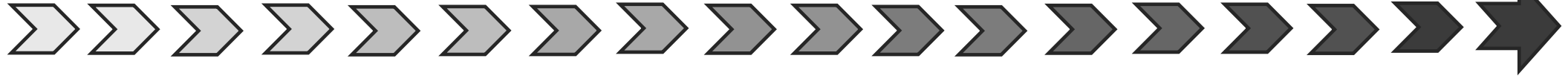# BIOMARKERS OF STRESS
…..are we there yet?

SIREN 2019
NEETA THAKUR, MD MPH
Neeta.Thakur@ucsf.edu
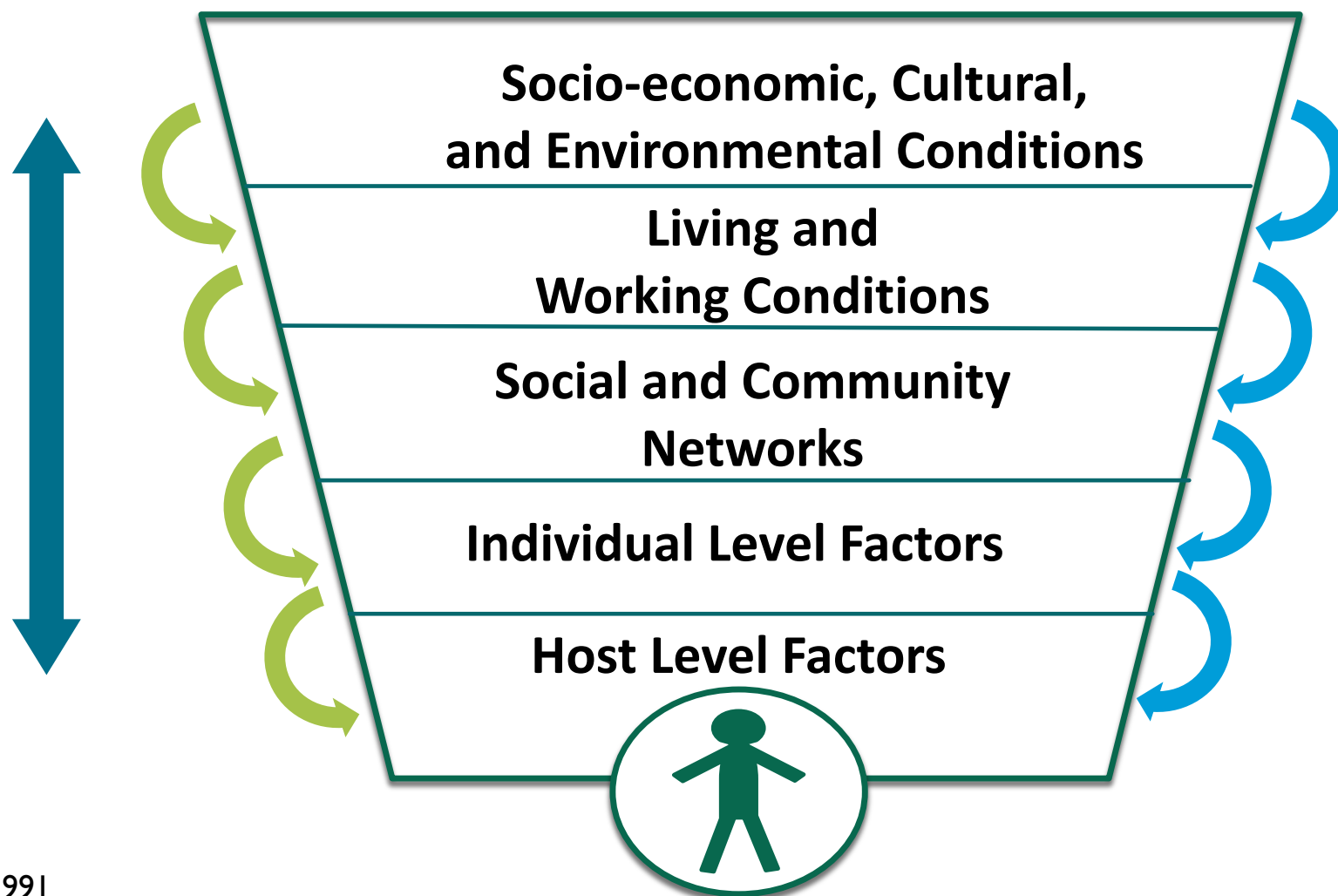
Time

Socioeconomic Status

Where you live
Type of work
Access

SOCIO-ECOLOGICAL MODEL OF HEALTH

Socio-economic, Cultural,
and Environmental Conditions

Living and
Working Conditions

Social and Community
Networks

Individual Level Factors

Host Level Factors

Dahlgren and Whitehead 1991

Number of Stressors for Poor vs. NonPoor Children
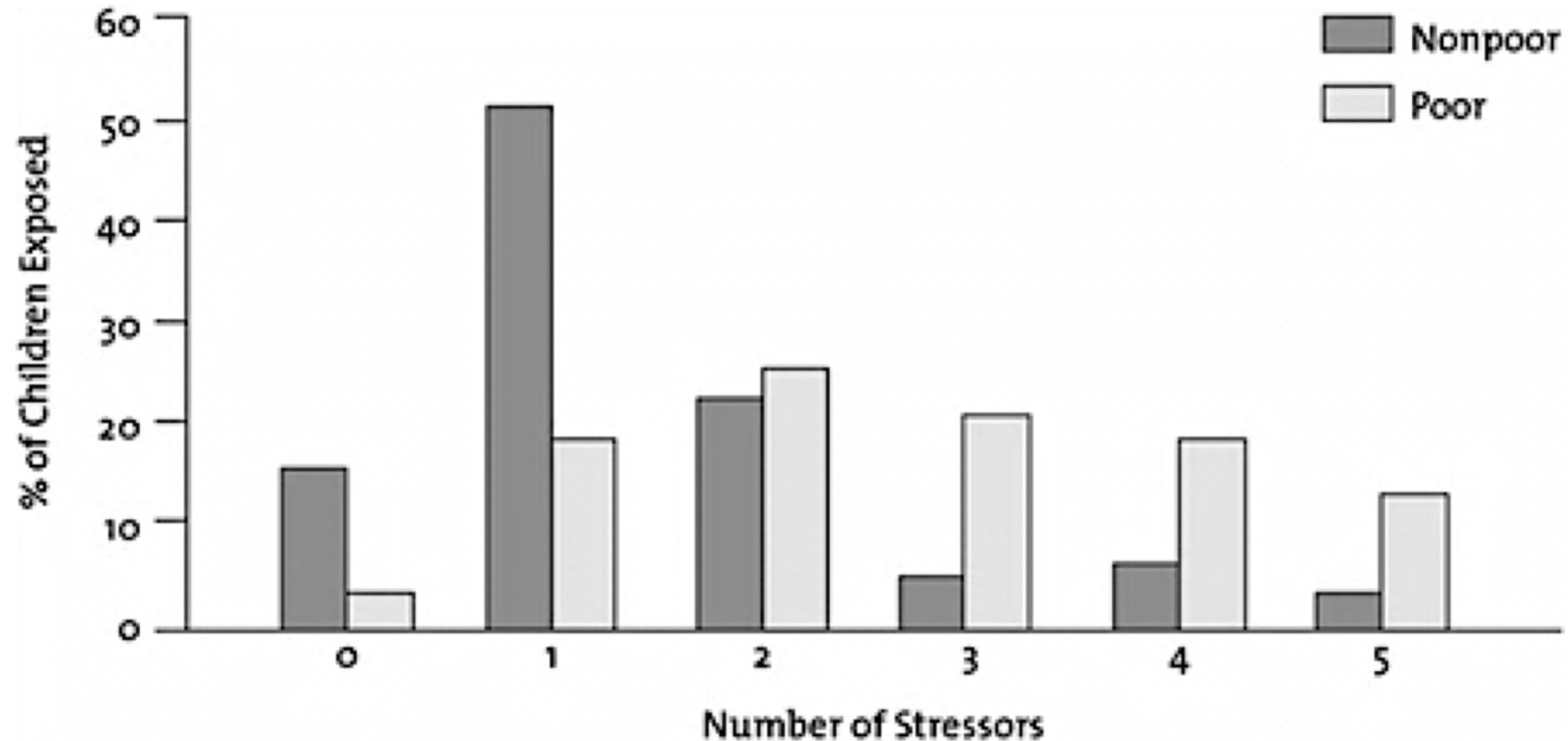
LONG TERM EFFECTS OF SOCIAL AND ENVIRONMENTAL STRESS

