA) System

These systems are regulated in the brain

Overview Model

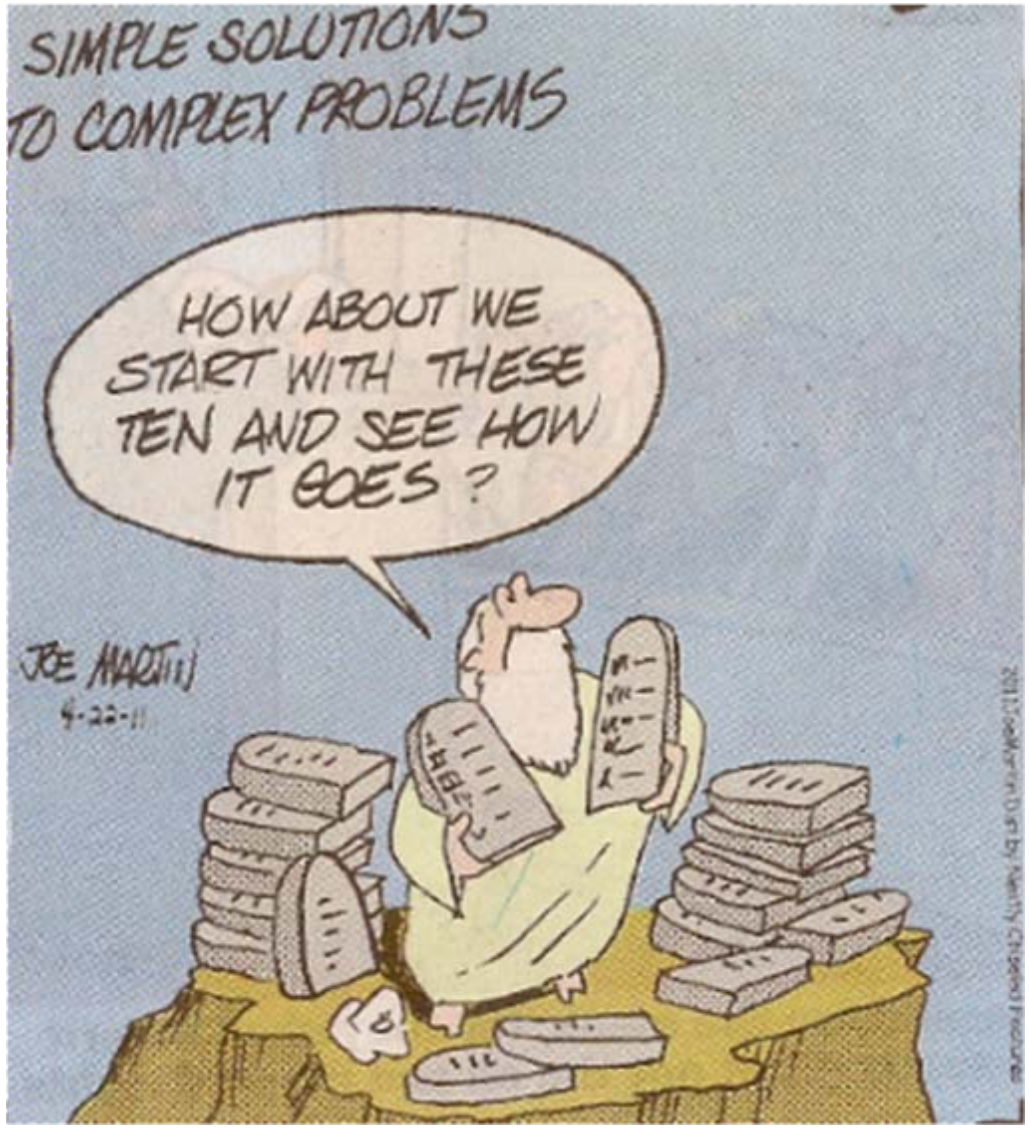


Wright et al, Thorax 1998
Wright et al, Cur Opin in All Clin Immunol 2005
Wright RJ, Biol Psychol 2010

