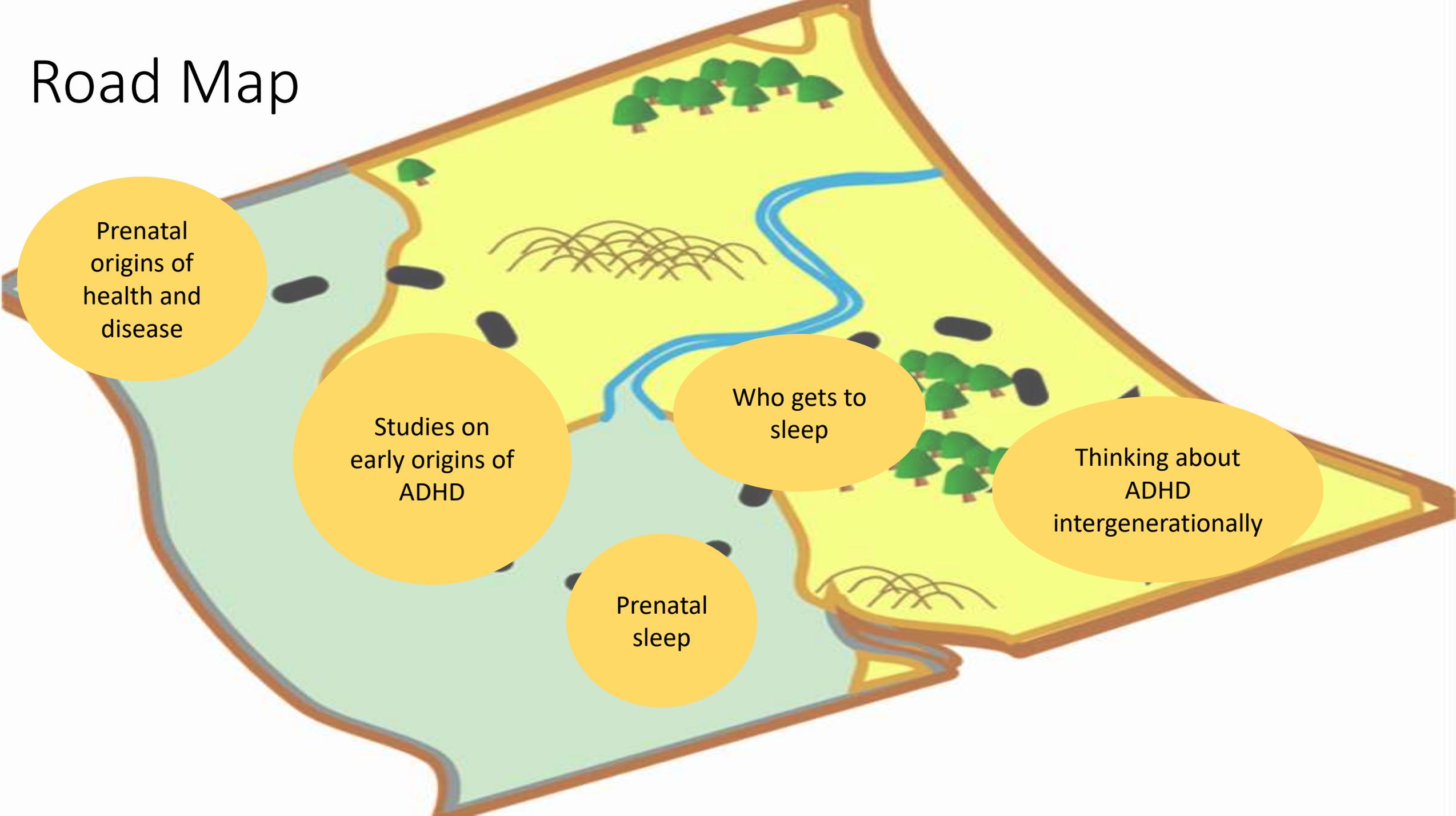


Prenatal Exposures and Experiences: Impact on Children's Early Brain Development and Risk for Disease

Claudia Lugo-Candelas, PhD
Estelle Bender-Fishbein Scholar in Child and Adolescent Psychiatry
Assistant Professor of Clinical Medical Psychology (in Psychiatry)
Columbia University Medical Center/New York State Psychiatric Institute