Socio-economic, Cultural, and Environmental Conditions

Living and Working Conditions

Social and Community Networks

Individual Level Factors

Host Level Factors

Cumulative Effects Over Time

Biology-Environment Interactions

Physiological Adaptation and/ or Disruption

Disease Risk

DISEASE Susceptibility and Morbidity
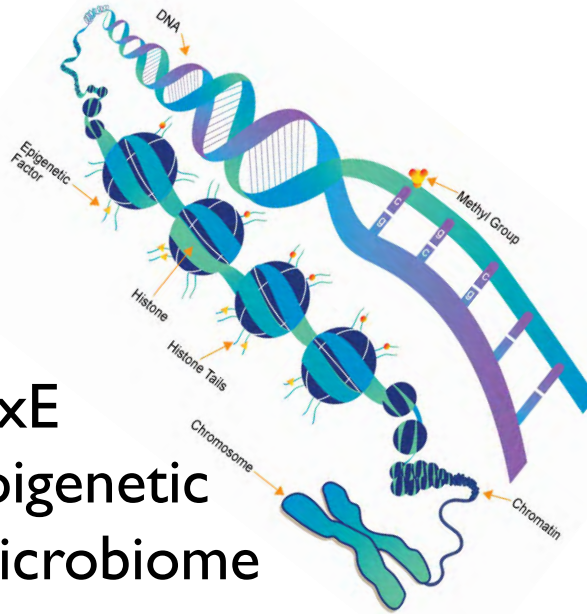
Biological Embedding
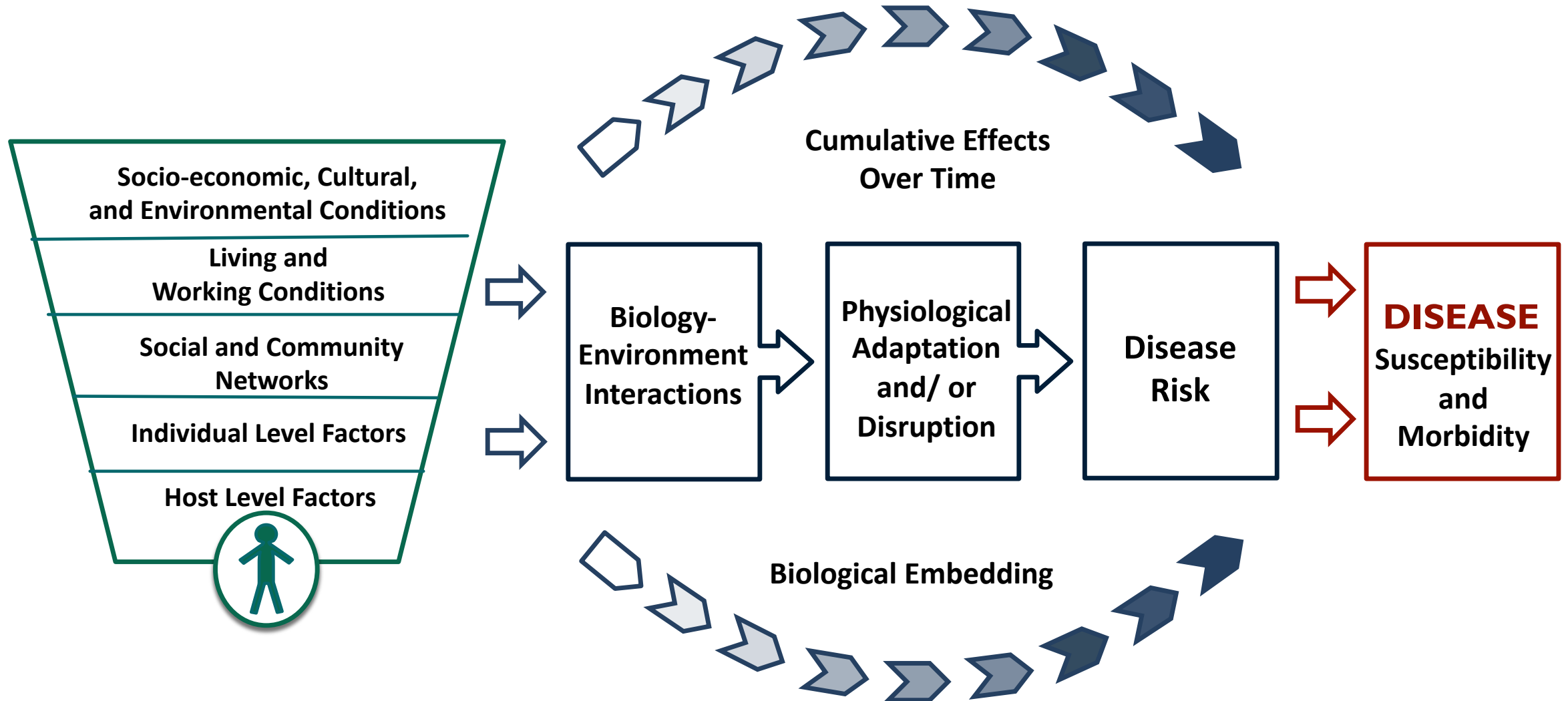
TYPES OF BIOLOGICAL RESPONSE