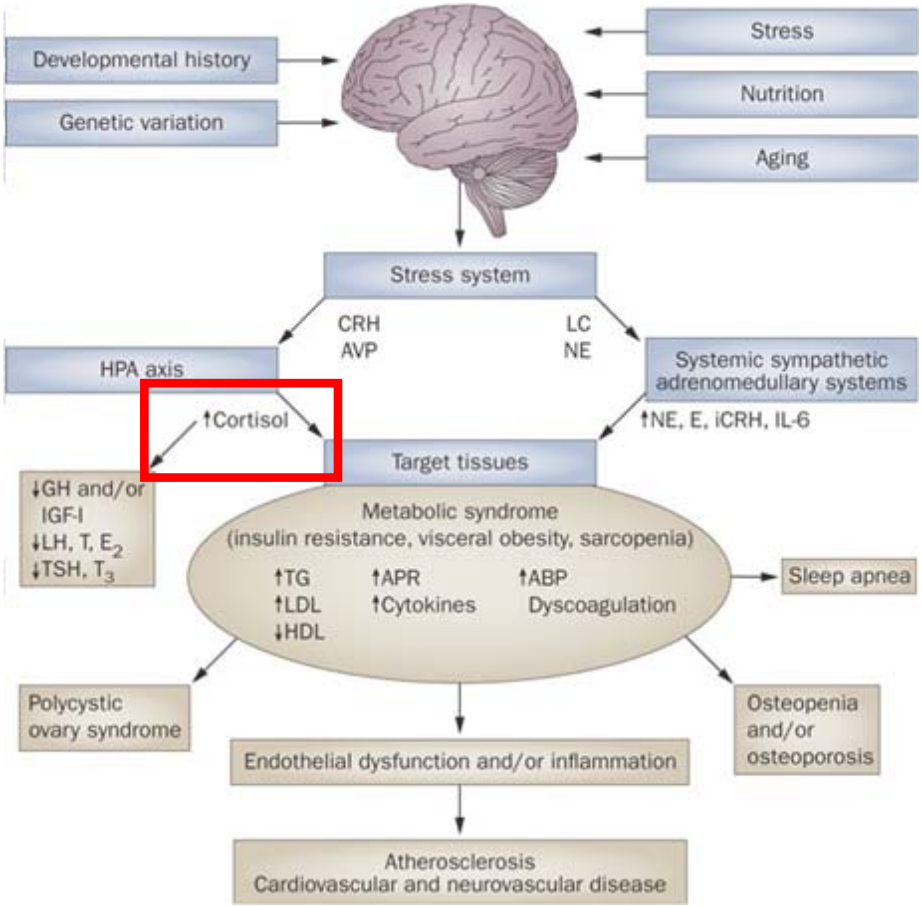


Wright RJ Curr Opin Pediatr 2009; 21(2):222-9

How to measure stress response in epidemiological research?



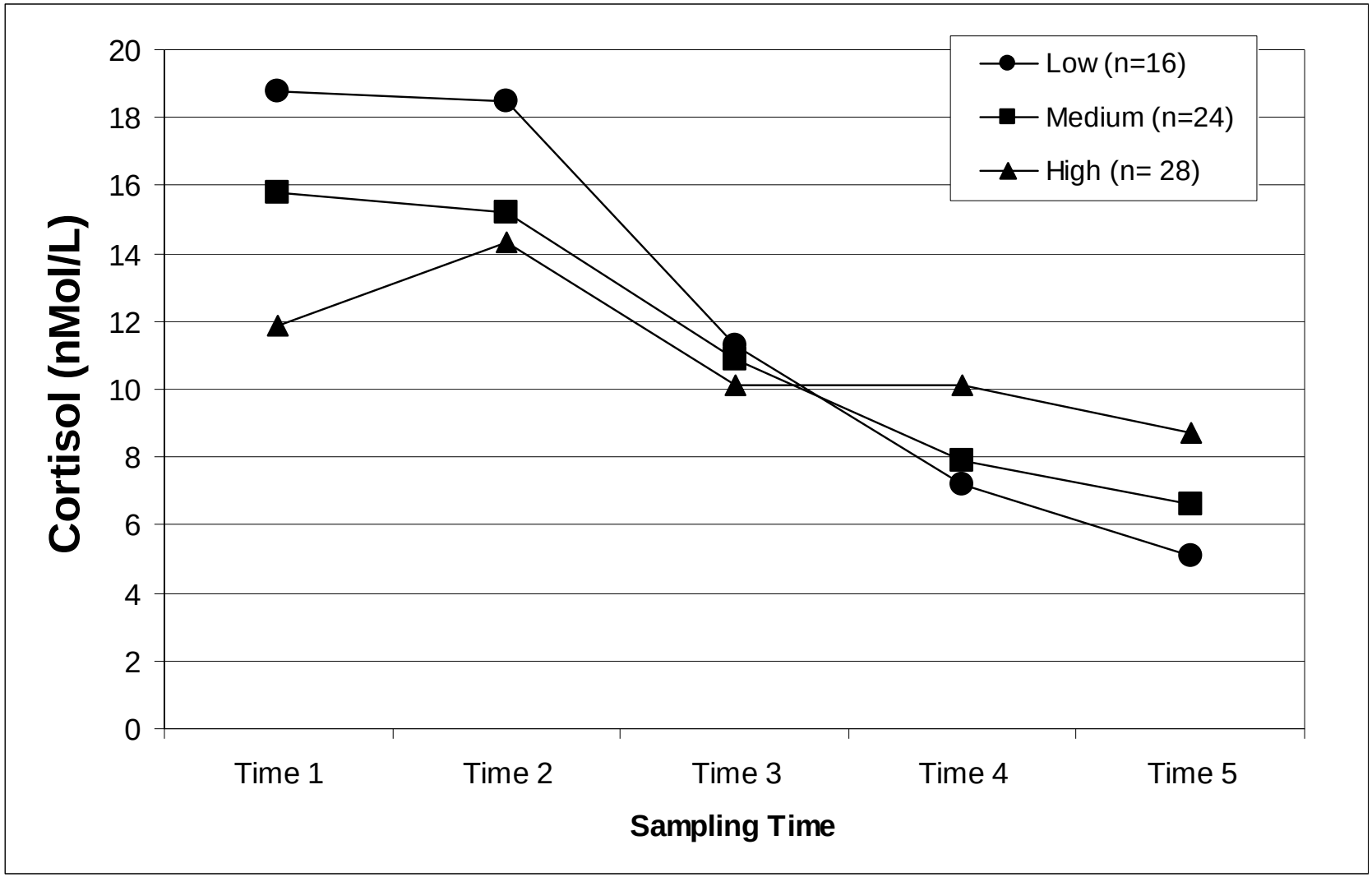
Chronic stress can lead to development of the metabolic syndrome



Chrousos, G. P. (2009) Stress and disorders of the stress system
Nat Rev Endocrinol doi:10.1038/nrendo.2009.106