Road Map



Prenatal
origins of
health and
disease

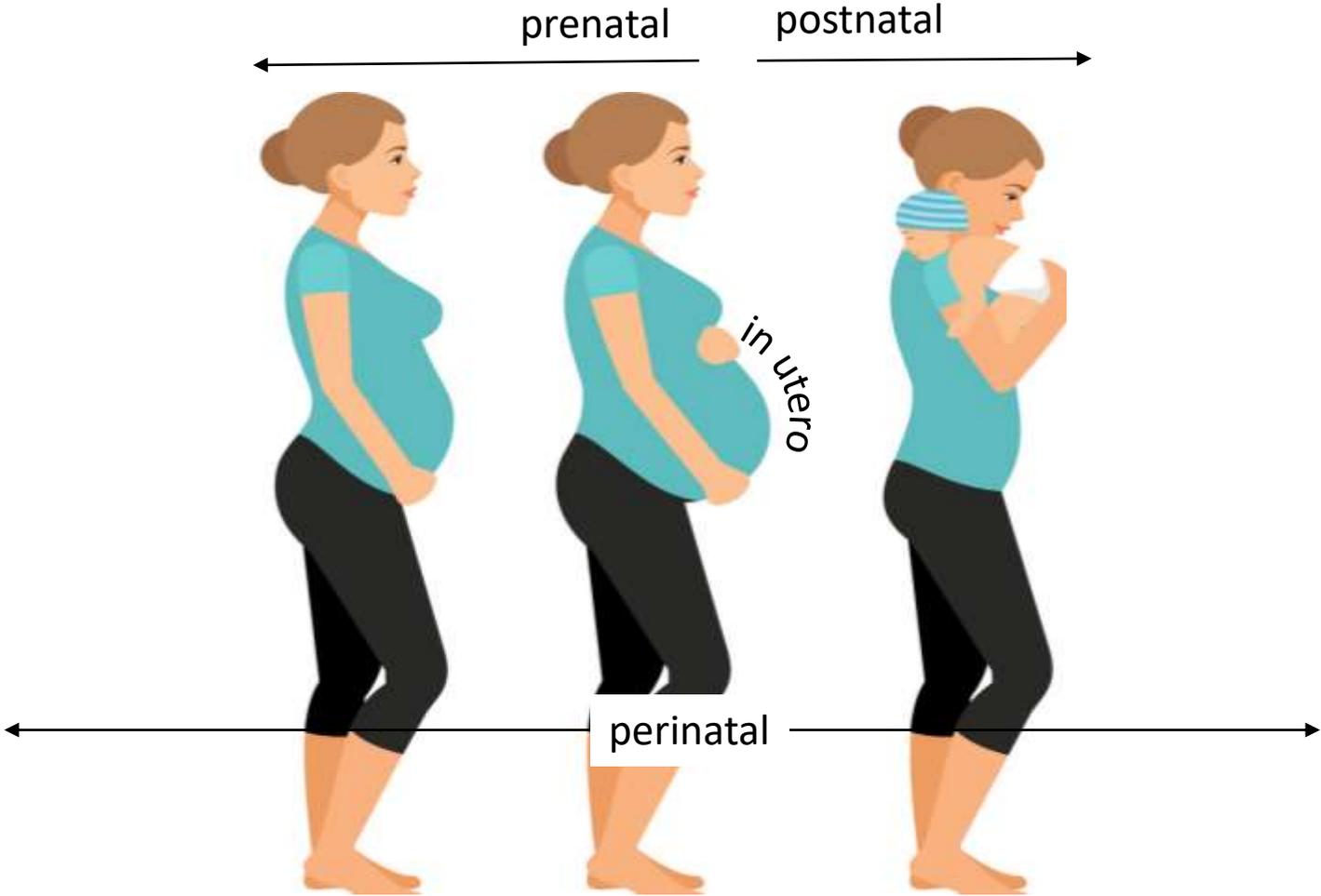
Studies on
early origins of
ADHD

Who gets to
sleep

Prenatal
sleep

Thinking about
ADHD
intergenerationally

Terms



TIME



How the first nine months shape the rest of your life

The new science of fetal origins

BY ANNIE MURPHY PAUL

Barker hypotheses

- development begins *before* birth
 - prenatal exposures and experiences may impact the early development of organs and tissues, in ways that carry on into adulthood

Dutch Hunger Winter Study

- In the winter & spring of 1944 the German occupation limited rations in the western region of the Netherlands.
 - 400–800 calories per day
- babies born underweight
- elevated rates of obesity & cardiovascular disease as adults
- inappropriate adaptation to undernourishment in pregnancy
 - not prepared for a postnatal environment with abundant food

beyond physical health

Exposure

Pathways & Processes

Adaptations/Outcomes

MOTHER



Psychological distress

Intrapersonal:
Emotion dysregulation

Interpersonal
Early adversity
Adverse life events

Socio/environmental
Low SES
Discrimination
Natural disasters and war

Health related Behaviors

Lower nutrient intake
Higher nutrient intake
Diabetes
Sleep disruption
Reduced physical activity