Neuro-hormonal and Inflammatory

Allostatic Load

Genetic

GxE
Epigenetic
Microbiome

Neuroplasticity

Poverty Shrinks Brain Networks

STRESS → NTs

Hypothalamus

CRH

AVP

Activation
Simpatho-
Adrenal axis

Pituitary

ACTH

Cortex

Medulla

Adrenal

Glucocorticoids

Catecholamines
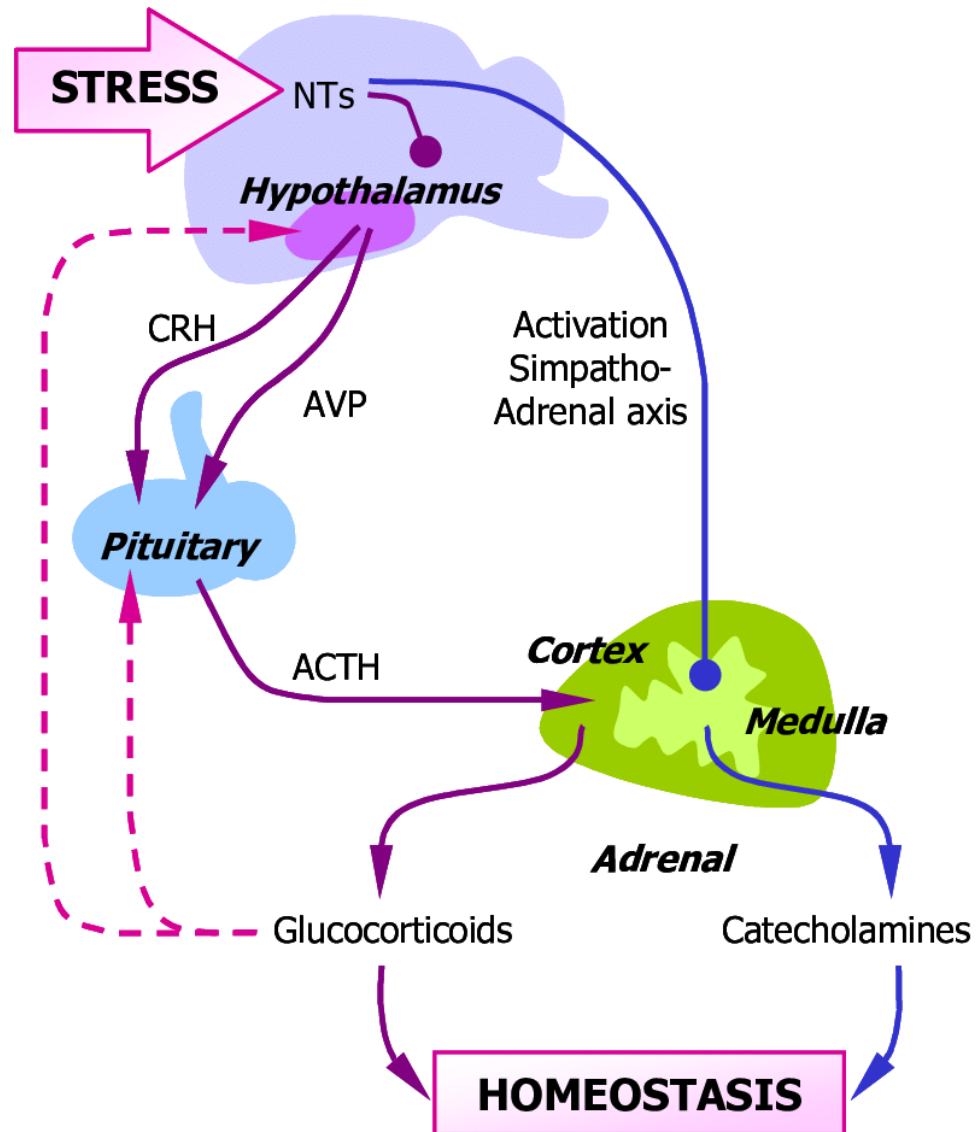
HOMEOSTASIS
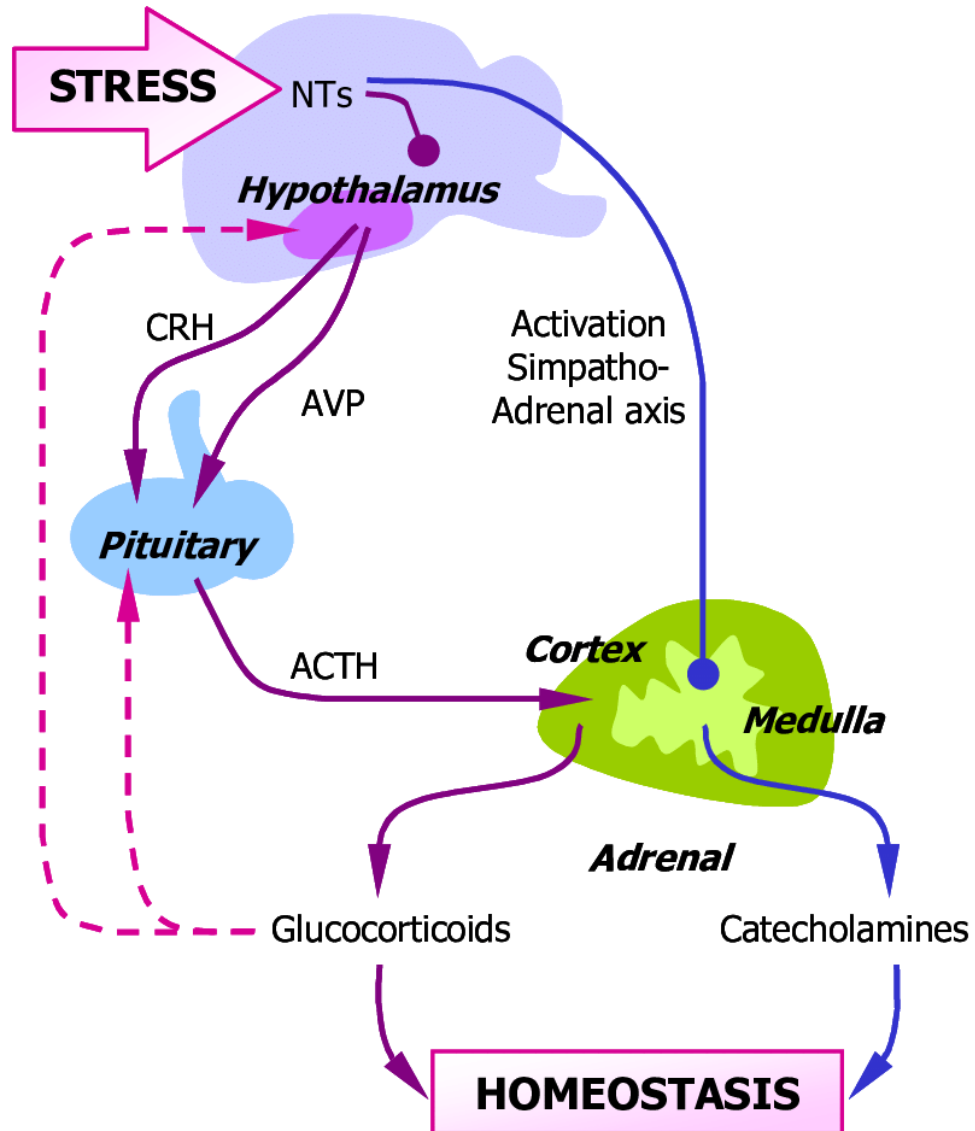
Primary Outcome
"Fight or Flight Response"
- Catecholamines
- HPA (cortisol)

