Origins of asthma: Risk & Resiliency

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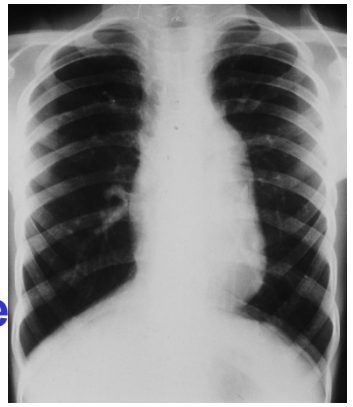
Institute for Exposomic Research

Origins of Asthma: Complex Picture–

Life Course Framework

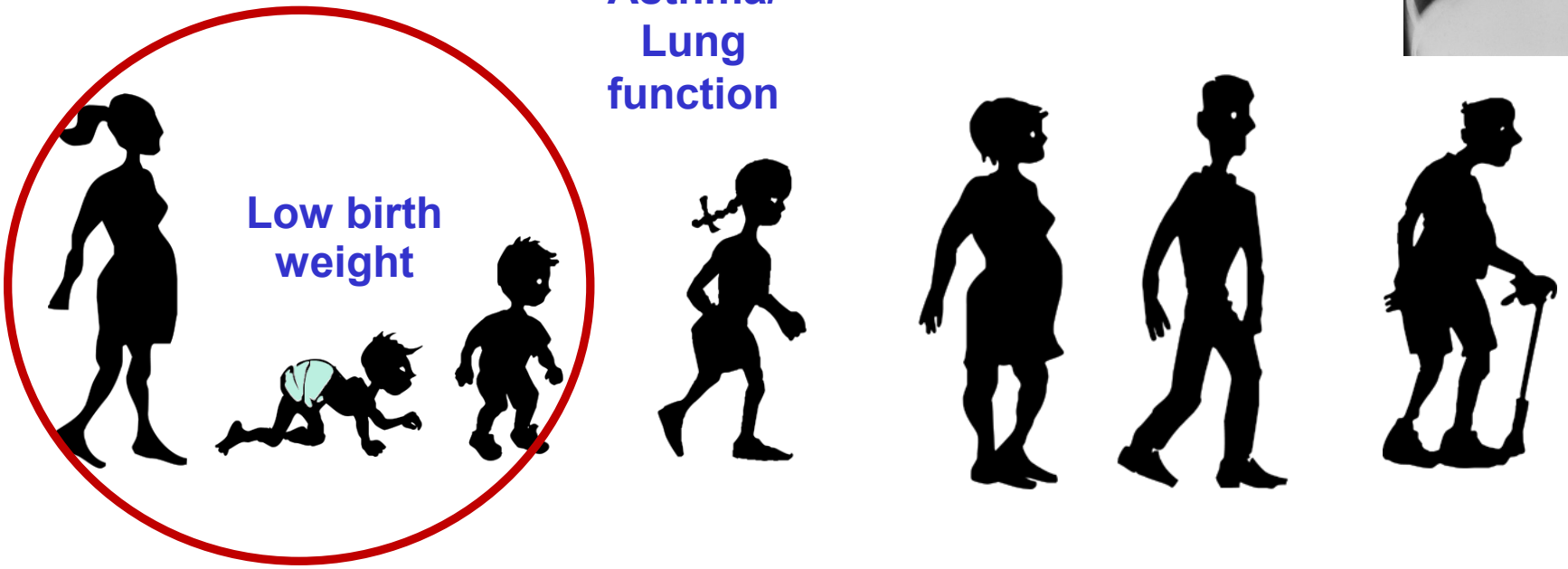


Toxic exposures

Low birth weight

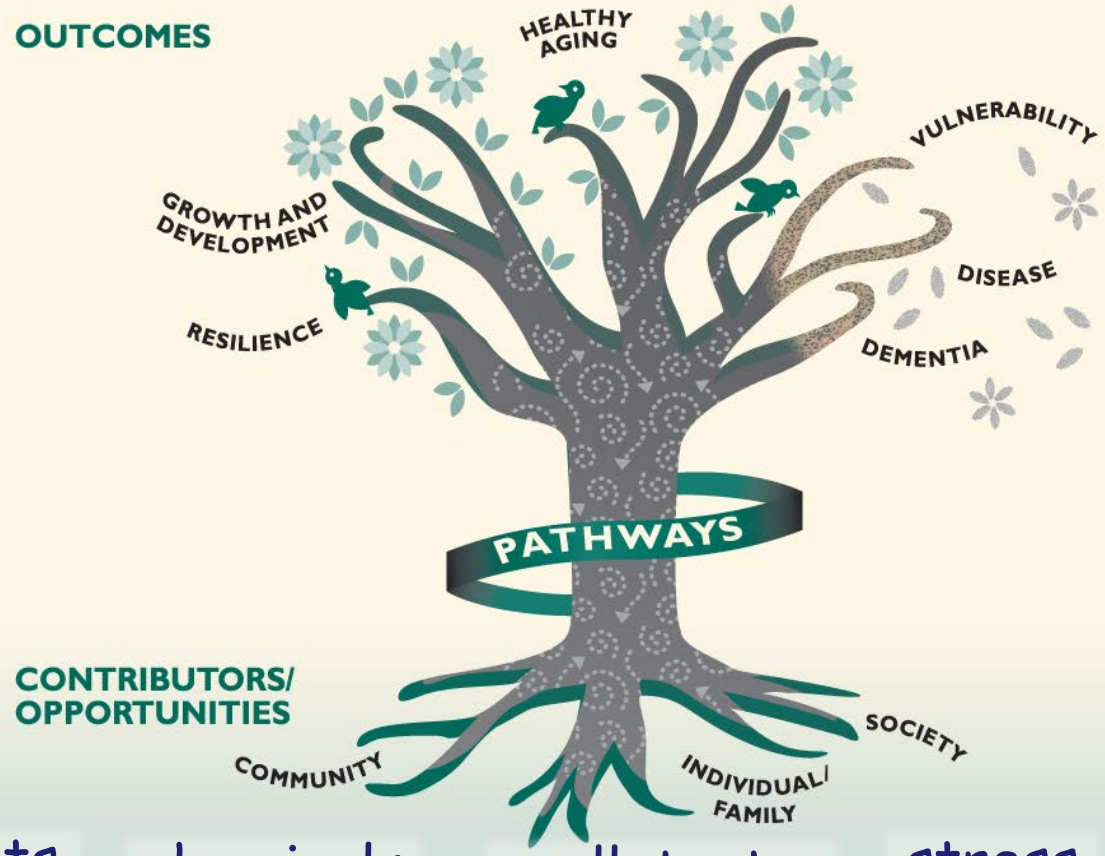
Wheeze/ Asthma/ Lung function

Obesity, HTN, CNS, CV/respiratory disease



How early life exposures influence development in childhood and across the life span.

Multiple Factors Influence Development



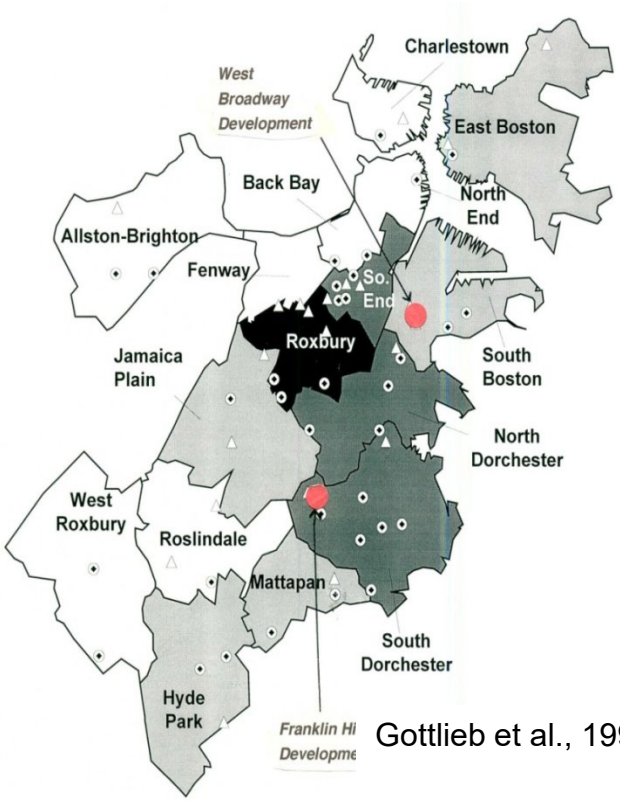
nutrients chemicals pollutants stress built environment

Asthma
Lung growth
Pathophysiology

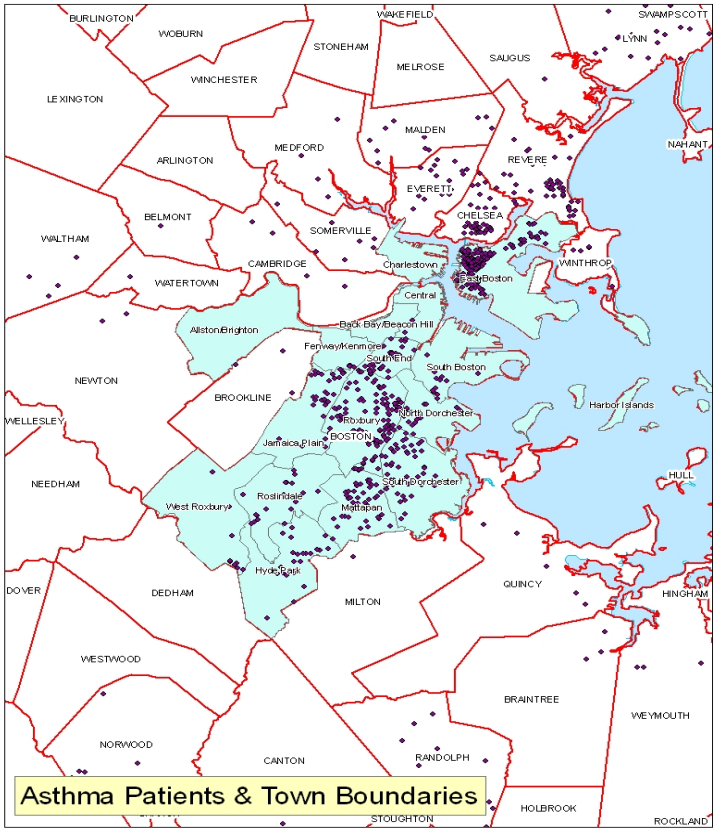
FUNDERS
NIEHS, NHLBI, NIMH, NIMHD,
ECHO national US consortium
Leaves of Grass Foundation