Birth outcomes

Reduced gestational age
Lower birth weight

Postnatal exposure

Shared environment
Maternal-infant interaction

FETUS

Neurobehavioral indices

Higher heart rate reactivity
Lower heart rate variability
Lower coupling

CHILD

Behavior

Attention difficulties
Socio-emotional problems
Aggressive behaviors

Child Psychopathology

ADHD
Anxiety
Depression
Autism
Schizophrenia



RISK ≠ disorder

Mechanisms

MOTHER

Physiological Adaptation

HPA axis activation
Immune activation
Microbiome dysregulation

PLACENTA

Epigenetic effects

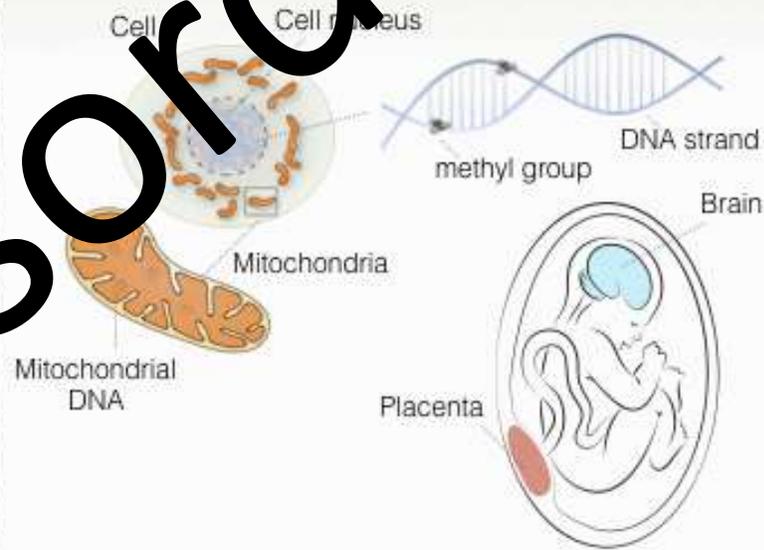
DNA methylation changes of glucocorticoids related genes FKBP5 HSD11β2, NR3C1

Altered gene expression
↓ barrier to glucocorticoids
↑ glucocorticoids passage and fetus exposure

Mitochondria dysfunction

Changes in mitochondria DNA copy number and mitochondrial DNA gene expression
↓ Energy producing capacity

Cellular dysfunction: reduction oxygen, nutrients and waste transport by the placenta



FETUS

Brain programming

Larger amygdala volume
Increased amygdala connectivity to other regions
Cortical thinning

ADHD

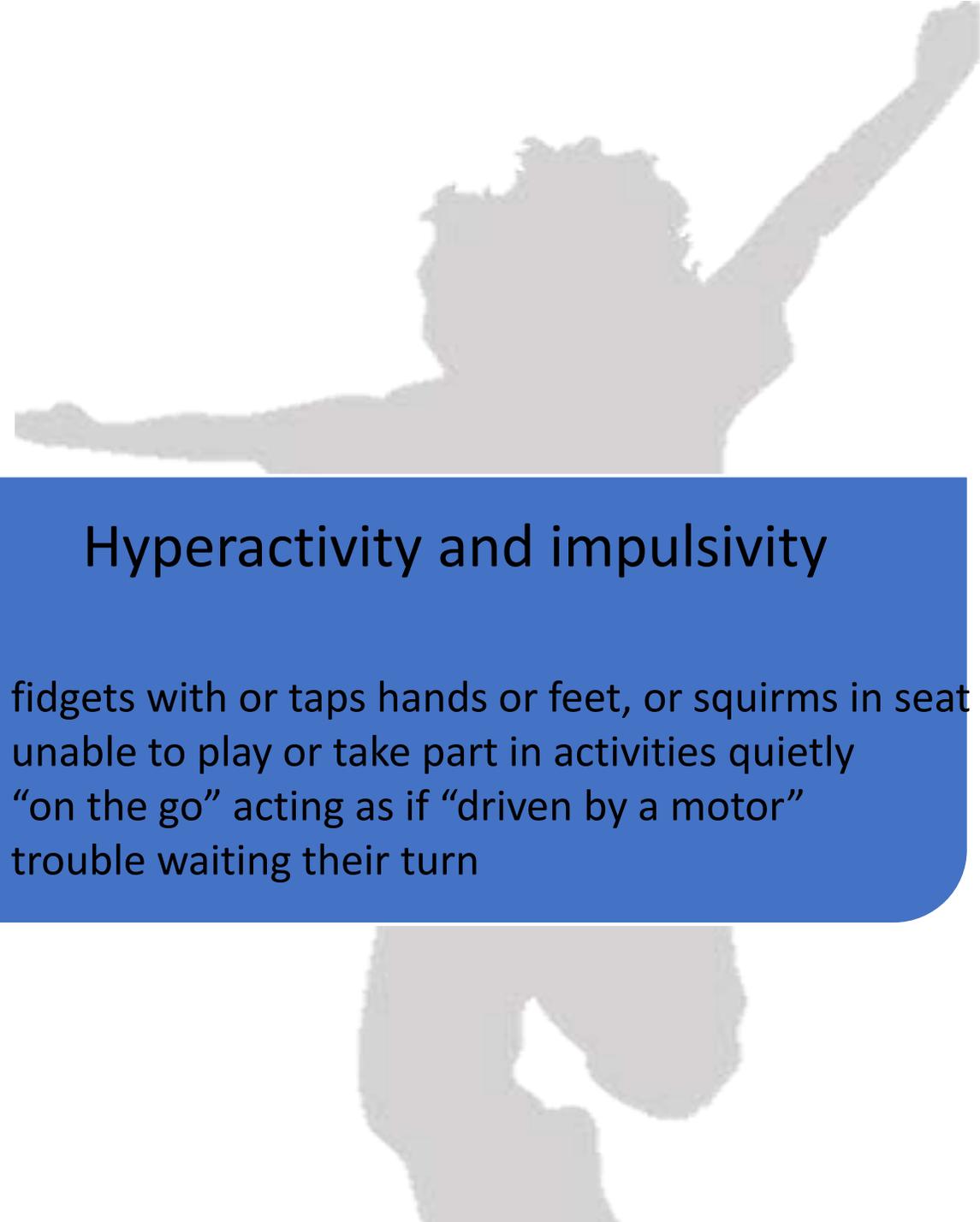
- ~10%
- attention, hyperactivity & impulsivity