Secondary Outcome
- Tissue/Organ specific
- e.g. blood pressure, lipid metabolism, and inflammation

Adapted from Matteri, Carroll & Dyer, 2000

ALLOSTATIC LOAD

STRESS → NTs

Hypothalamus

CRH

AVP

Activation Simpatho-Adrenal axis

Pituitary

ACTH

Cortex

Medulla

Adrenal

Glucocorticoids

Catecholamines

HOMEOSTASIS

Cumulative Effect over time leads to new set point.

↑ Allostasis

↓ Homeostatic recovery

New (altered) set point

Allostatic load

Set point for homeostasis

Stress stimuli

Chronically repeated stress stimuli

Time

Adapted from Matteri, Carroll & Dyer, 2000
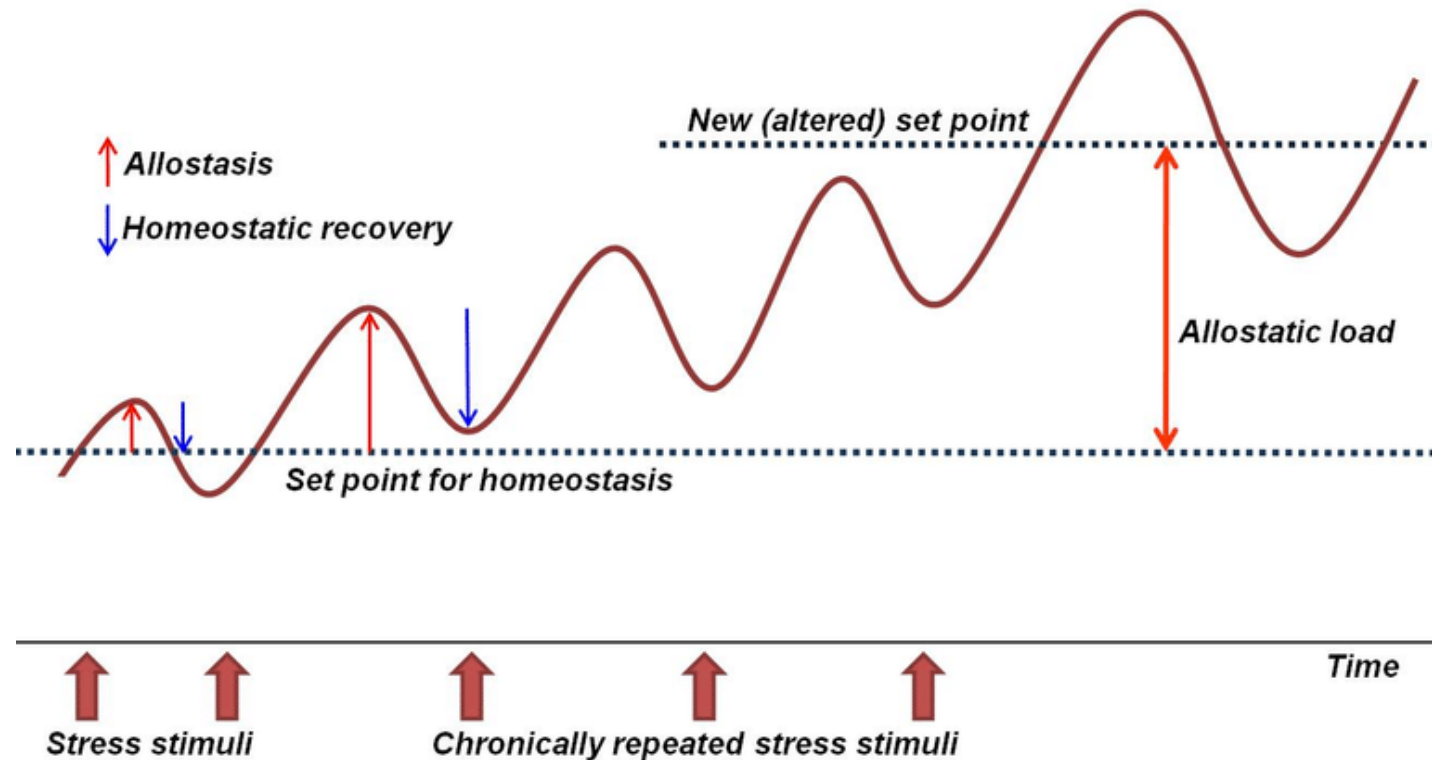
ALLOSTATIC LOAD AND SOCIOECONOMIC STATUS