ACCESS

Asthma Coalition for Community, Environment and Social Stress



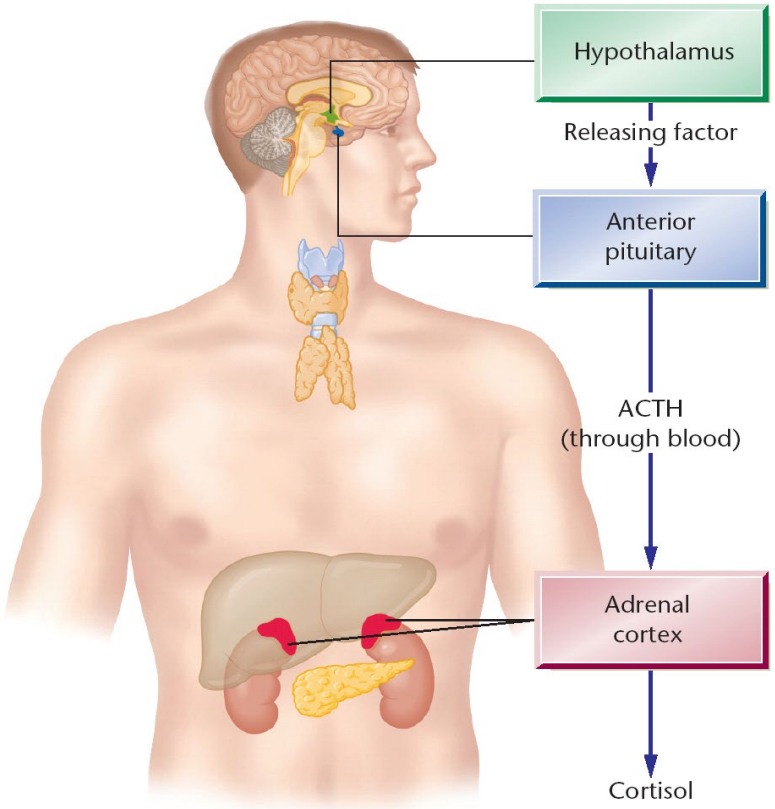
Gottlieb et al., 1995

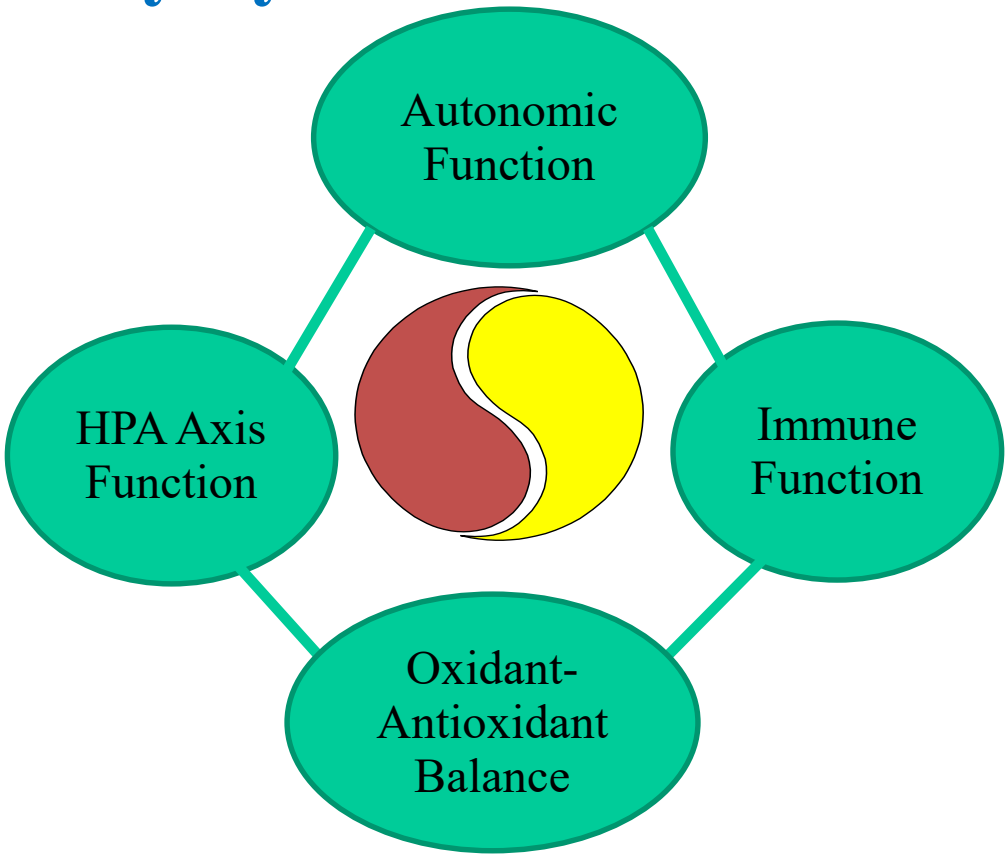


Motivation

How does psychological stress “get under the skin” to influence respiratory health?

Key Regulatory Systems

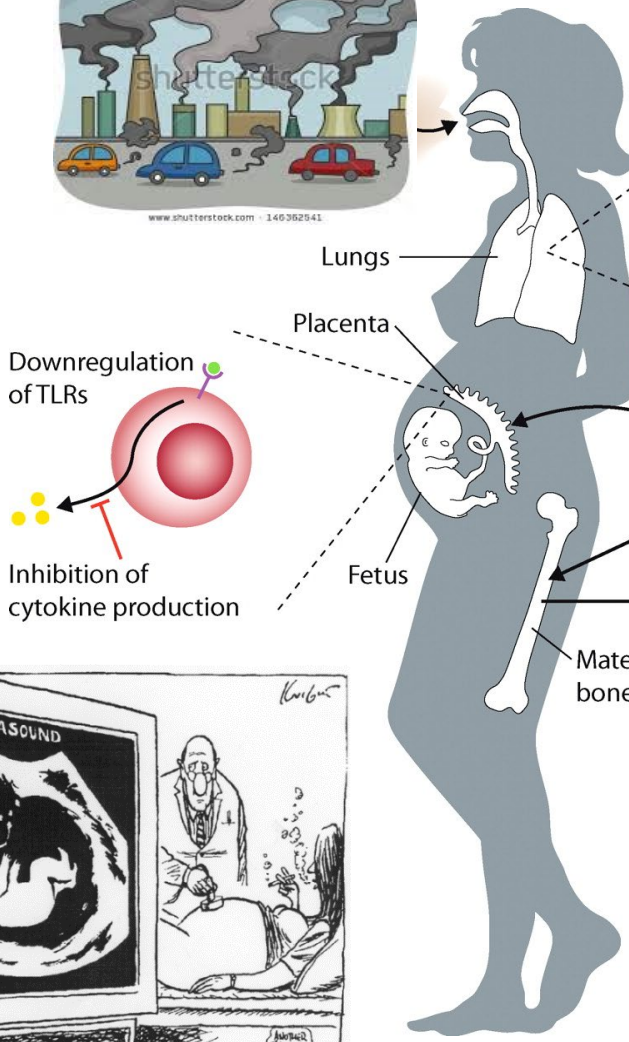


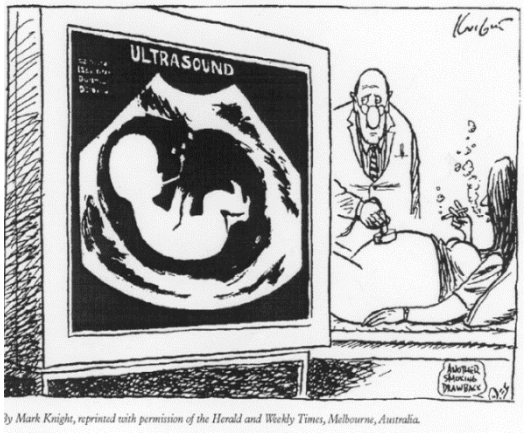


OPTIMAL BALANCE = HEALTH

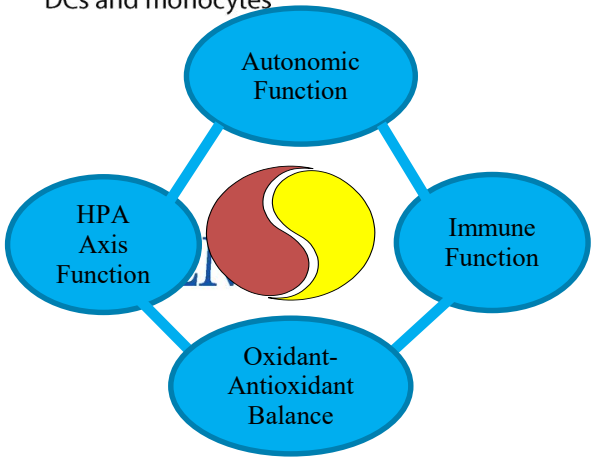
Stress physiology organized around 2 key systems – SAM & HPA

Interact with immune function & oxidant balance



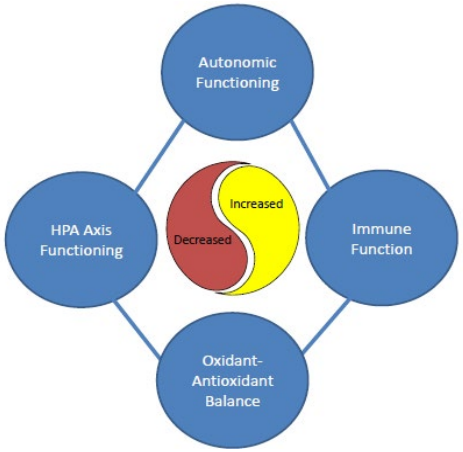


by Mark Knight, reprinted with permission of the Herald and Weekly Times, Melbourne, Australia.



Are children born to mothers who experience greater stress during pregnancy more likely to develop asthma?

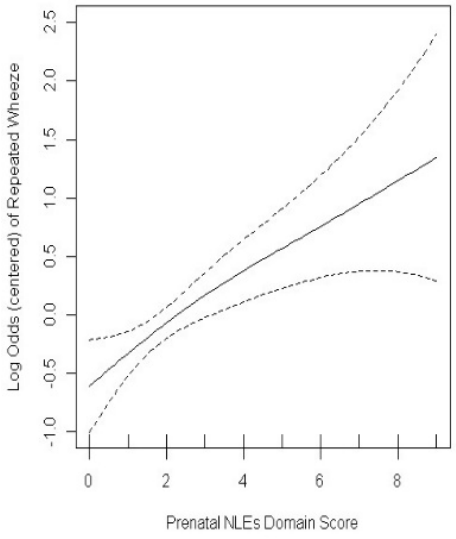
Maternal prenatal & early life stress

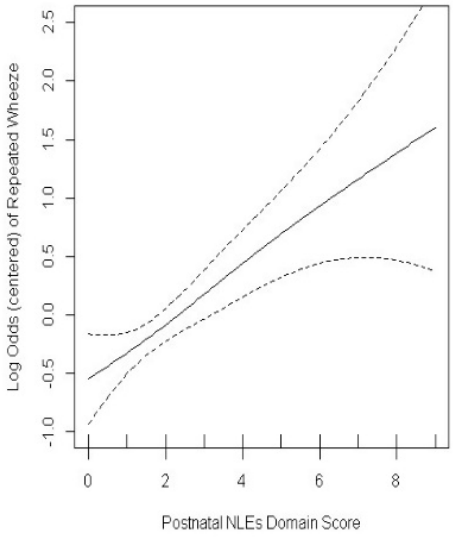


- Crisis in Family Systems-Revised (CRISYS-R) survey assess chronic life events in 11 domains (financial, legal, neighborhood & personal safety, etc).