Inattention

- trouble holding attention on tasks or play activities
- trouble organizing tasks and activities
- easily distracted
- forgetful in daily activities

Hyperactivity and impulsivity

- fidgets with or taps hands or feet, or squirms in seat
- unable to play or take part in activities quietly
- “on the go” acting as if “driven by a motor”
- trouble waiting their turn



ADHD

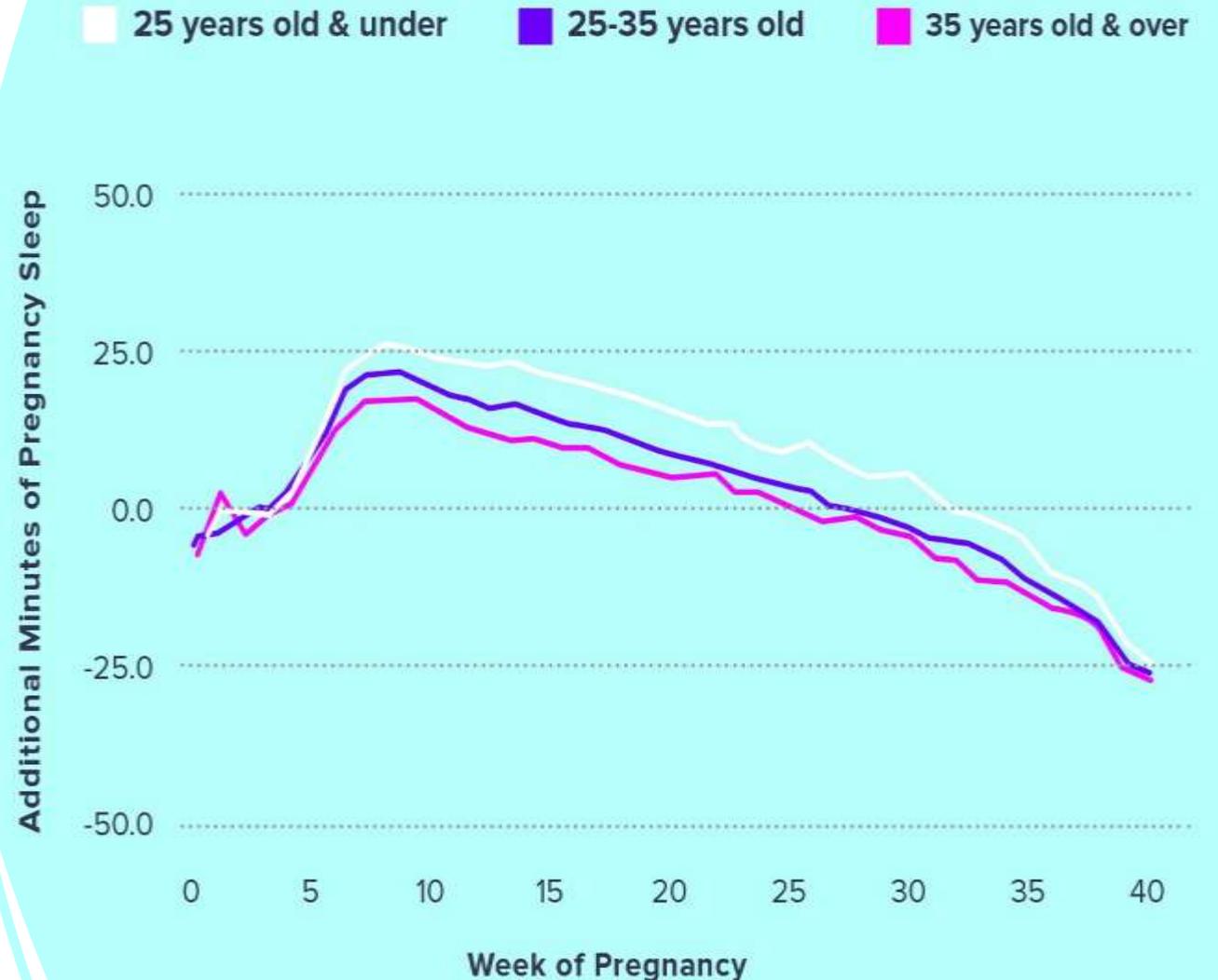
- disorder of childhood (12)
- distress/impairment
- etiology (i.e., origins) remains largely unknown
- largely heritable disease – it runs in families
 - ~20% in genetic studies;
 - environmental influences are thought to account for up to 40% of risk for ADHD
 - prenatal environment