Cardiovascular

Metabolic

Immune Response

HPA Axis

Respiratory

Parasympathetic Nervous System

+ Kidney/Liver Function

Allostatic Load Index

Gustafsson J Epidemiology Health 2011, Johnson Social Science & Medicine 2017
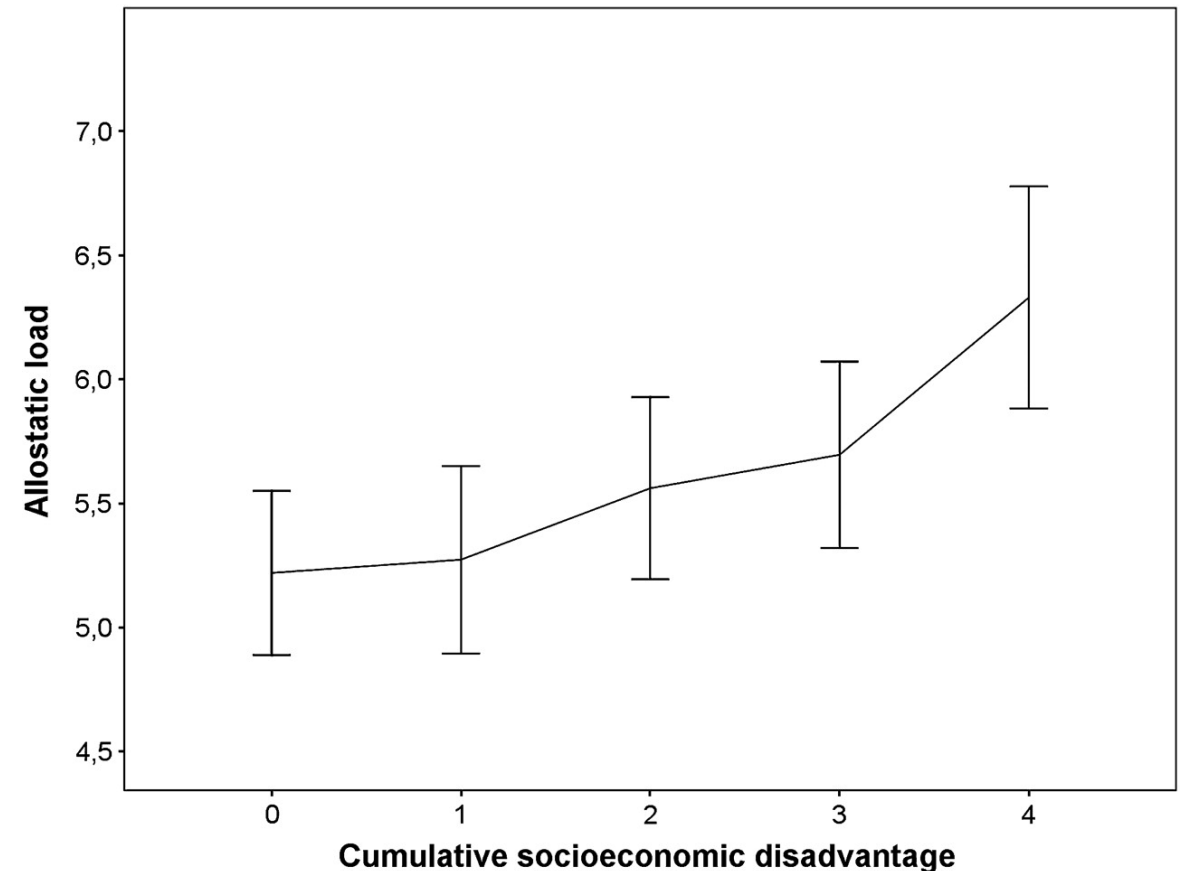
ALLOSTATIC LOAD

Candidate Stress-Related Biomarkers

Cardiovascular   <u>Physiologic</u>: **Blood pressure**, heart rate, ankle-brachial index

<u>Biomarker</u>: Myeloperoxidase, endothelin-1, VEGF-A

Metabolic   <u>Physiologic</u>: **Waist-hip circumference/BMI**

<u>Biomarker</u>: **Lipids**, **HA1C**, insulin, leptin

Immune System   <u>Biomarker</u>: **CRP**, fibrinogen, cytokines (IL-6, TNF-a), white count

HPA Axis   <u>Biomarker</u>: *hair cortisol*, DHEA-S, epinephrine, norepinephrine

Respiratory   <u>Physiologic</u>: Spirometry, bronchodilator response

Parasympathetic Nervous System   <u>Physiologic</u>: Heart beat variation

Kidney/Liver Function   <u>Biomarker</u>: Creatinine
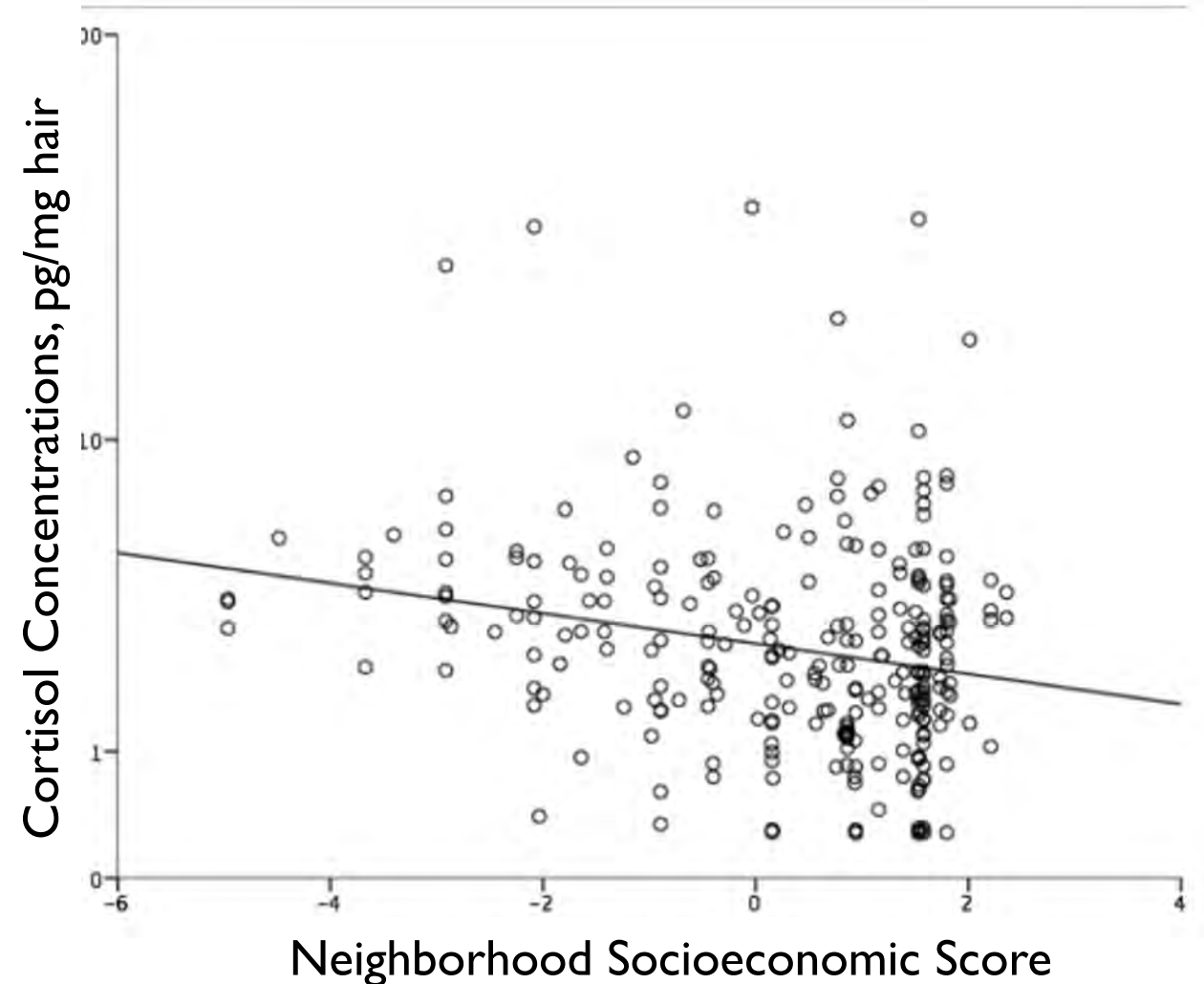
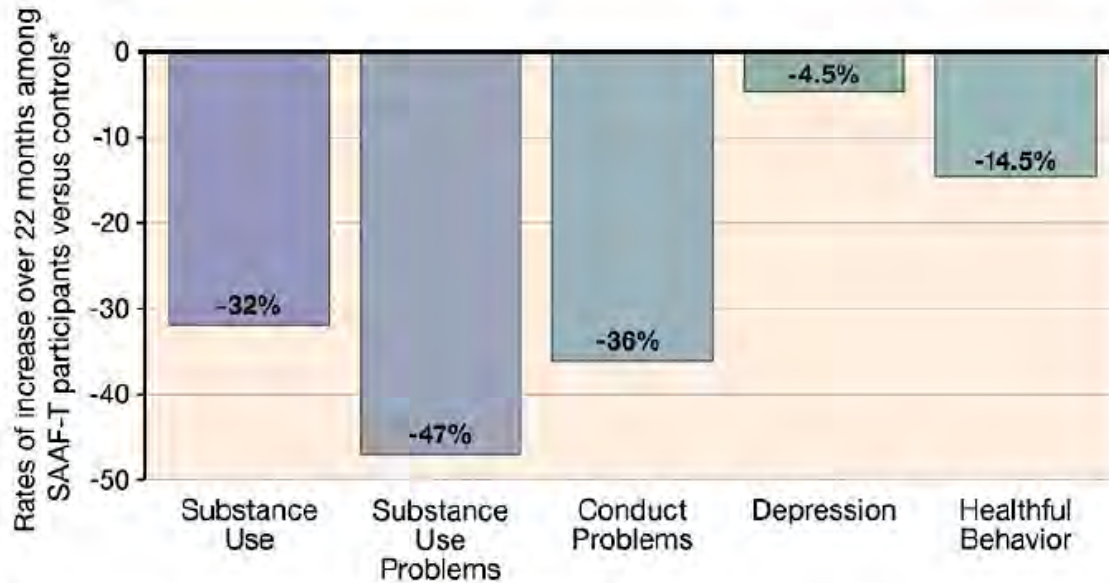# CORTISOL REGULATION