nature REVIEWS ENDOCRINOLOGY

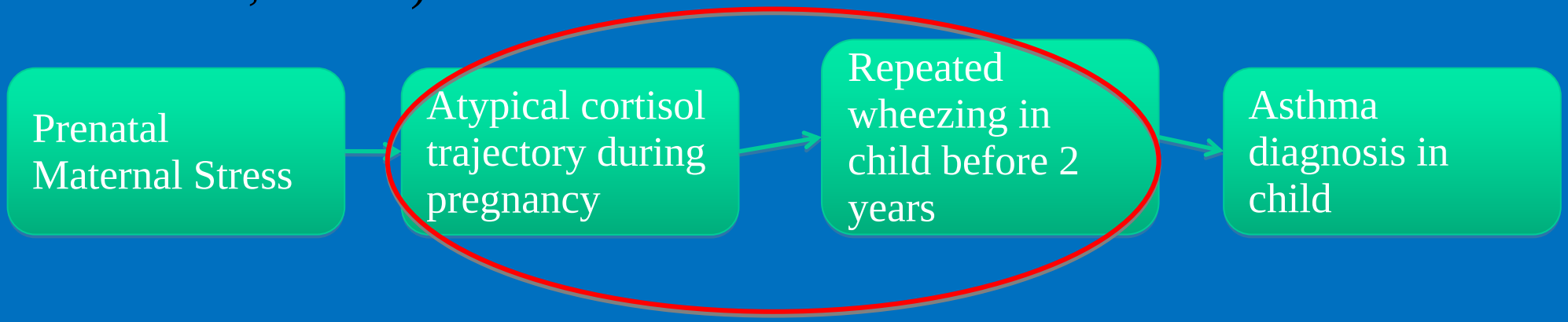
Prenatal Stress and Maternal Diurnal Cortisol Rhythms

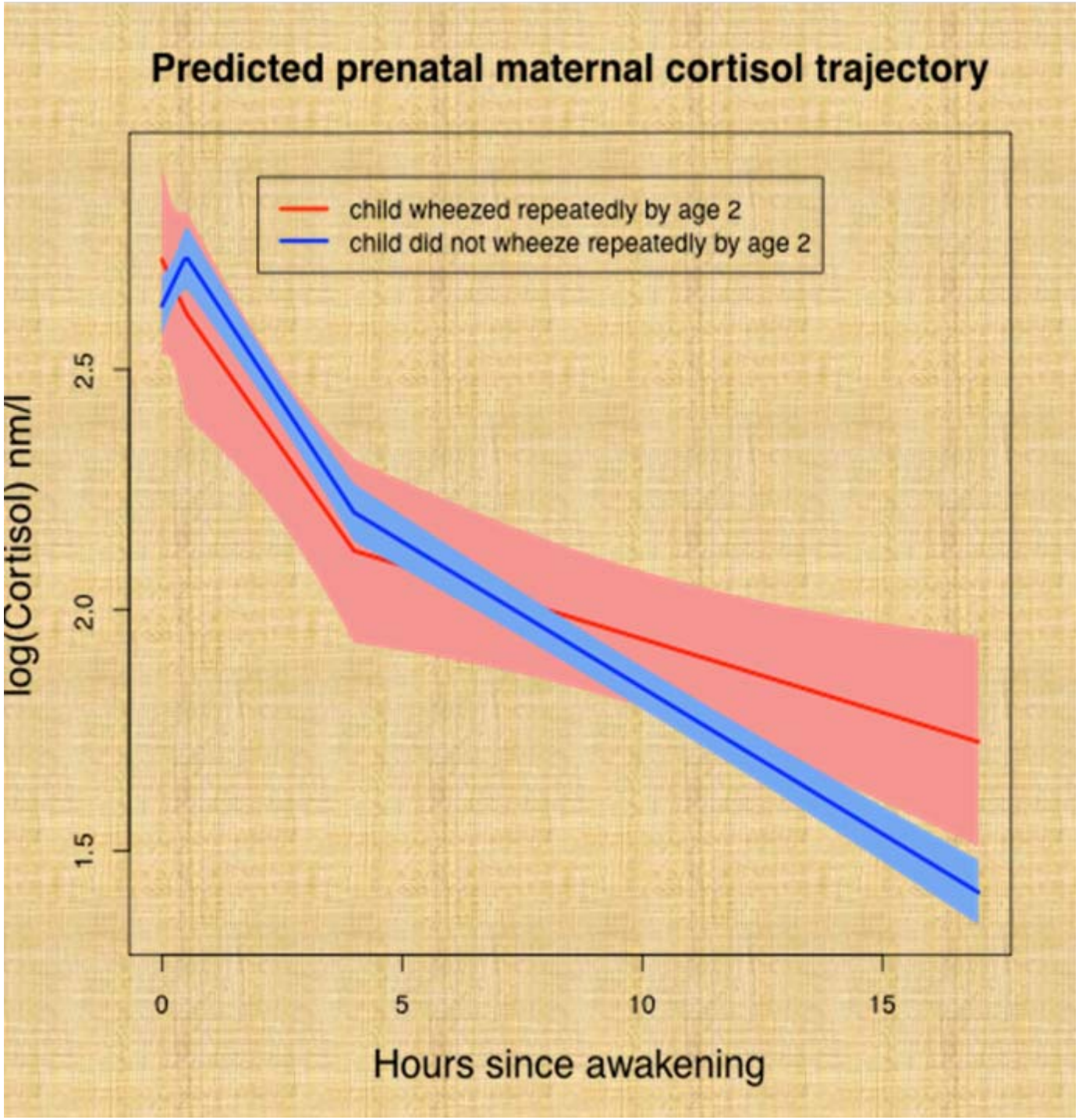


Suglia SF et al., Psychol Trauma 2010; 12:326-34.

Does cortisol pattern predict wheeze?

- **Stress**-elicited dysregulation of **biologic systems** may have implications on health risks.
- When systems are disrupted during **pregnancy** there may be **health consequences** for both the mother and **her child**.
- Prenatal maternal hypothalamic-pituitary-adrenocortical (HPA) axis function (indexed by **cortisol patterns**) may be one mechanism leading to **deviated fetal immune response** that may manifest as increased wheezing risk (Wright RJ, Paediatric Perinatal Epidemiol 2007; 3:8-14)





Wright RJ, et al. Presented at the International ATS Meetings, May 2011

Psychoneuroendocrinology (2009) 34, 1423–1436

available at www.sciencedirect.com

journal homepage: www.elsevier.com/locate/psyneuen

Assessing salivary cortisol in large-scale, epidemiological research

Emma K. Adam [a,1], Meena Kumari [b,1,*]

[a] School of Education and Social Policy and Institute for Policy Research, Northwestern University, United States
[b] International Centre for Lifecourse Studies in Society and Health, Department of Epidemiology and Public Health, University College London, London WC1E 6BT, United Kingdom

Time Scales of Cortisol Measurement

Cortisol in Hair: Biological Marker of Chronic Stress?