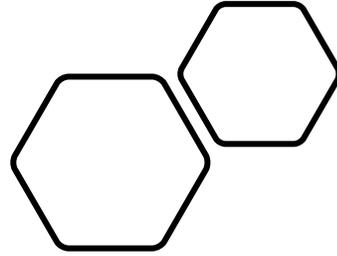
Prenatal Maternal Sleep

- undergoes changes throughout pregnancy due to reproductive hormones, need to use bathroom, and body aches (Pien & Schwab, 2004)
- increased duration during 1st trimester - gradually decreases throughout, becoming shorter and more fragmented
- sleep loss can place pregnant person and offspring at risk for negative outcomes, including poor birth outcomes (Palagini et al., 2014)

Difference in Sleep Time Before & During Pregnancy, by Age



But what
about long-
term effects
on children's
development?

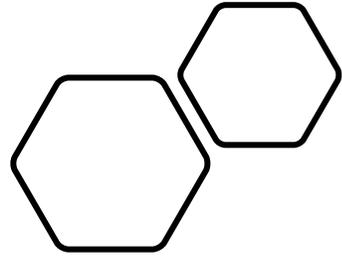


1/3 of development

sleep impacts maternal health:

- inflammation (immune system)
- stress system (HPA axis)

But what about long-term effects on children's development?



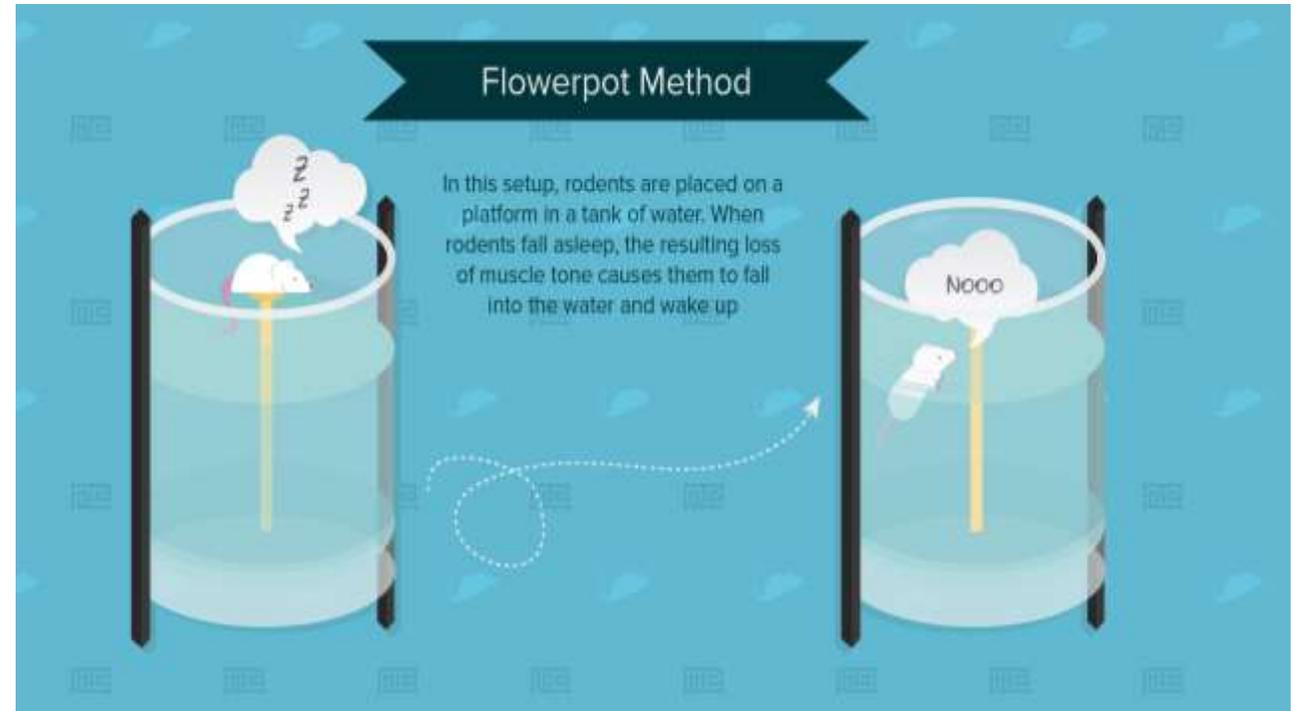
inflammatory proteins
(cytokines)