Hair Cortisol consistently associated with low SES

Change in levels seen with interventions targeted at:

- Intense parenting interventions
- Nutrition focused
- Time frame: Months

Vliegenthart Psychoneuroendocrinology 2016

STRONG AFRICAN AMERICAN FAMILY

Fig. 1. Youth whose families participated in SAAF had less inflammation than did controls. The endpoint is a composite indicator of inflammation, formed by summing each subject's z-scored values for interleukins-1β, 6, 8, and 10, plus tumor necrosis factor-α and IFN-γ. Dots represent individual data points. Within each group, the wide horizontal bar is the mean composite score, and the error bars reflect 95% confidence intervals.

*The control intervention was a family-based intervention that was designed to encourage healthful behaviors such as good nutrition and exercise.
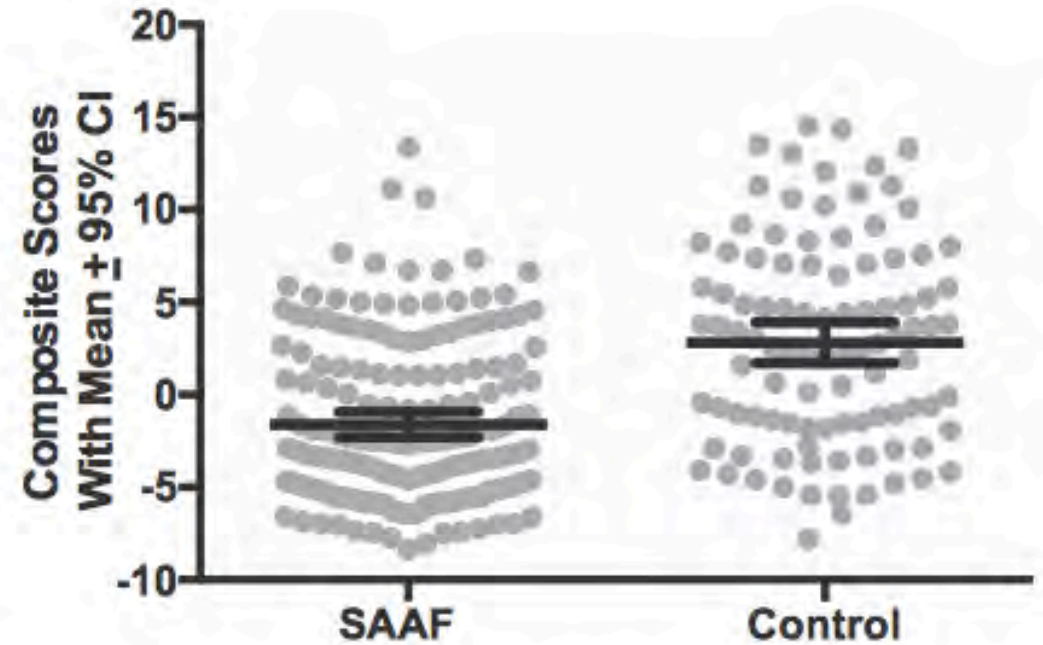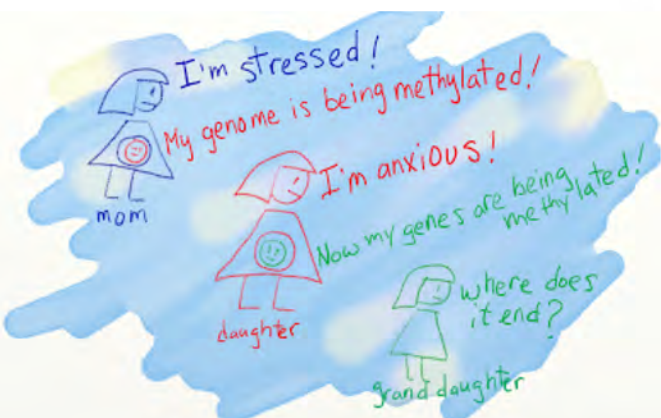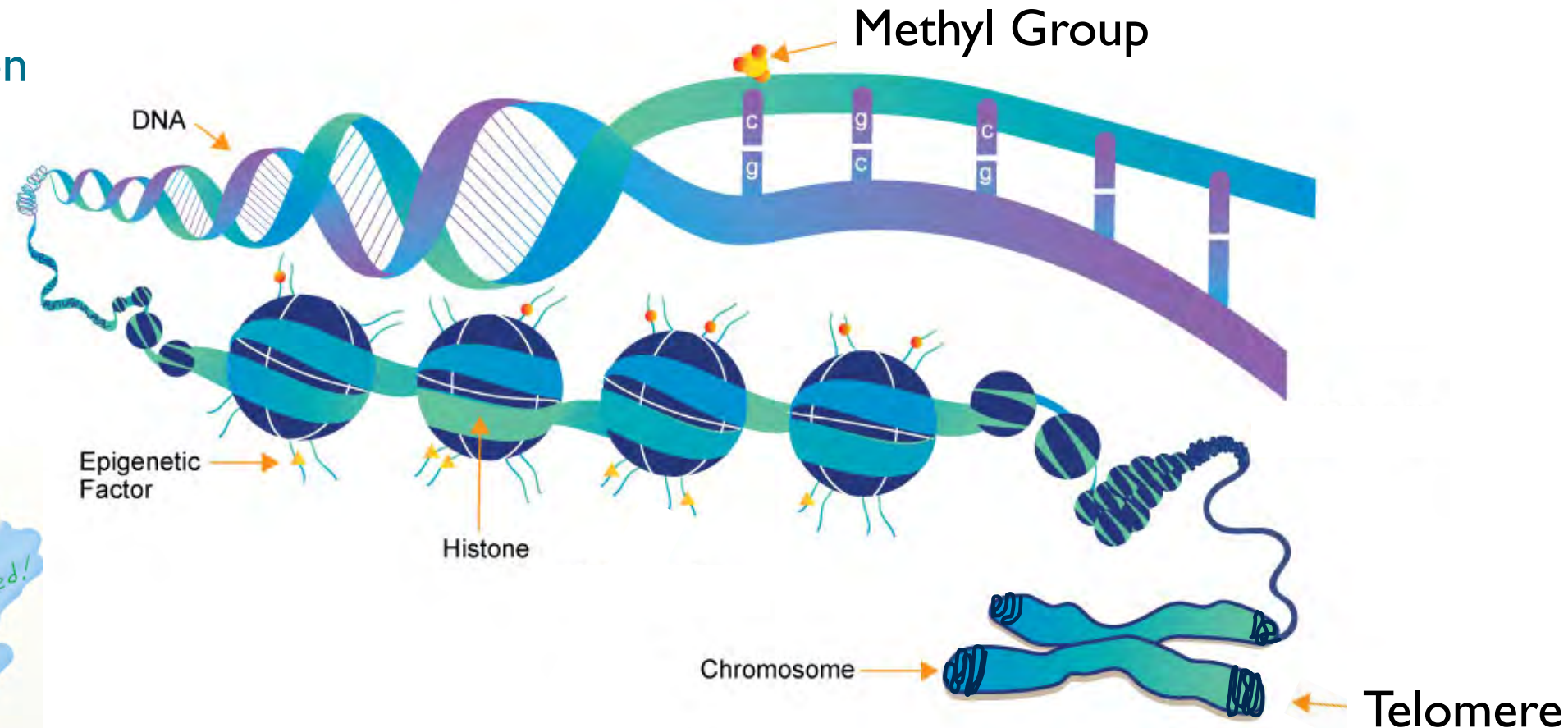
Brody Pediatrics 2012, Miller PNAS 2014