Psychoneuroendocrinology (2009) 34, 32–37

available at www.sciencedirect.com

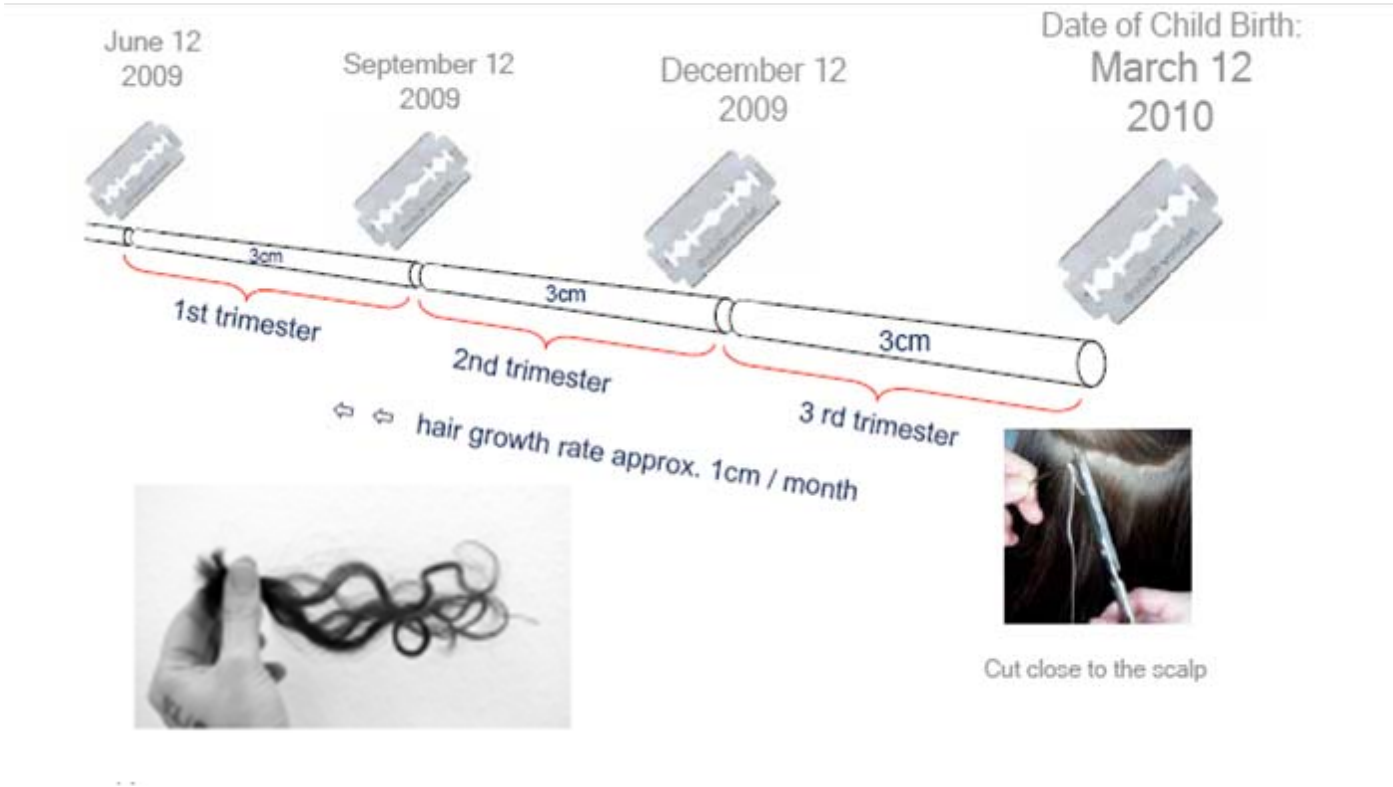
journal homepage: www.elsevier.com/locate/psyneuen

Hair as a retrospective calendar of cortisol production—Increased cortisol incorporation into hair in the third trimester of pregnancy

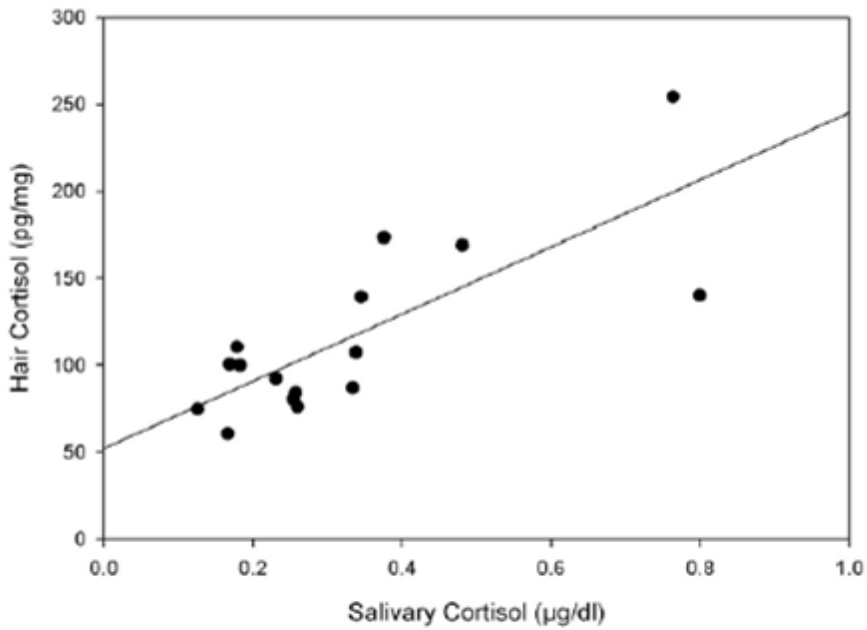
Clemens Kirschbaum *, Antje Tietze, Nadine Skoluda, Lucia Dettenborn