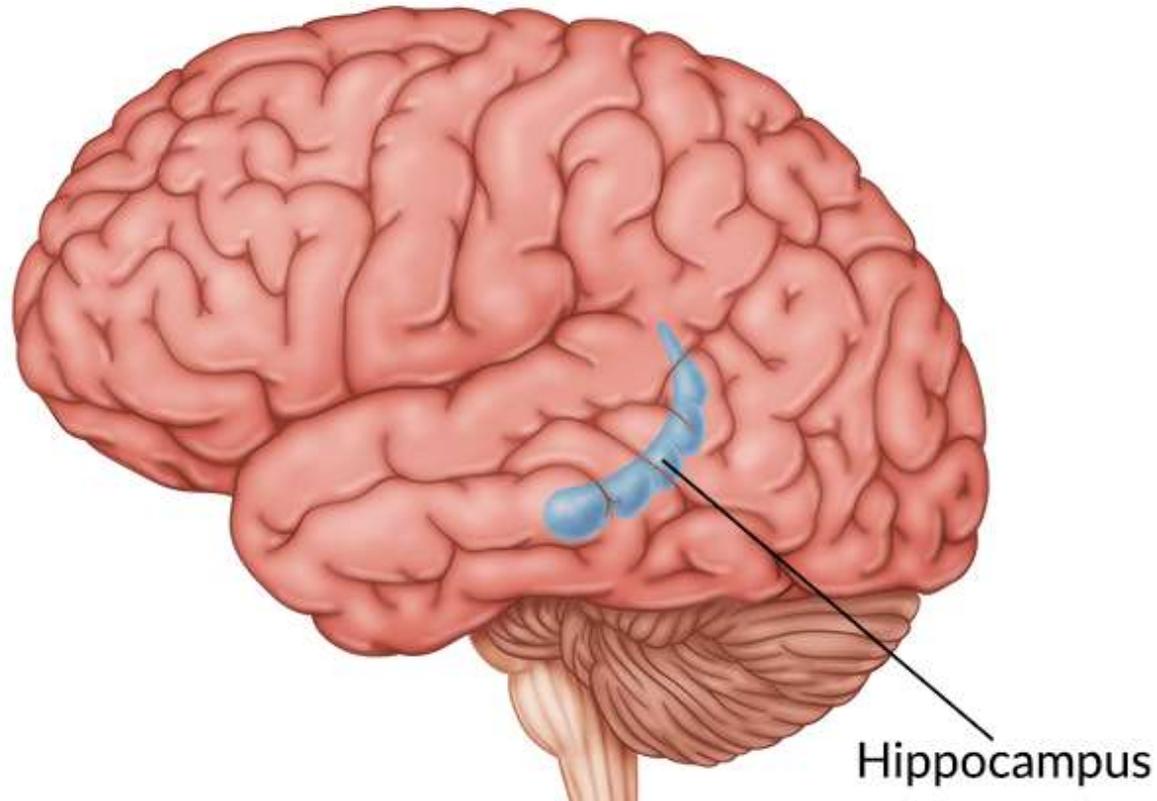
stress hormones (cortisol)

Prenatal Sleep

- intrauterine inflammation
- increased hyperactivity
- decreased hippocampal neurogenesis, smaller hippocampus