Shalowitz et al, Health Serv Res.1998

Repeated wheeze





Chiu Y-HM, et al., *Am J Resp Crit Care Med* 2012

Why do we measure both social and chemical stressors?

Stress enhances effects of chemical toxins!

‘Place-based’ Exposures: Geomarker Data

Addresses → **Geocode** → **Link / Derive Geomarker Data**

Home, school, work, etc addresses

Convert address to coordinates to facilitate GIS

Link spatial locations to environmental, census, EHR data, etc.

1) Collect Addresses and Dates

2) Construct Individual Residential Timelines

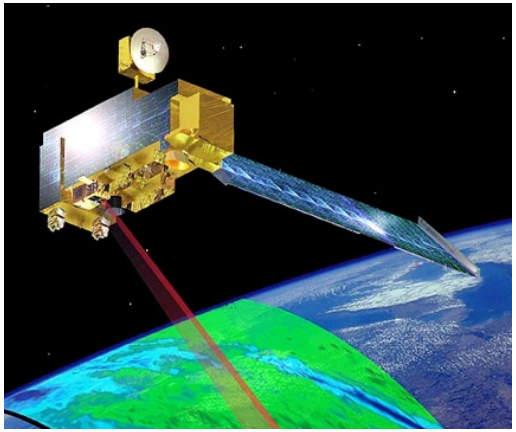
3) Geocode Addresses (lat/lon coordinates)

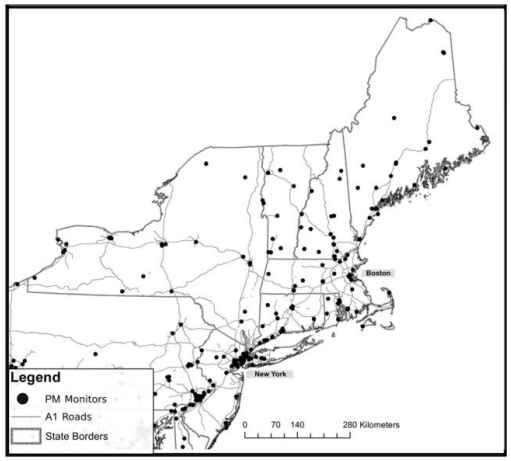
4) Assign Exposures

- Crime/violence
- Green space
- Traffic related air pollution
- Industrial air pollution

Exposure Assessment

Daily $PM_{2.5}$ exposure estimated for each participant using a high-resolution satellite-based hybrid model:

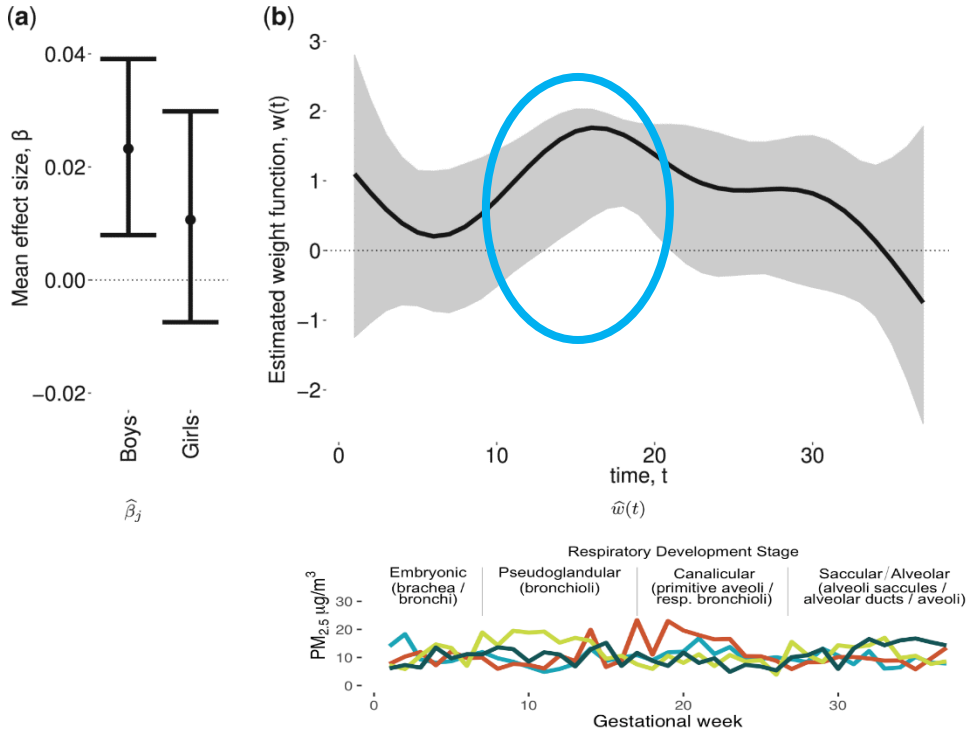




Kloog, I., et al. Atmos Environ (2014)

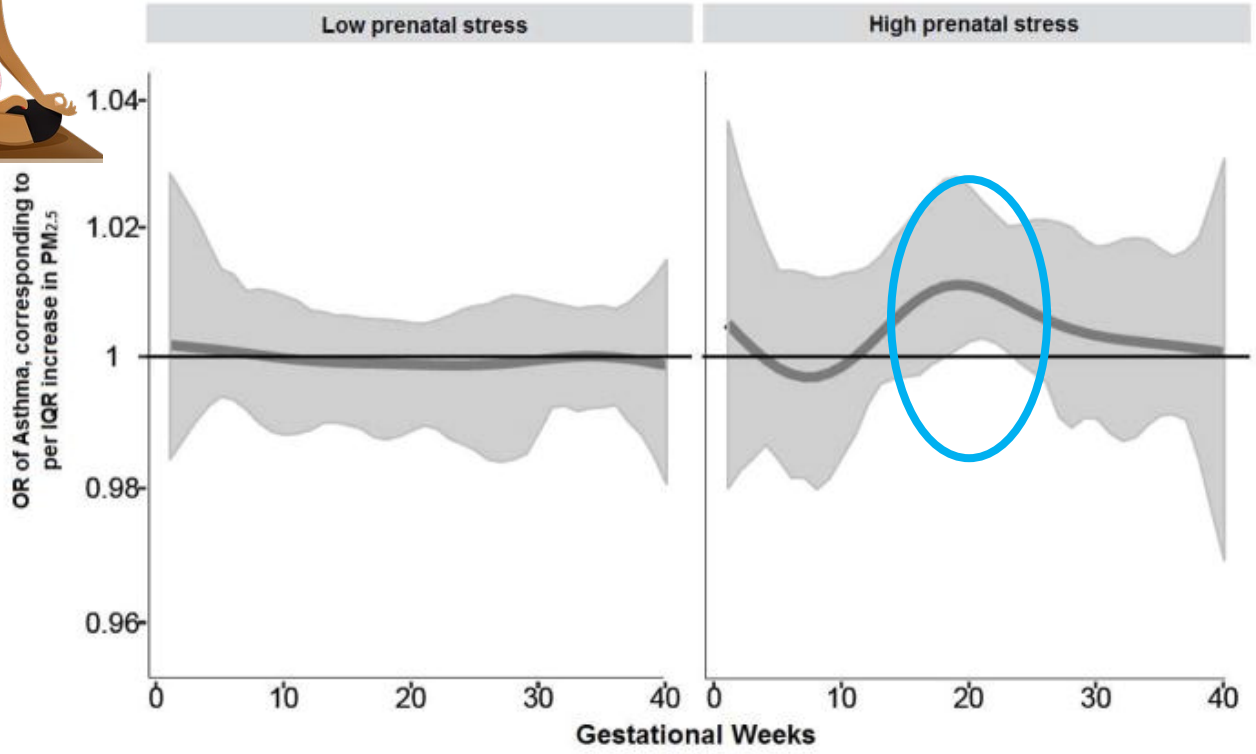
Prenatal PM2.5 linked to children's asthma risk

Hsu HH, et al *Am J Respir Crit Care Med* 2015



X

Lee AG, et al., *J Allergy Clin Immunol* 2018



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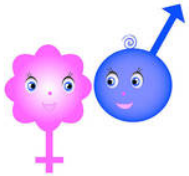
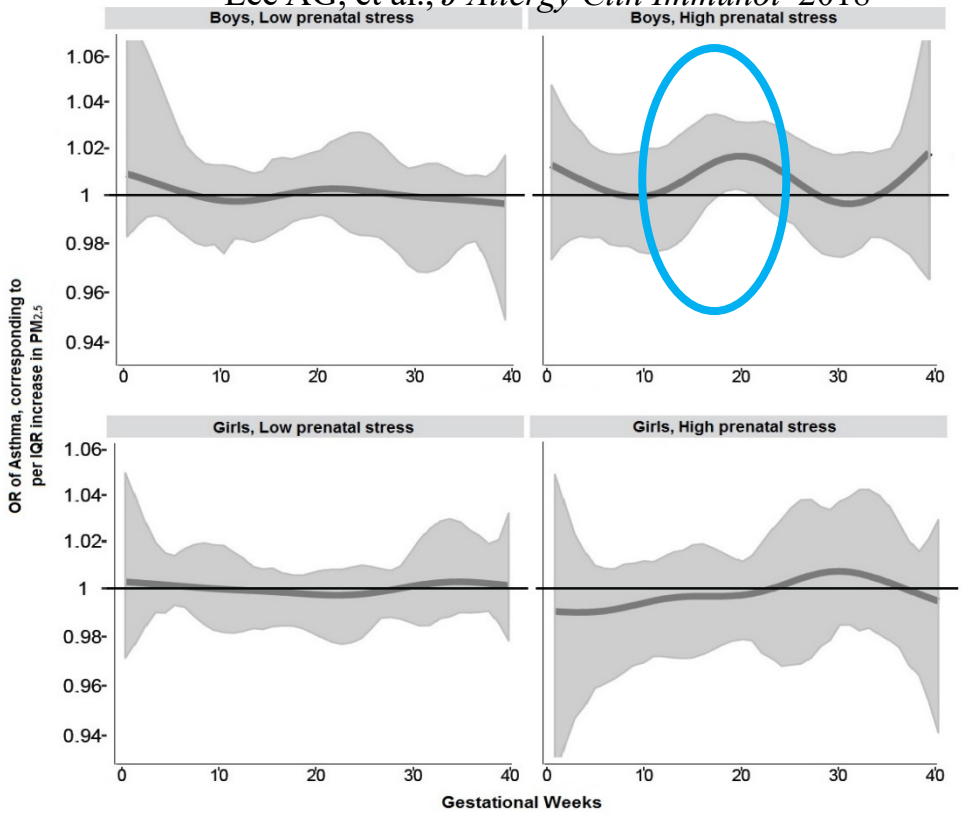