Department of Psychology, Technical University of Dresden, 01062 Dresden, Germany

Endocrine Time Tunnel



Correlation with Salivary Cortisol



Davenport et al., 2006

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

Psychoneuroendocrinology (2009) 34, 50–61

available at www.sciencedirect.com

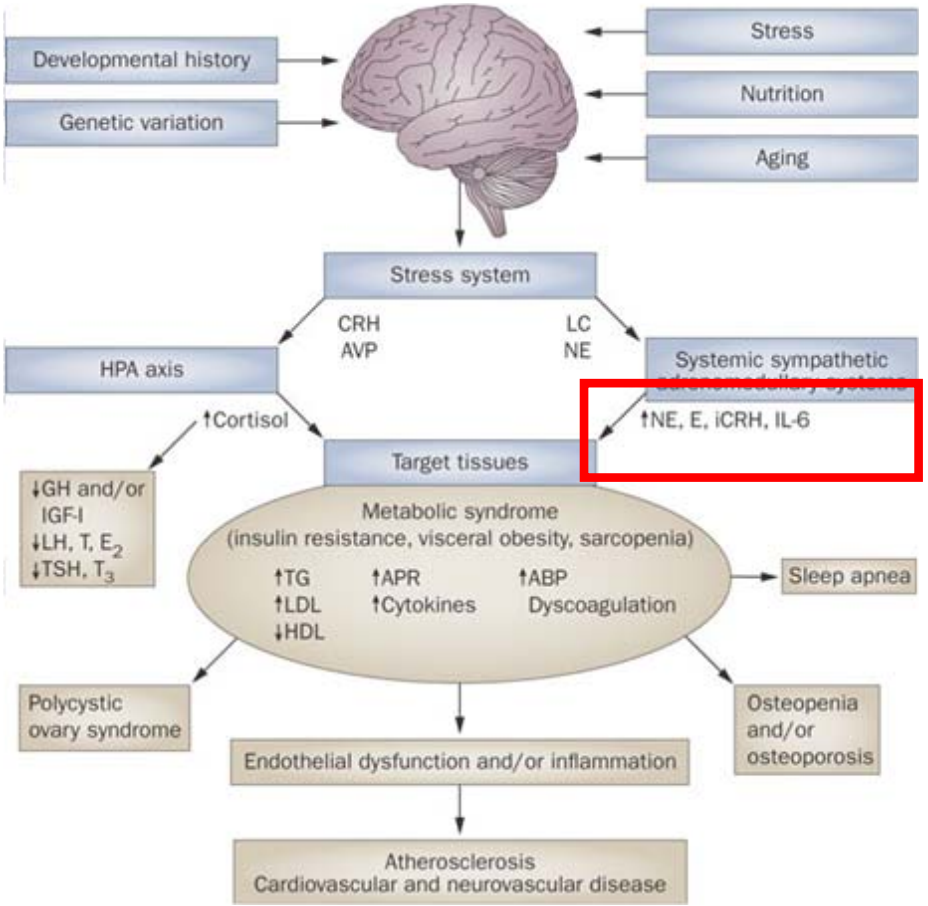
journal homepage: www.elsevier.com/locate/psyneuen

Identifying atypical cortisol patterns in young children: The benefits of group-based trajectory modeling

Mark J. Van Ryzin [a], Melissa Chatham [a], Erin Kryzer [a], Darlene A. Kertes [b], Megan R. Gunnar [a,*]

[a] *Institute of Child Development, University of Minnesota, 51 East River Road, Minneapolis, MN 55455, United States*
[b] *Department of Psychiatry, Virginia Institute of Psychiatric and Behavioral Genetics, Virginia Commonwealth University, Box 980126, 800 East Leigh Street, Richmond, VA 23298, United States*

Chronic stress can lead to development of the metabolic syndrome



Chrousos, G. P. (2009) Stress and disorders of the stress system
Nat Rev Endocrinol doi:10.1038/nrendo.2009.106