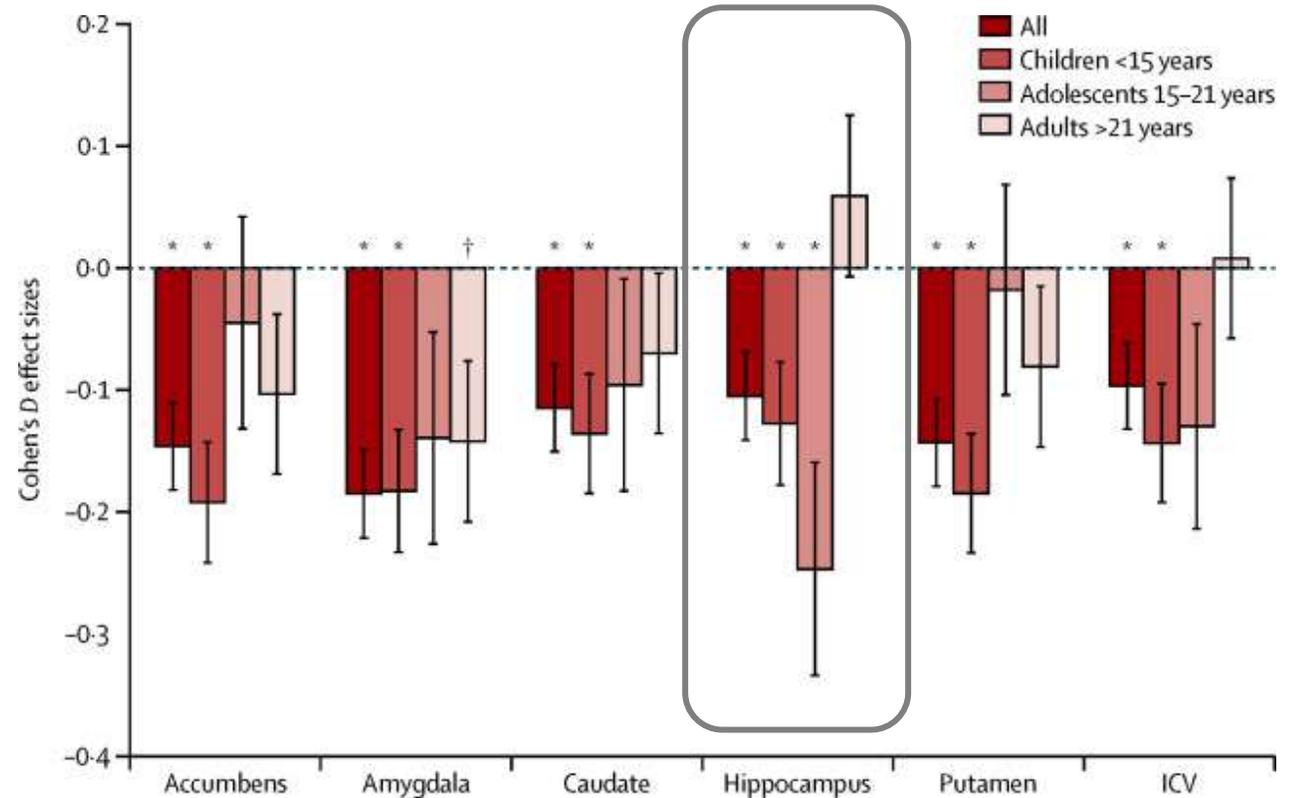


Hippocampus



- Small, but complex
- Important for learning and memory, but also implicated in psychiatric disorders
- Emotion regulation:
 - which, how, and when emotions are experienced and expressed

Hippocampus and ADHD



- Smaller hippocampal volumes detected in children with ADHD
- Emotion regulation is impaired in ADHD, and a source of significant impairment.
 - difficulties with peer relationships; difficulties with aggression

Prenatal sleep and ADHD: Human studies

	Unadjusted		Model 1		Model 2	
	% difference in number of symptoms (95% CI) ^a		% difference in number of symptoms (95% CI) ^a		% difference in number of symptoms (95% CI) ^a	
ADHD-H						
Anxiety						
Never	0	(Ref)	0	(Ref)	0	(Ref)
Lifetime diagnosis	16.8	(8.0–26.2)	14.6	(6.1–23.8)	13.5	(4.8–22.8)
Pre-pregnancy	2.3	(–11.1–17.7)	0.7	(–12.4–15.6)	1.2	(–12.0–16.4)
During pregnancy	23.2	(12.5–34.9)	20.9	(10.4–33.3)	19.2	(8.6–31.0)
Sleep disorder						
Never	0	(Ref)	0	(Ref)	0	(Ref)
Lifetime diagnosis	30.3	(9.3–55.4)	32.1	(10.7–57.6)	29.8	(8.1–55.9)
Pre-pregnancy	11.0	(–18.1–50.4)	11.9	(–17.0–50.8)	12.6	(–17.2–53.0)
During pregnancy	41.2	(13.9–75.1)	44.2	(16.0–79.2)	40.3	(11.8–76.1)
Depression						
Never	0	(Ref)	0	(Ref)	0	(Ref)
Lifetime diagnosis	15.1	(2.6–29.1)	12.8	(0.6–26.5)	11.9	(–0.5–25.8)
Pre-pregnancy	15.3	(–1.7–35.3)	11.3	(–5.2–30.7)	10.5	(–6.0–30.0)
During pregnancy	14.8	(–2.3–35.0)	14.3	(–2.7–34.1)	13.4	(–4.0–33.9)
ADHD-I						
Anxiety						
Never	0	(Ref)	0	(Ref)	0	(Ref)
Lifetime diagnosis	12.9	(5.4–20.9)	11.8	(4.5–19.6)	11.3	(3.8–19.3)
Pre-pregnancy	8.3	(–4.3–22.6)	8.0	(–4.4–22.0)	8.7	(–3.9–23.0)
During pregnancy	14.8	(5.9–24.3)	13.4	(4.7–22.7)	12.4	(3.5–22.1)
Sleep disorder						
Never	0	(Ref)	0	(Ref)	0	(Ref)
Lifetime diagnosis	15.9	(–0.4–34.9)	18.5	(1.9–37.9)	15.4	(–1.5–35.1)
Pre-pregnancy	6.5	(–18.6–39.3)	5.5	(–18.9–37.2)	3.6	(–20.9–35.6)
During pregnancy	20.6	(0.4–44.8)	25.5	(4.4–50.9)	22.0	(0.5–48.1)
Depression						
Never	0	(Ref)	0	(Ref)	0	(Ref)
Lifetime diagnosis	11.8	(1.0–23.8)	11.9	(1.2–23.8)	10.0	(–0.8–22.0)
Pre-pregnancy	11.7	(–3.1–28.7)	10.5	(–4.1–27.4)	8.7	(–5.8–25.5)
During pregnancy	11.9	(–3.0–29.1)	13.3	(–1.6–30.5)	11.4	(–3.8–29.0)

CI, confidence interval, Model 1: Adjusted for maternal age and education, child gender and first-born status, Model 2: Adjusted as Model 1 and additionally adjusted for maternal smoking and alcohol use during pregnancy; ADHD-H, ADHD hyperactive-impulsive score; ADHD-I, ADHD inattentive score.