Not ready for PRIME time

GENETICS: EPIGENETIC CHANGES

- Telomere Length

- DNA Methylation

TELOMERE LENGTH

Author, Year (Reference No.)	Age Range, years	Sample Size (n)	Higher SES: Shorter TL	Higher SES: Longer TL	SMD (95% CI)
Houben, 2011 (42)	73–91	192			0.035 (−0.316, 0.387)
Steptoe, 2011 (52)	53–76	221			0.350 (0.009, 0.691)
Zheng, 2010 (34)—RPCI	43–69	328			−0.173 (−0.421, 0.076)
Honig, 2006 (40)	66–103	257			−0.018 (−0.265, 0.228)
Lee, 2011 (44)	18–90	257			0.203 (−0.042, 0.448)
Hou, 2009 (41)	21–79	272			0.250 (0.009, 0.491)
Mather, 2010 (45)—≥60	64–70	295			0.071 (−0.158, 0.299)
Nordfjall, 2009 (48)	25–74	310			0.150 (−0.074, 0.373)
Kananen, 2010 (43)	30–87	471			0.092 (−0.127, 0.310)
Mather, 2010 (45)—≥40	44–49	350			0.057 (−0.153, 0.266)
Shiels, 2011 (51)	35–64	382			0.102 (−0.099, 0.302)
Risques, 2010 (23)	65–69	615			0.143 (−0.032, 0.318)
Mirabello, 2009 (46)	55–74	760			0.097 (−0.046, 0.240)
Harris, 2010 (22)	68–70	1,048			−0.090 (−0.213, 0.032)
Chan, 2010 (35)	>64	2,566			0.005 (−0.073, 0.083)
Overall ($Q = 19.4$, $I^2 = 28.0\%$, $P = 0.149$)					0.060 (0.002, 0.118)

−0.50   0.00   0.50   1.00

Strong evidence with perceived stress….
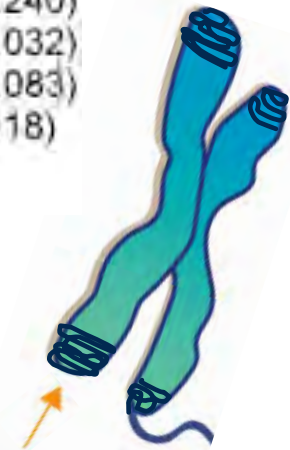
Telomere

TELOMERE LENGTH

Author, Year (Reference No.)	Age Range, years	Sample Size (n)	Higher SES: Shorter TL — Higher SES: Longer TL	SMD (95% CI)
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Overall ($Q = 19.4$, $I^2 = 28.0\%$, $P = 0.149$)				0.060 (0.002, 0.118)

−0.50   0.00   0.50   1.00

Building evidence with education, less evidence with other measures of socioeconomic status