Lee AG, et al., *J Allergy Clin Immunol* 2018



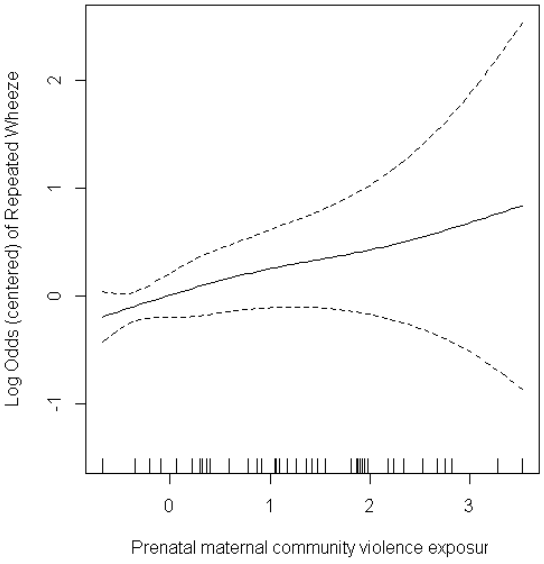
Need for Multi-level exposure assessment

Prenatal ECV and black carbon (BC) Exposure Predict Wheeze Similarly

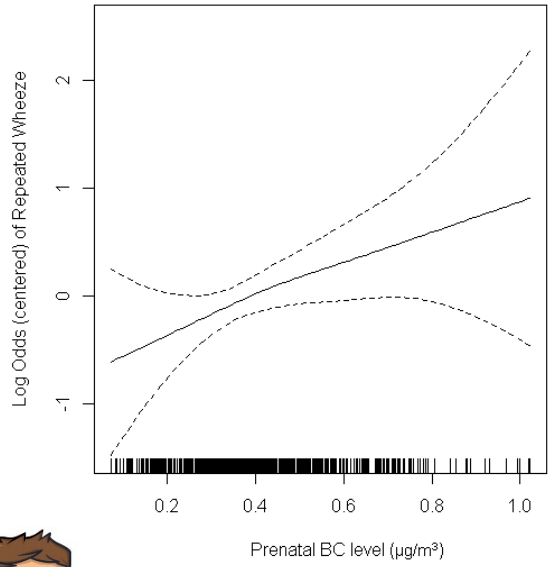
Independent of individual-level factors

Chiu YH, et al., JACI 2014

Community Violence



Ambient air pollution

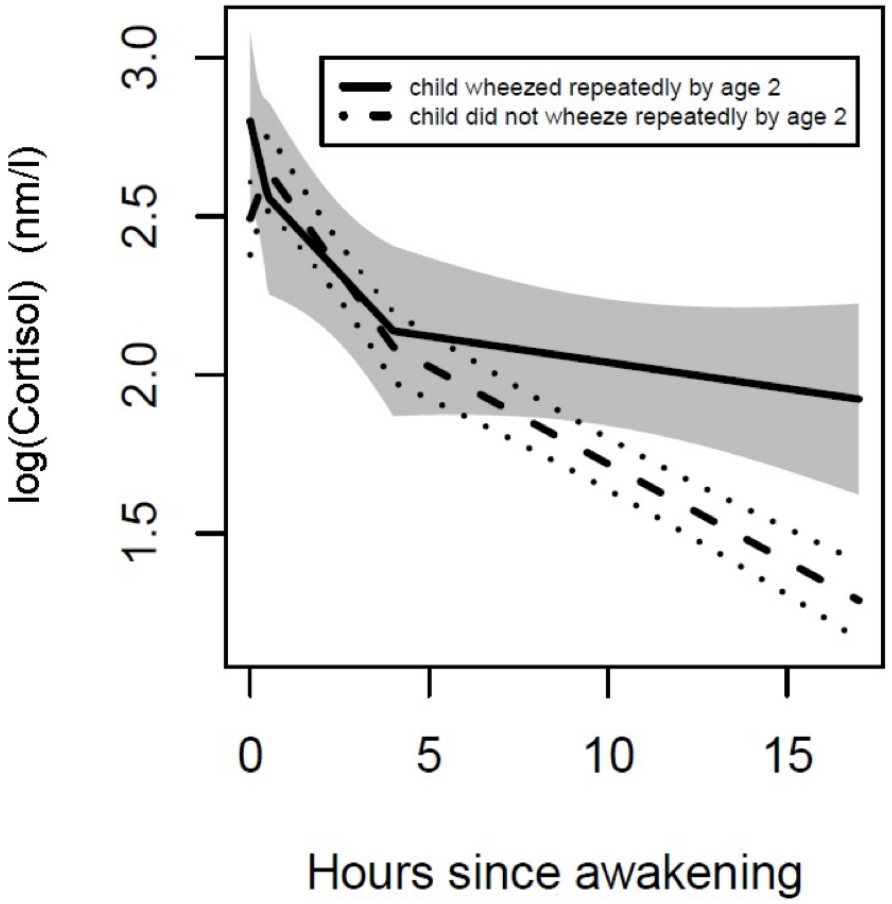


Repeated wheeze

Where you live matters!

How does stress “get under the skin” to influence respiratory health?

Maternal prenatal cortisol trajectory associated with repeated wheeze in children

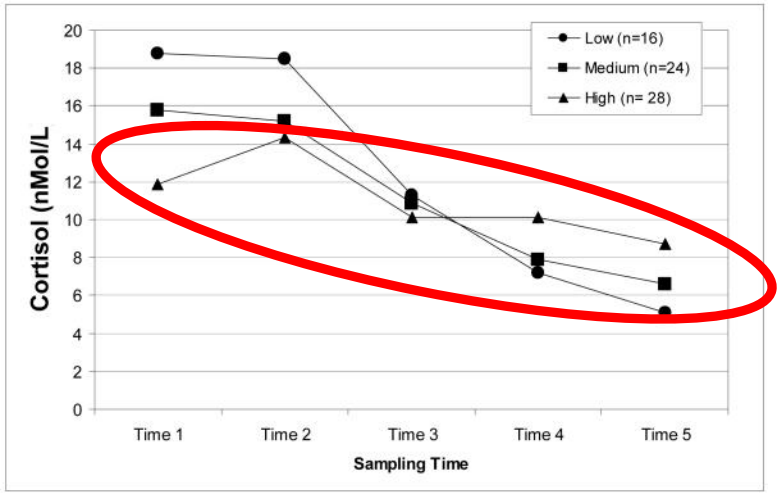


- 5 samples/day over 3 days
- Awakening, 30-45 minutes after, lunch, dinner, bedtime

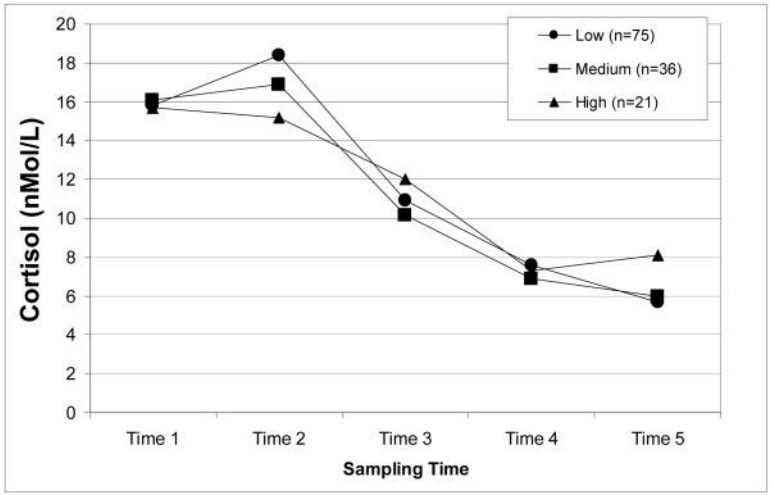
Wright RJ et al. *Am J Resp Crit Care Med* (2013)