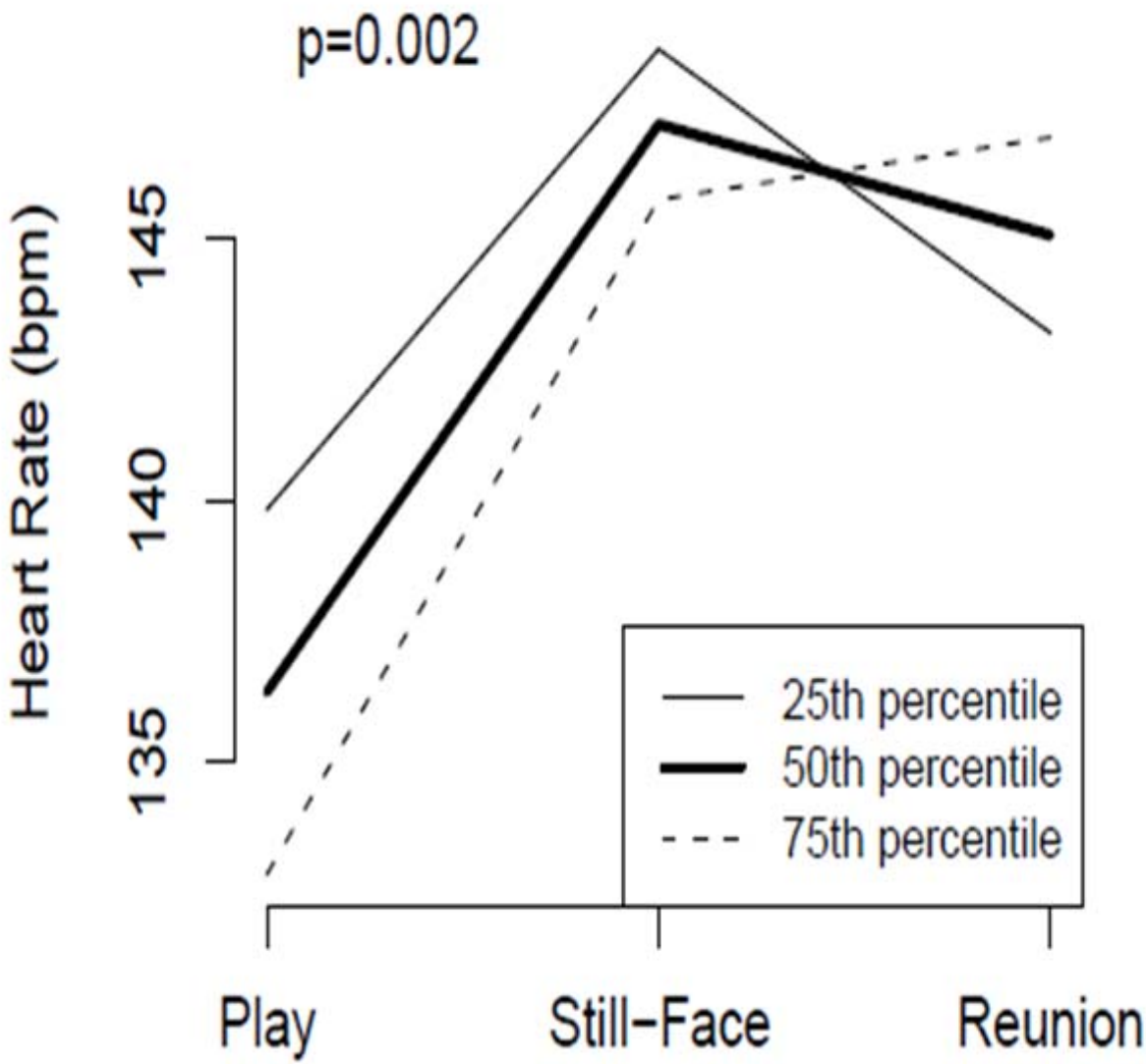
nature REVIEWS ENDOCRINOLOGY

Measuring the Autonomic Response (Sympathovagal Balance)

- Sympathetic and parasympathetic ANS branches innervate myocardium
- Continuous interplay between these branches (autonomic balance) reflects the ANS ability to respond to stressors and return to homeostasis
- ANS balance can be indexed by the heart's beat-to-beat variability (HRV)
  - Greater HRV = better ability to respond to psychological and physical stressors