Telomere

Robertson Epidemiologic Reviews 2012
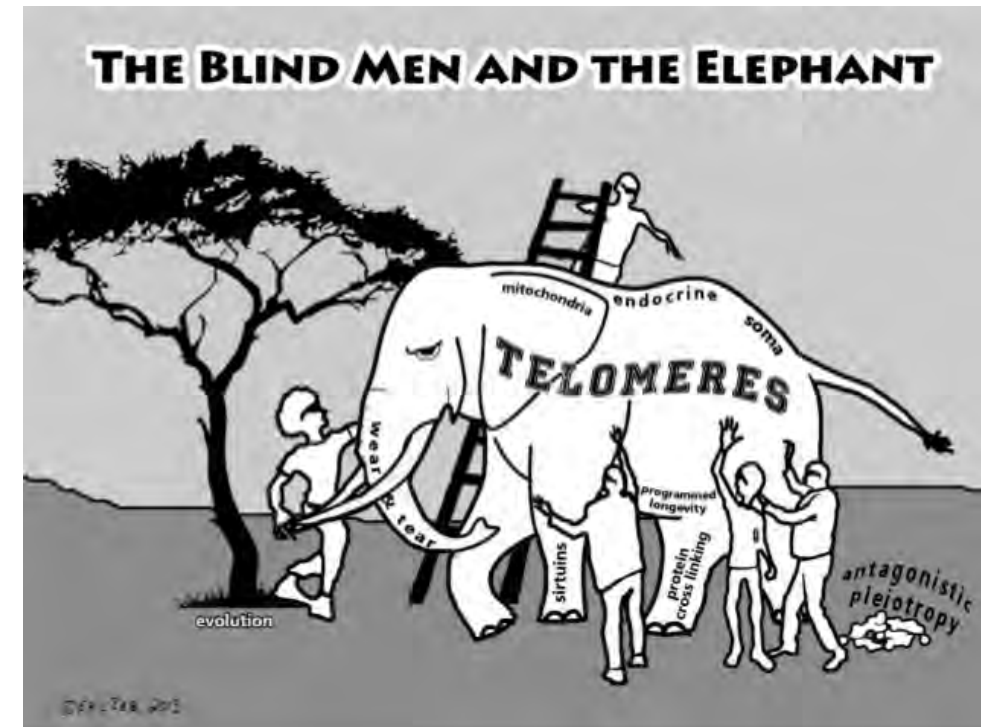
TELOMERE LENGTH AND INTERVENTION
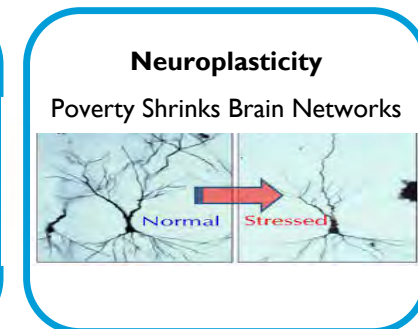
Change seen with interventions targeted at 'stress'
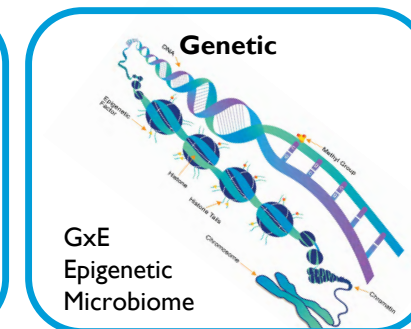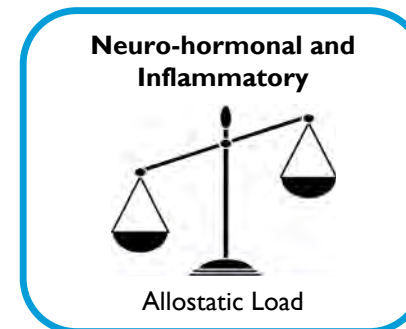
- Meditation
- Exercise
- Lifestyle change
- Timeframe: months to 1 year

Difficult to extrapolate

THE BLIND MEN AND THE ELEPHANT

TAKE HOME

- ## Biomarkers are helpful at establishing baseline effects
  - Candidate biomarkers: Allostatic Load, Hair Cortisol, Telomere Length

- ## More Research Needed
  - Do biomarkers change with intervention?
  - Does the change in biomarkers equate change in the health outcome of interest?

Neuro-hormonal and Inflammatory

Allostatic Load

Genetic

GxE
Epigenetic
Microbiome

Neuroplasticity

Poverty Shrinks Brain Networks

Normal   Stressed

TAKE HOME

Lasting thought:

- Can biomarkers be used to identify individuals at high risk for poor outcomes?

- If elevated at baseline, would these individuals benefit the most from intervention?

  - Help with allocating resources in low-resource settings

  - Help reduce negative studies

Neuro-hormonal and Inflammatory

Allostatic Load

Genetic

GxE
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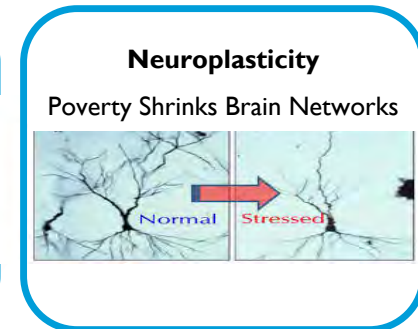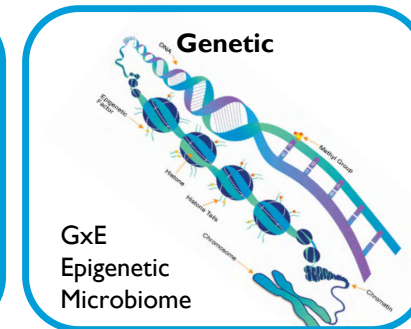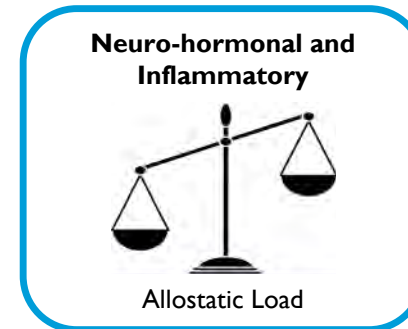
QUESTIONS?

EXTRA SLIDES

Positive stress
Brief increases in heart rate
Mild elevations in stress hormones

Tolerable stress
Serious, *temporary* stress responses
Buffered by supportive relationships

Toxic stress
Prolonged stress response activation
Absence of protective relationships

J Shonkoff Harvard University Center on the Developing Child

Stressors
Trauma, Access, Demographics

Violence, Neighborhood deprivation, Air pollution

Nature of stressor

Positive stress
Brief increases in heart rate
Mild elevations in stress hormones

Tolerable stress
Serious, *temporary* stress responses
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Stressors
Trauma, Access, Demographics

Violence, Neighborhood deprivation, Air pollution

Individual Characteristics
Sex, genes, development, experience, behavior

Nature of stressor

How stressor is perceived

Ability to cope

Positive stress
Brief increases in heart rate
Mild elevations in stress hormones

Tolerable stress
Serious, *temporary* stress responses
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J Shonkoff Harvard University Center on the Developing Child

Stressors
Trauma, Access, Demographics

Violence, Neighborhood deprivation, Air pollution

Individual Characteristics
Sex, genes, development, experience, behavior

Biologic Response
Neuro-endocrine and humoral response, epigenetics, GxE interaction, microbiome

Nature of stressor

How stressor is perceived

Ability to cope

Physiologic response

Positive stress
Brief increases in heart rate
Mild elevations in stress hormones

Tolerable stress
Serious, *temporary* stress responses
Buffered by supportive relationships

Toxic stress
Prolonged stress response activation
Absence of protective relationships

J Shonkoff Harvard University Center on the Developing Child