Cumulative psychological stress & diurnal cortisol profiles

Blacks

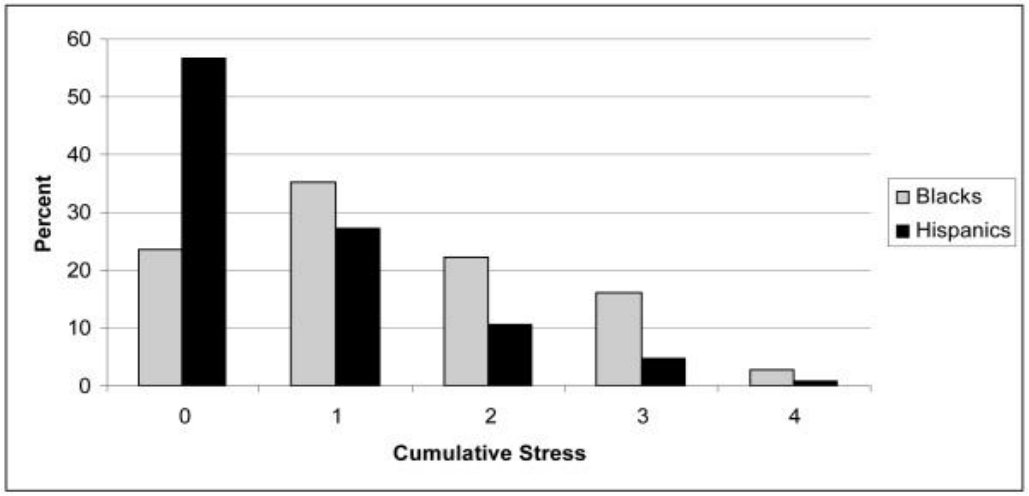


Hispanics



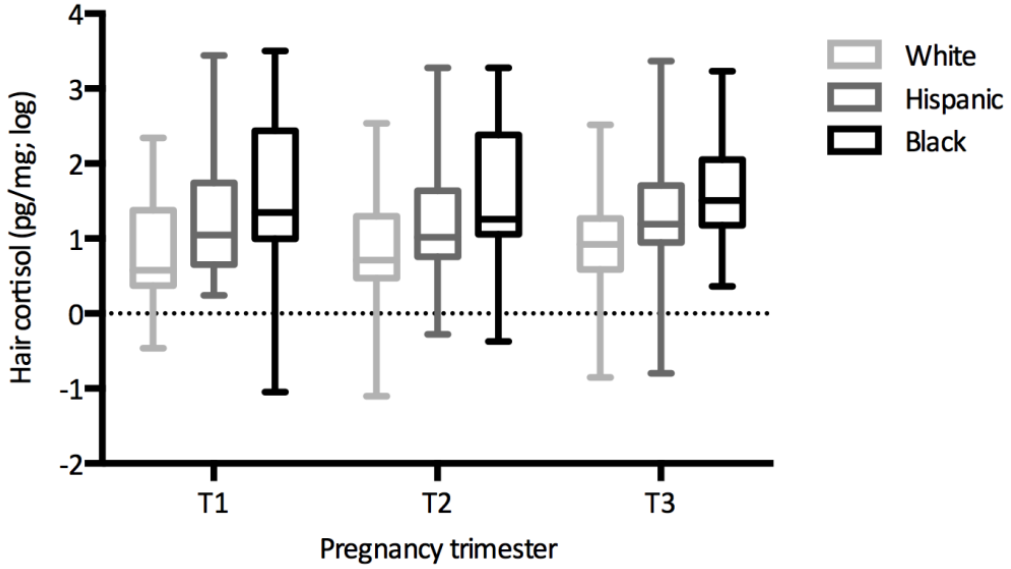
Cumulative Stress Domains

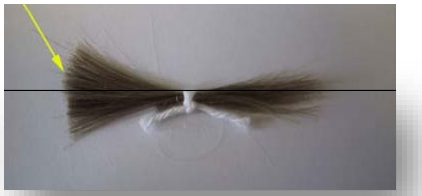
-Interpersonal violence
-Community violence
-Discrimination
-Other negative life events

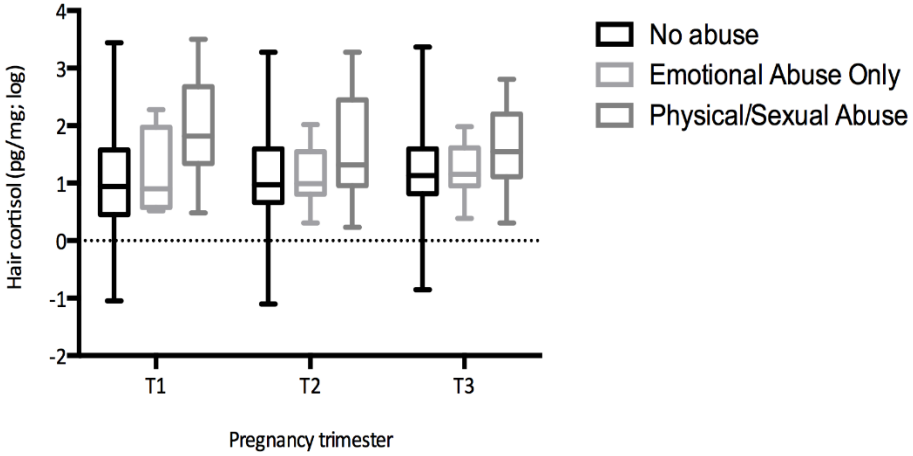


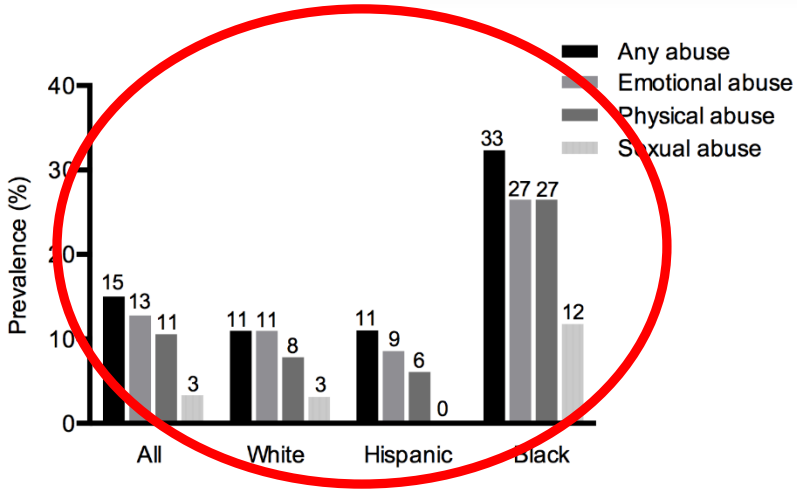
Franco Suglia S, et al., *Psychol Trauma* 2010

Integrated measure HPA axis in pregnancy: hair cortisol









Schreier HM, et al., *J Epidem Comm Health* 2015

What can we do about it?

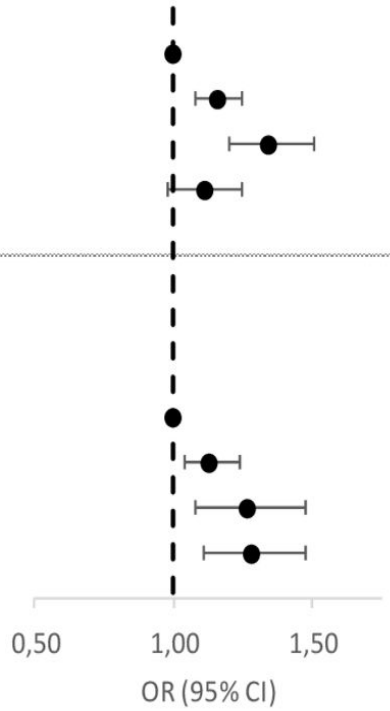
Can we prevent stress-induced asthma/wheeze?

ACEs in early life (0/≥1) and asthma

Kathrine Pape et al. Thorax doi:10.1136/thoraxjnl-2020-214528

THORAX

	n	Cases	OR (95% CI)	OR[a] (95% CI)	OR[b] (95% CI)
Boys					
Asthma phenotypes					
No asthma	207 267	7 788	1.00 (ref)	1.00 (ref)	1.00 (ref)
Early-onset transient asthma	18 808	871	1.24 (1.16-1.34)	1.17 (1.08-1.26)	1.16 (1.08-1.25)
Early-onset persistent asthma	6 460	320	1.34 (1.19-1.50)	1.34 (1.18-1.52)	1.34 (1.20-1.51)
Late-onset asthma	6 865	278	1.08 (0.96-1.22)	1.03 (0.90-1.19)	1.11 (0.98-1.25)
Girls					
Asthma phenotypes					
No asthma	207 635	7 778	1.00 (ref)	1.00 (ref)	1.00 (ref)
Early-onset transient asthma	11 740	532	1.22 (1.12-1.33)	1.12 (1.11-1.23)	1.13 (1.04-1.24)
Early-onset persistent asthma	3 511	165	1.27 (1.08-1.48)	1.27 (1.07-1.51)	1.27 (1.08-1.48)
Late-onset asthma	4 270	198	1.25 (1.08-1.44)	1.24 (1.05-1.46)	1.28 (1.11-1.48)



Kathrine Pape et al. Thorax doi:10.1136/thoraxjnl-2020-214528

THORAX

Early adversity predicts repeated wheeze and blunted cortisol slope (N=676)

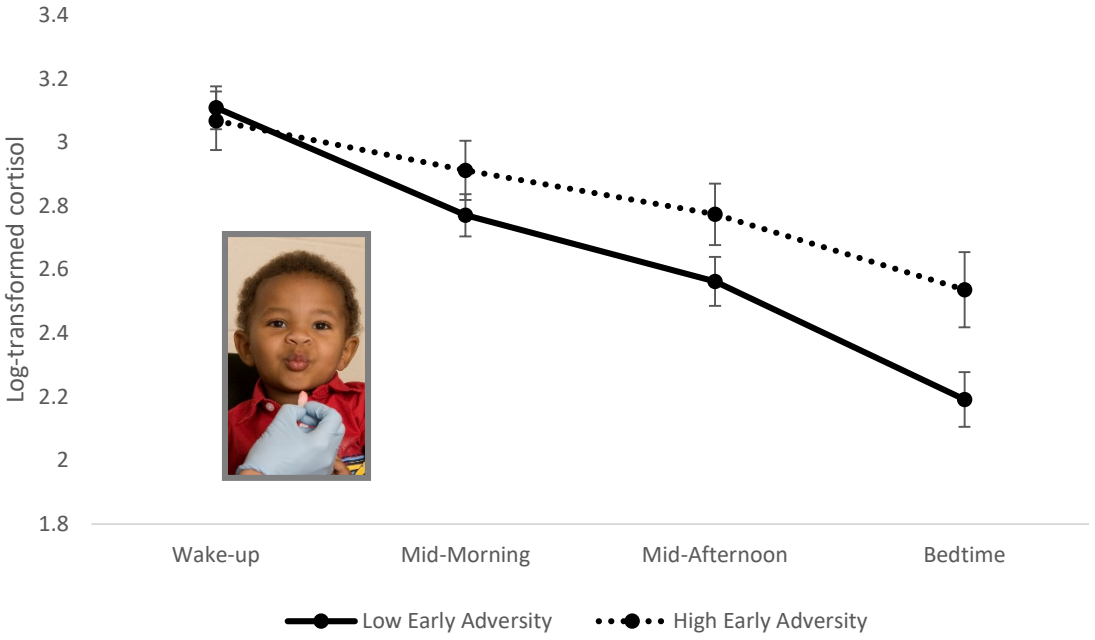
Early Adversity
Birth-6 months

.29*

Wheeze frequency
6-30 months

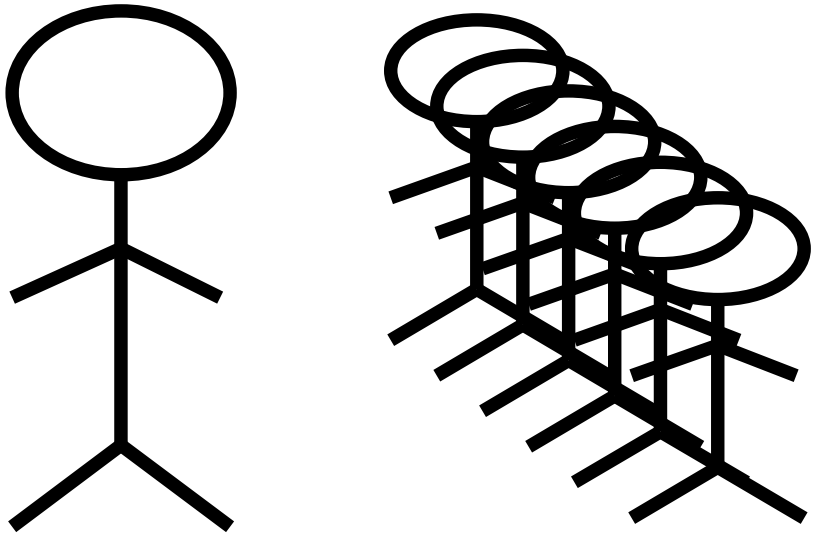
.03*

Blunted Cortisol
Slope
6 months



Frost A, et al., *Child Develop* (accepted manuscript)