LifeShirt System: Autonomic Reactivity

SFP: Infant ANS Regulation



Maternal Lifetime Trauma Exposure

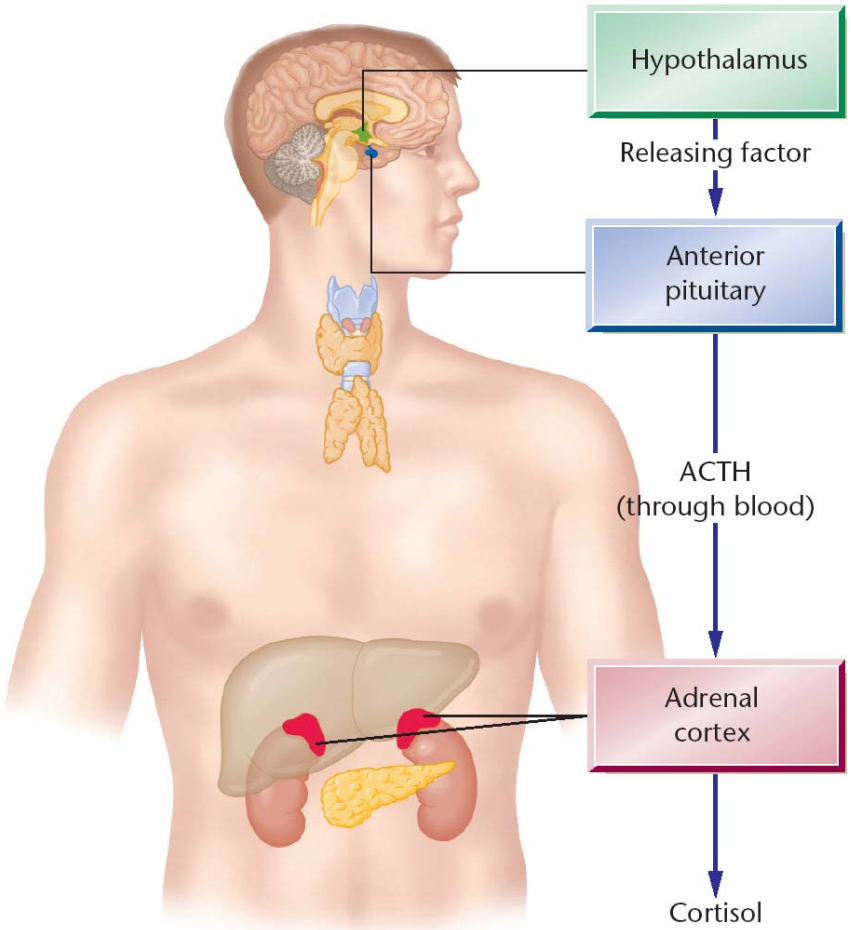
------- High Exposure

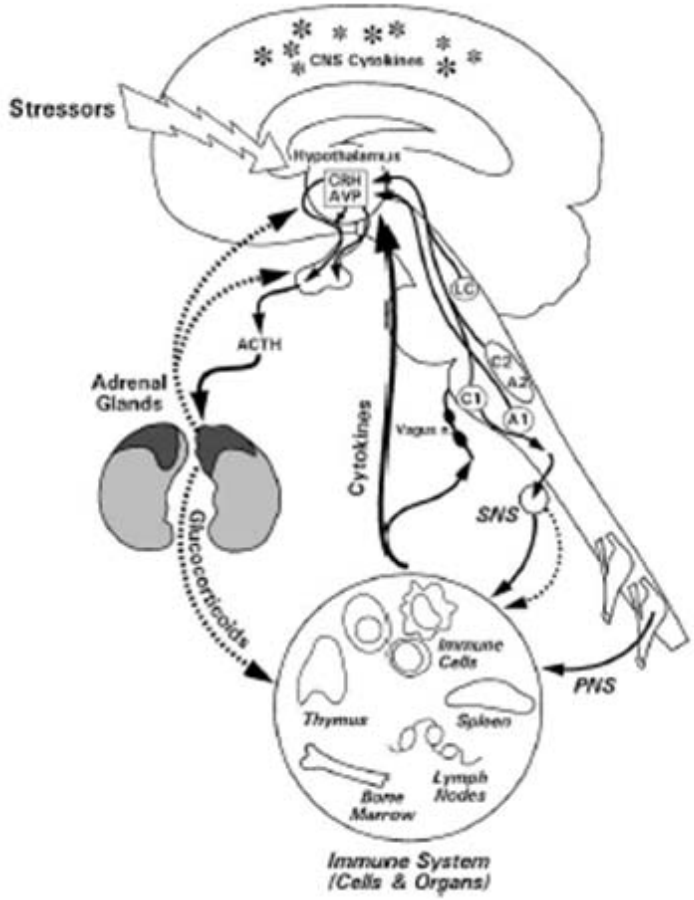
——Moderate Exposure

——Low Exposure

Bosquet Enlow et al., 2009

Neuroendocrine - Immune Interactions





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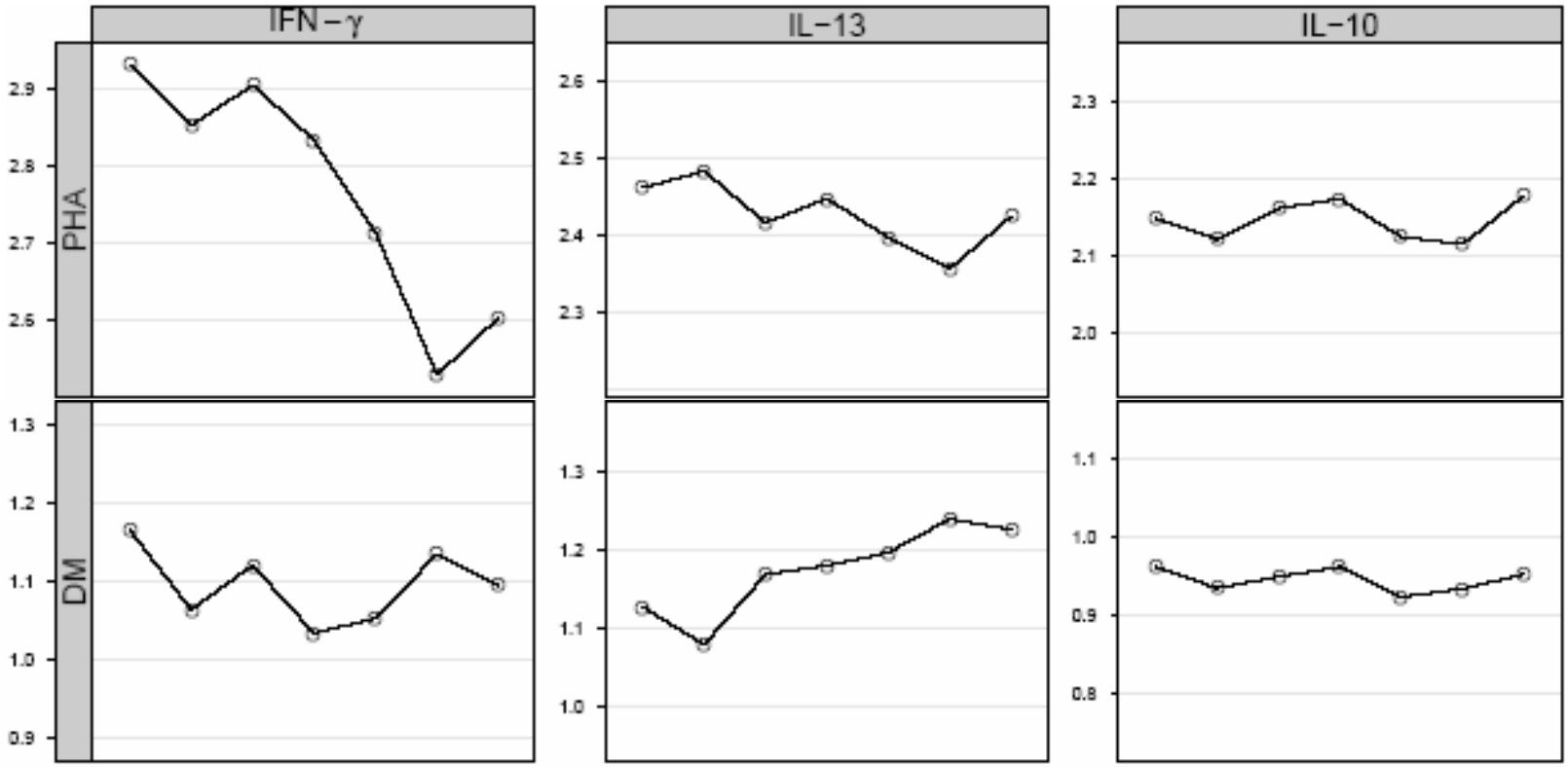
Relationship of composite stress score and cytokine responses (average log-transformed values): Adaptive Panel



Low ➠ High Stress Low ➠ High Stress Low ➠ High Stress

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

Schizophrenia Bulletin
doi:10.1093/schbul/sbp028

Concurrent Measurement of "Real-World" Stress and Arousal in Individuals With Psychosis: Assessing the Feasibility and Validity of a Novel Methodology