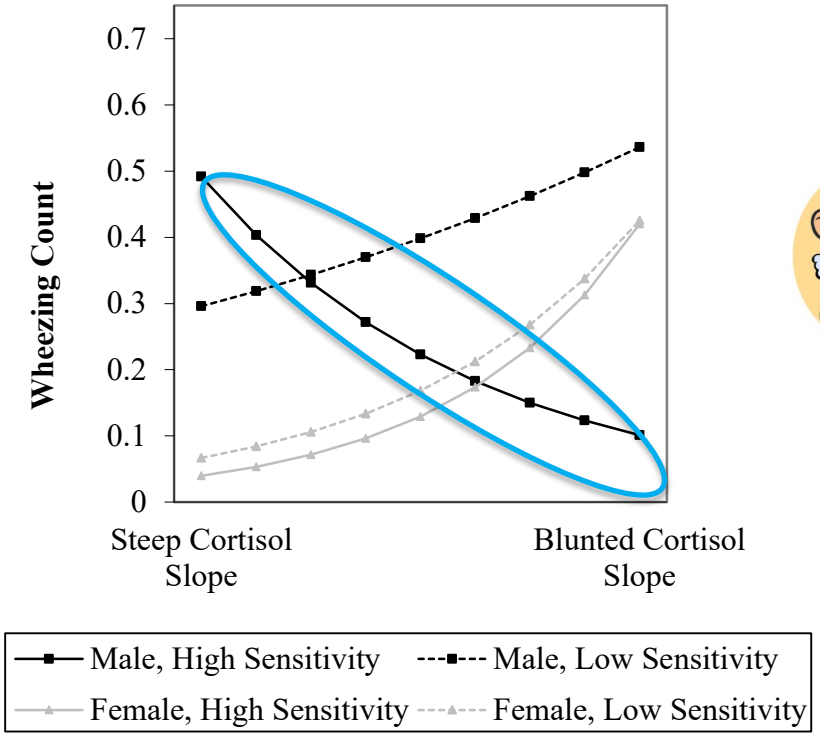
Social Relationships & Health



Can they buffer toxic stress effects on wheeze/asthma?

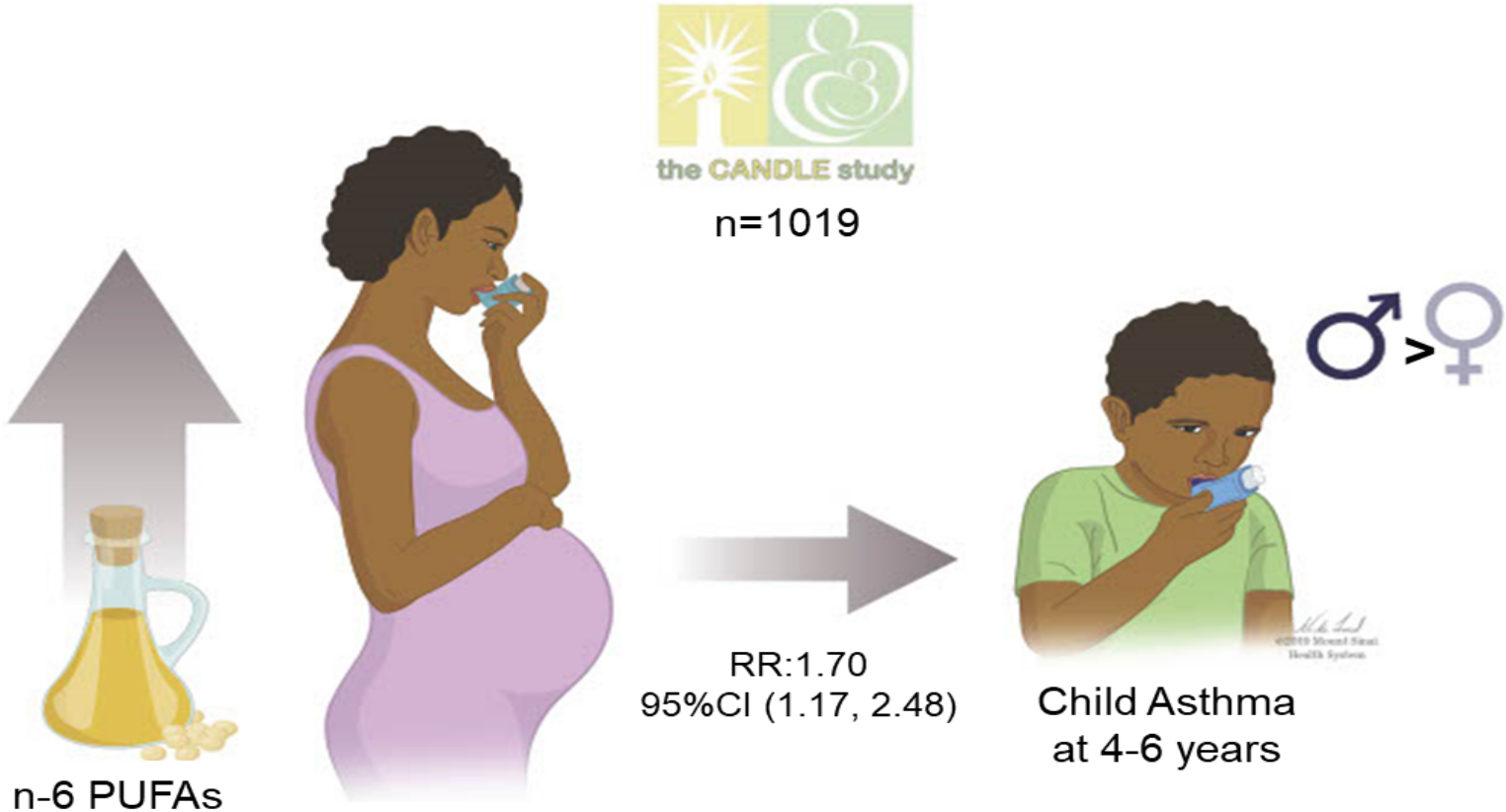
Altered infant cortisol profiles, sex, caregiver sensitivity

Frost A, et al., *Child Develop* (accepted manuscript)



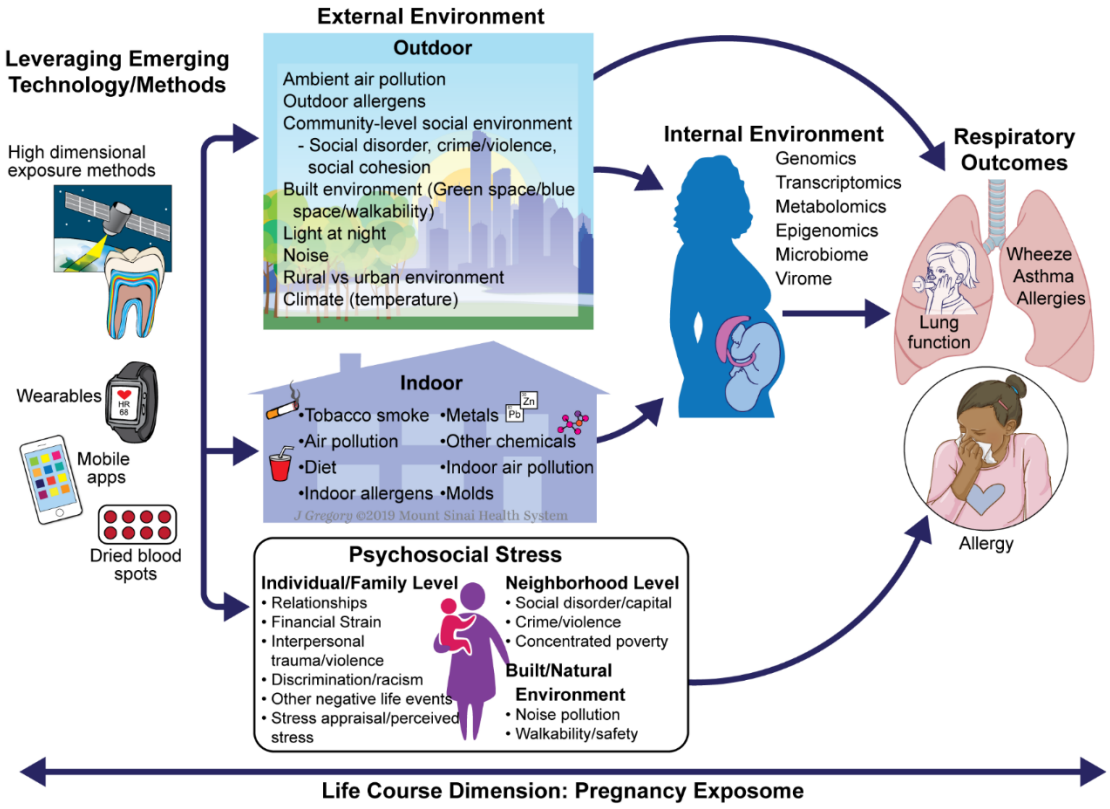
- Girls – blunted (atypical) cortisol slope linked to increased wheeze frequency regardless of maternal sensitivity
- Boys whose mothers show <u>low sensitivity</u> had ↑ wheeze frequency when cortisol slope was blunted (atypical)
- Boys whose mothers show <u>high sensitivity</u> had ↓ wheeze when cortisol slope was blunted (atypical)

Prenatal polyunsaturated fatty acids (PUFAs) and child asthma: effect modification by maternal asthma and child sex



Rosa MJ, et al. *J Allergy Clin Immunol.* 2020;145(3):800-807.

Disentangling what begets asthma



Promise of the Exposome: Scaling it up

The totality of exposure from pre-conception to death

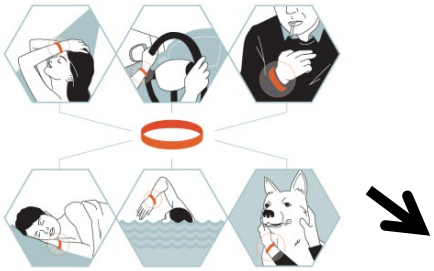
Common elements of the exposome concept

Measure as much as you can, if not 'the totality'	Multi-scale Integration	Identify stressors that impact health
Multiple stressors Mixtures	Multiple time points Exposure and Response	Data Driven (untargeted) Discovery

An untargeted (hypothesis free) assessment of the totality of environmental exposures.

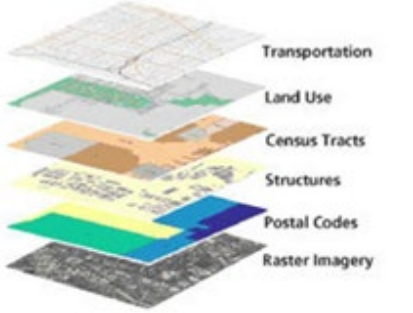
Christopher Wild (2005)
Rappaport and Smith (2010)

Step 1:
Expanding measurement of the external exposome



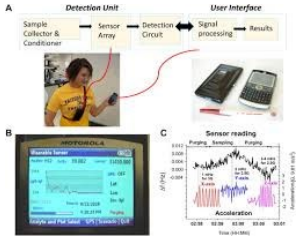
Wearable sensors

Google Maps: GIS layers
Organized by Geographical Positioning



Smartphones & smartwatches

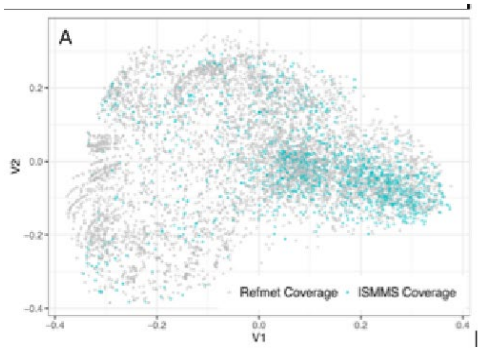
Networked monitors & remote sensing



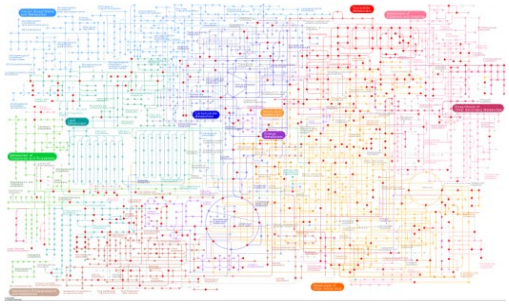
Next Step 2: Untargeted measures using omics

To understand the complexity of the human exposome, we must adopt **analytical strategies and study designs** that incorporate **untargeted measures of exposure**

Exposomics scan

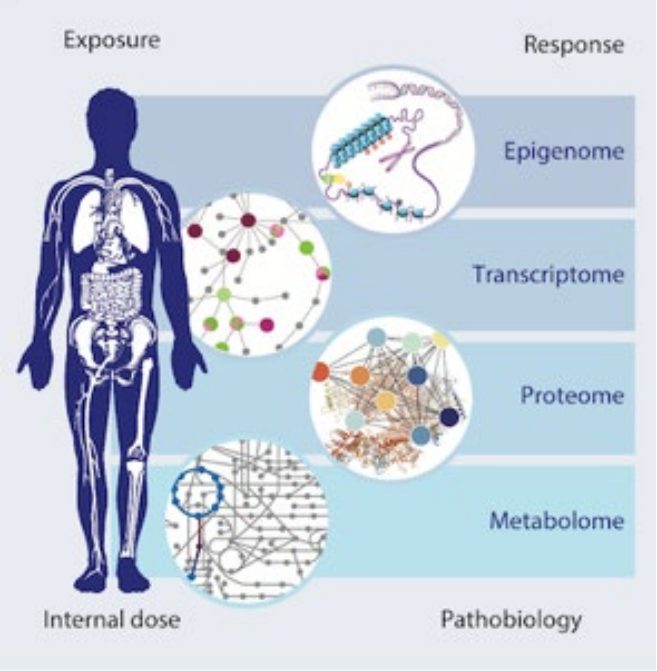


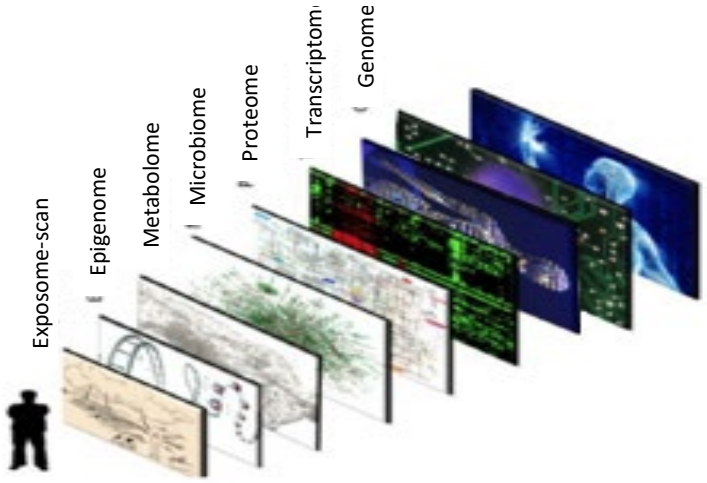
Metabolomics scan



Next Step 3:

To understand the complexity of the internal exposome, we must adopt **analytical strategies and study designs** that incorporate **integrated omics approaches** to understanding biological response





Biological response to environmental exposures

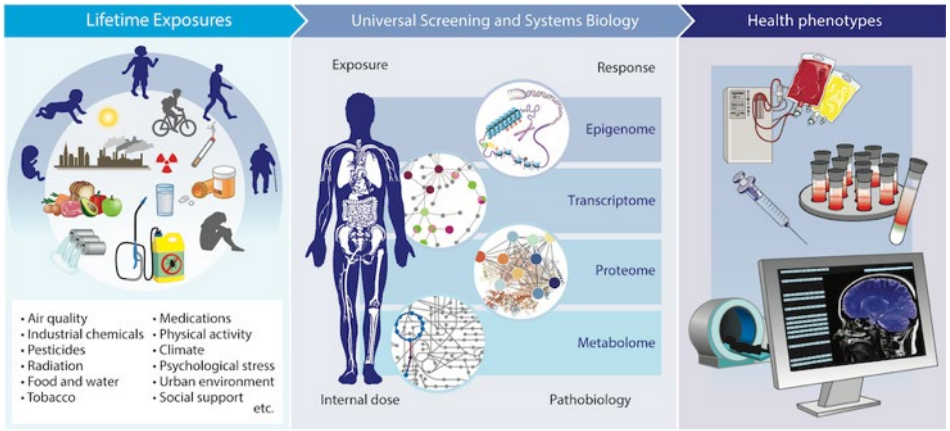
How do we incorporate exposomics into translational science?

Expand analytic approaches to include network and systems modeling!!!

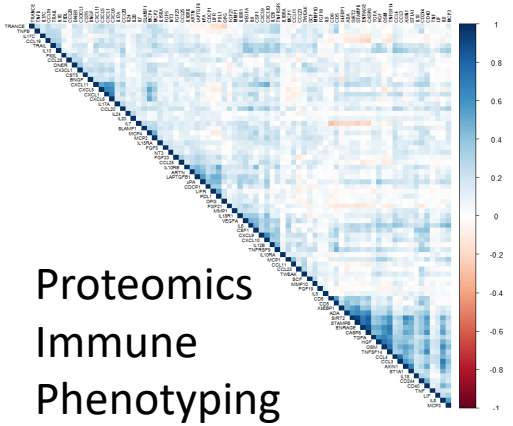
Exposure

Biological Response

Disease

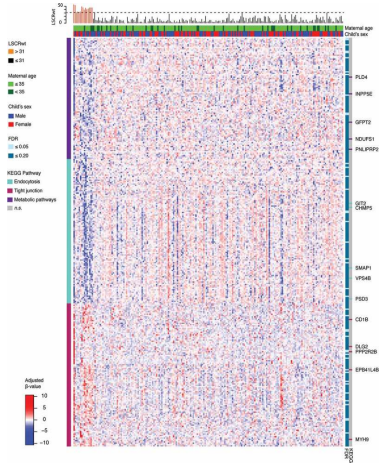


Niedzwiecki MM, Walker DI, et al.
The Exposome : Molecules to Populations
Annual Reviews of Pharm and Tox, 2019