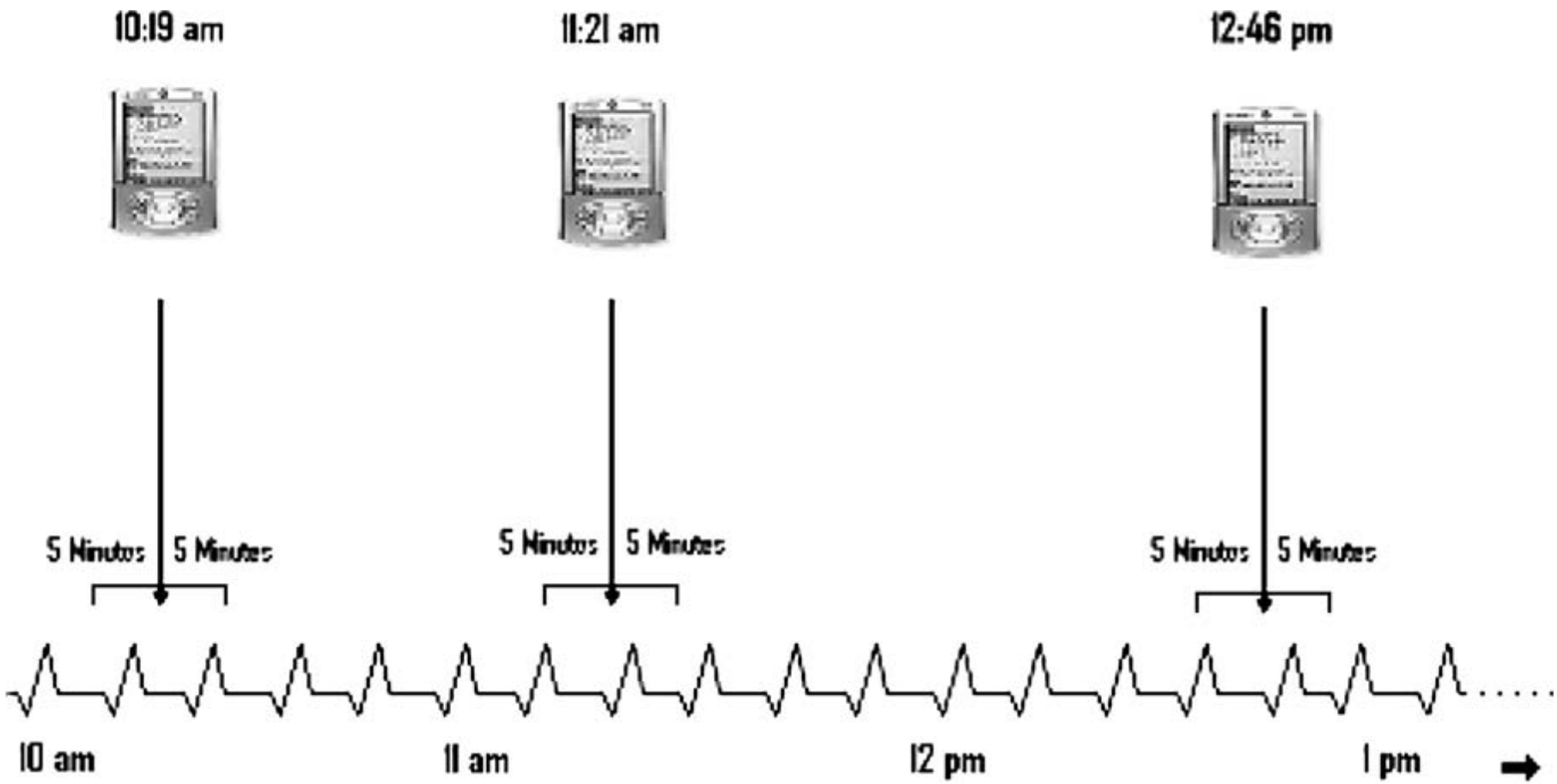
David Kimhy[1–3], Philippe Delespaul[4], Hongshik Ahn[5], Shengnan Cai[5], Marina Shikhman[2], Jeffrey A. Lieberman[2,3], Dolores Malaspina[6], and Richard P. Sloan[2,3]

[2]Department of Psychiatry, Columbia University, New York, NY; [3]New York State Psychiatric Institute, New York, NY; [4]Departments of Psychiatry and Neuropsychology, Maastricht University, Maastricht, The Netherlands; [5]Department of Applied Mathematics and Statistics, State University of New York (SUNY), Stony Brook, NY; [6]Department of Psychiatry, New York University Medical Center, New York, NY

ity of our methodology in individuals with psychosis. The methodology offers a novel way to study in high time resolution the concurrent, "real-world" interactions between stress, arousal, and psychosis. The authors discuss the methodology's potential applications and future research directions.

Key words: psychosis/schizophrenia/stress/arousal/heart rate variability/vagal/cardiac autonomic regulation/experience sampling method/palm computers

Sampling of Momentary Stress (Negative Mood) and Epochs of Physiological Arousal as Part of Daily Functioning in Natural Environments



Kimhy D et al. Schizophr Bull 2010;36:1131-1139

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Schizophrenia Bulletin

Sample Screen Shots of Questions Presented on the Palm Computer Screen.

Kimhy D et al. Schizophr Bull 2009;schbul.sbp028

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Schizophrenia Bulletin

Summary

- Literature on physiological correlates of stress and health has a number of methodological difficulties
  - Hypothalamic-pituitary-adrenal (HPA) axis (e.g., cortisol)
  - Autonomic Nervous System (ANS)
  - Immune system
- Advances have been made to address a number of these making it feasible to incorporate physiological assessments into large-scale epidemiologic studies
- Advanced statistical approaches to data analysis also evolving
- Critical to understanding main effects of stress but also understanding synergistic effects between stress and other physical toxins may better inform children's environmental health vulnerabilities