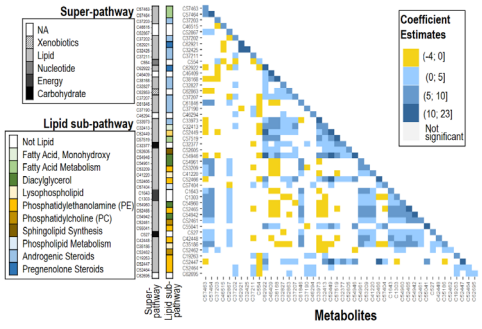


Proteomics
Immune
Phenotyping

Epigenetics

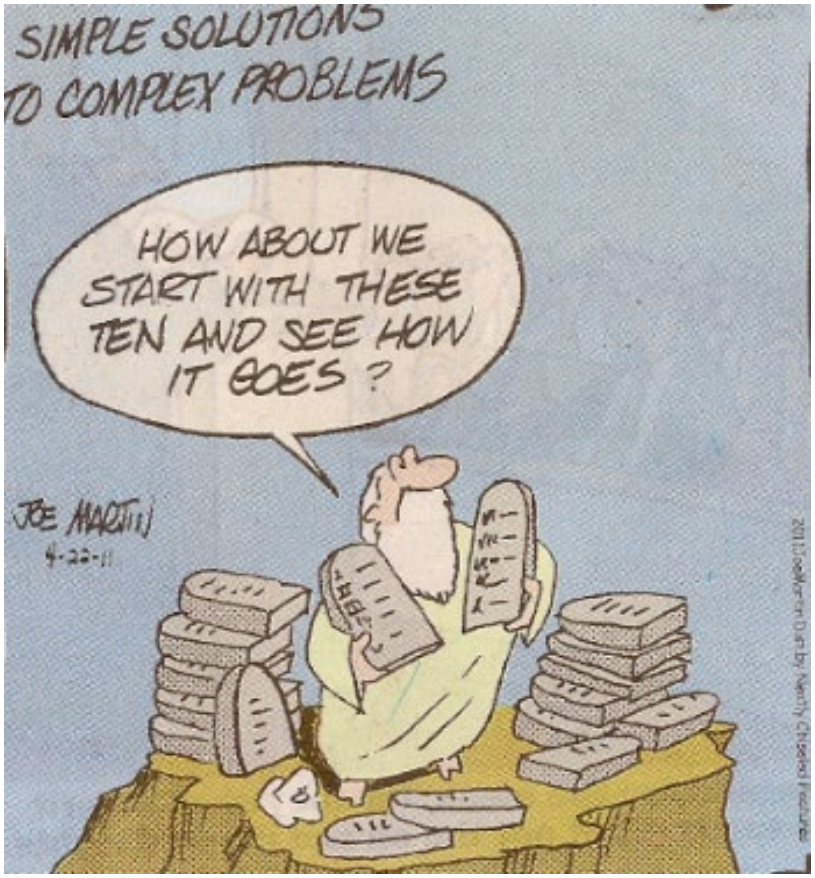


Metabolomics

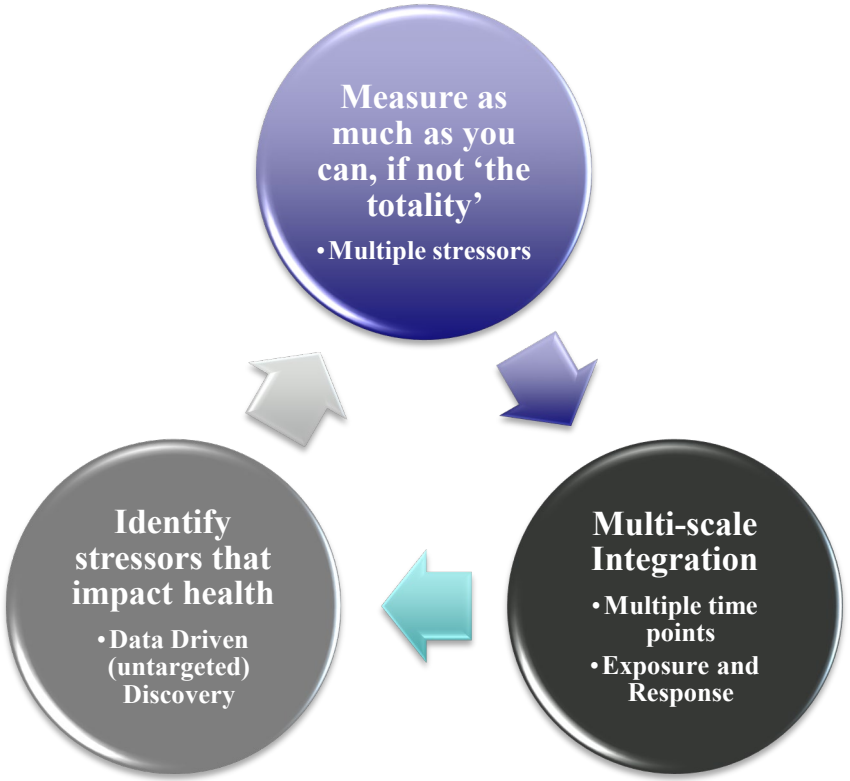


Brunst KJ, et al., *Epigenetics* 2018
Cowell W, et al., *Stress* 2020
Colicino E, et al., *Environ Res* 2020

How to measure the exposome?



Rappaport and Smith (2010)



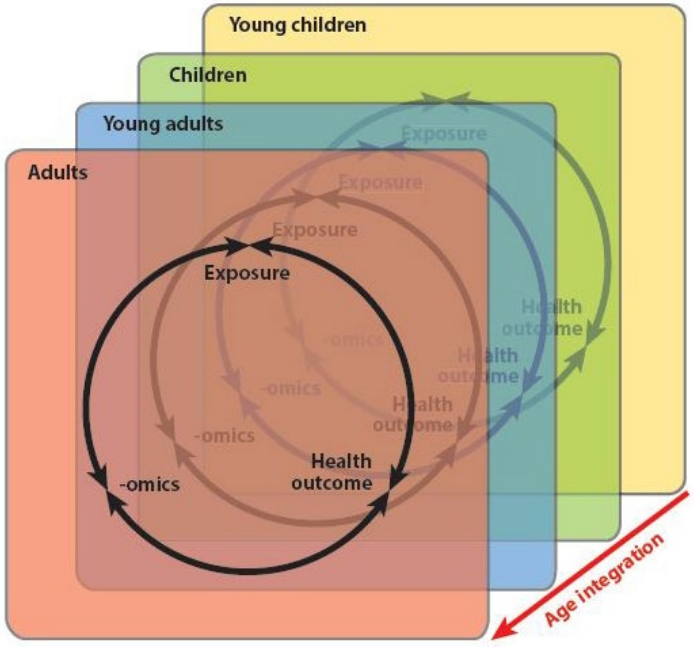
Do <u>not</u> need to measure it all to make significant progress!

Looking ahead…..

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

Frederick Douglas

Integrating Data Across Individual Cohort Studies to Advance Life Course Research



Stingone et al., Ann Rev Public Health, 2017

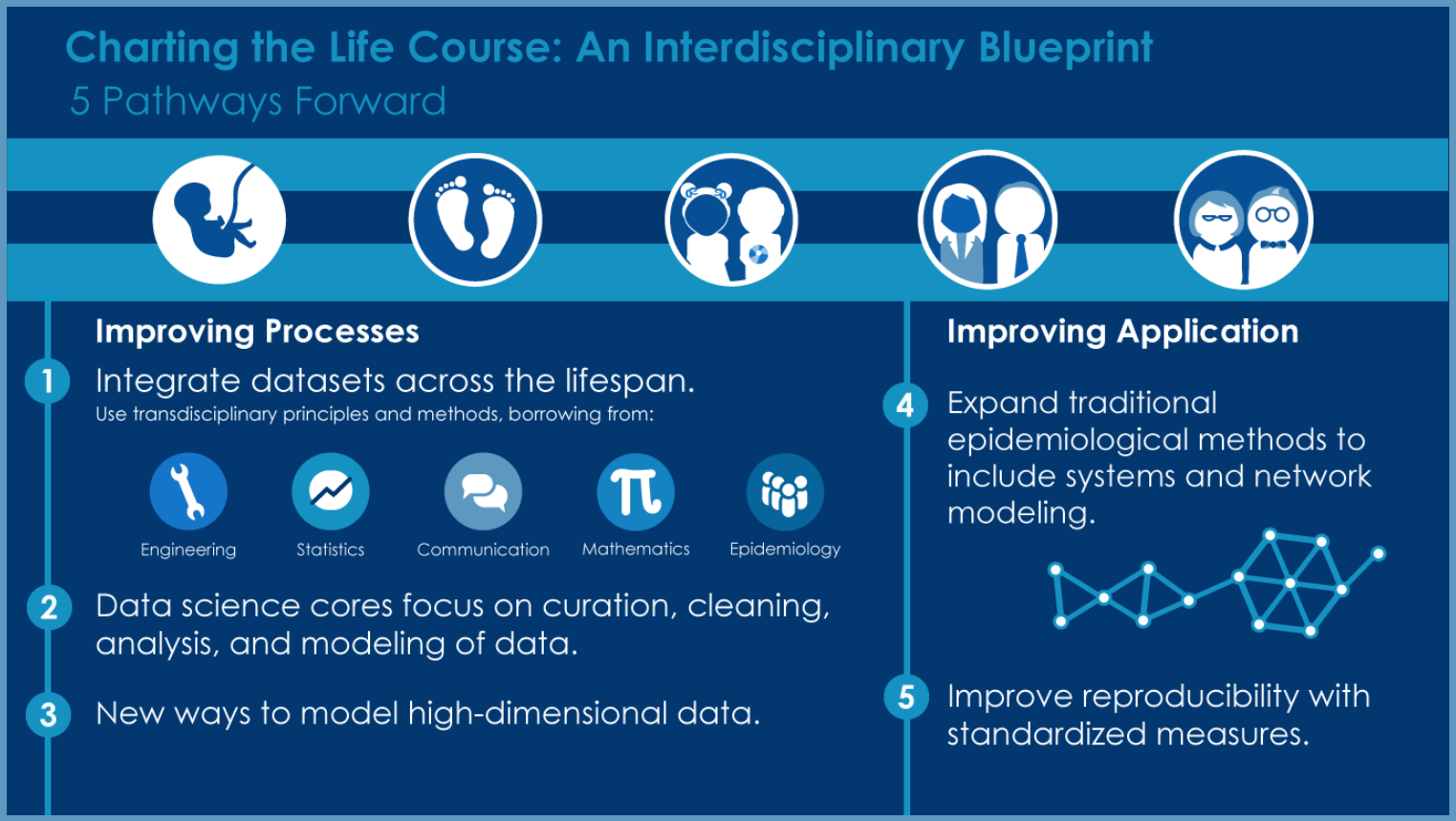
ECHO

Environmental influences on Child Health Outcomes

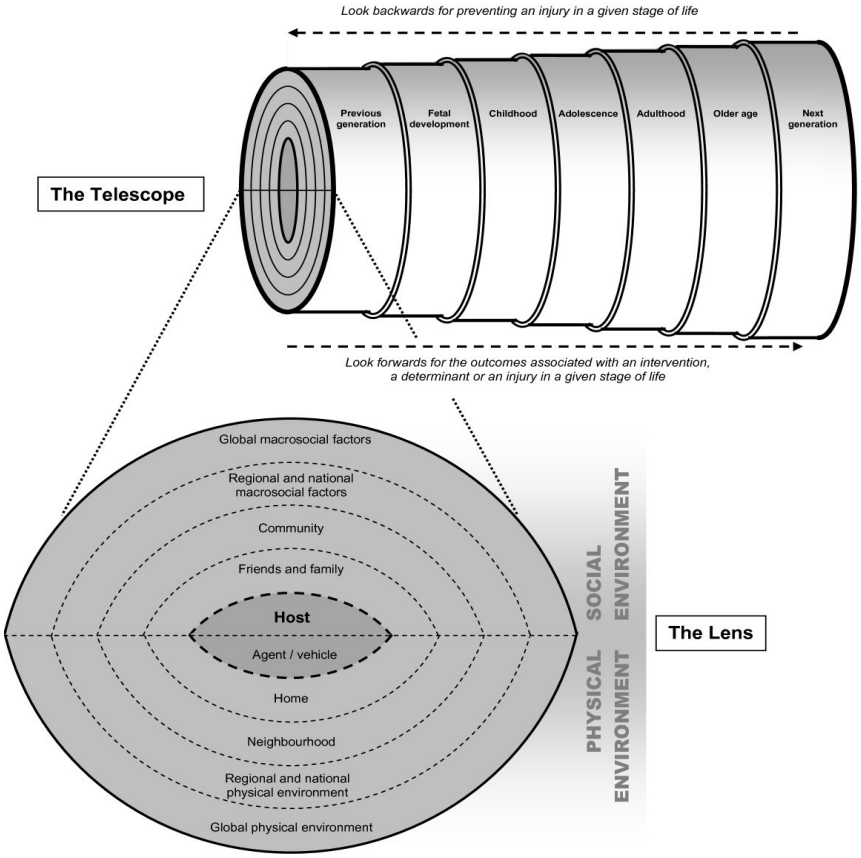
A program supported by the NIH

Merging data across different cohorts focused on specific life stages is one approach to mimic the life-course and explore changes in the exposome over time.

Creating educational materials: Integrating exposomics into translational science



Lifespan Enterprise Committee



Evolving towards an exposomic framework