^aNegative values indicate a relative decrease in the number of ADHD sub-scale symptoms.

BBRF Young Investigator Award

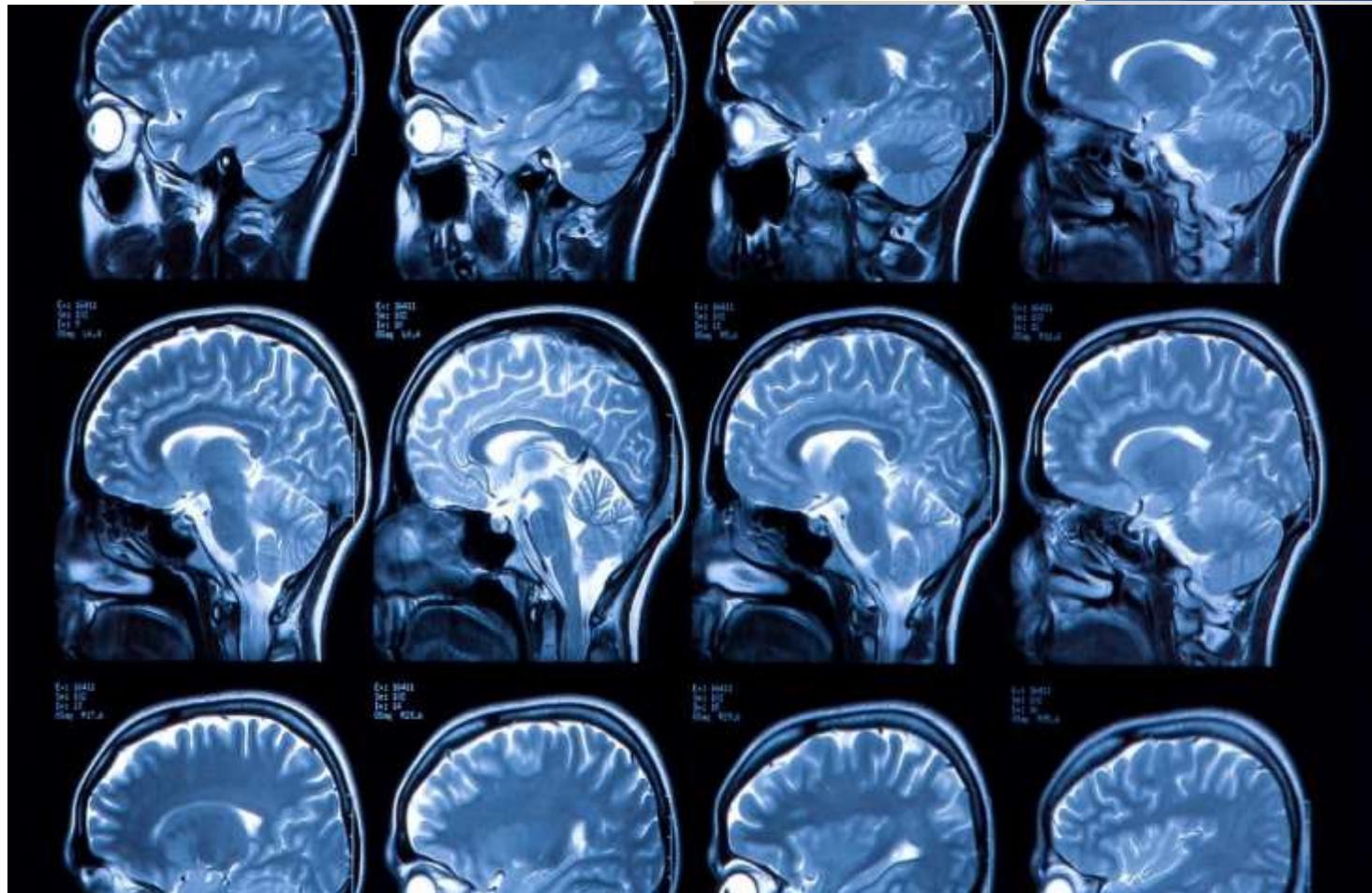
- Prenatal sleep may be related to offspring risk for ADHD, but we still don't know how this happens.
- Examine if prenatal maternal sleep impacts newborn brain development and risk for ADHD

4 main gaps

1. underlying neural markers – how is prenatal sleep impacting that developing brain



Neonatal neuroimaging (MRI)



4 main gaps

1. underlying neural markers – how is prenatal sleep impacting that developing brain
2. how things would look like if we measured sleep objectively
 - previous studies looked at maternal reports of their sleep



Turns out, we might not be great at reporting our own sleep

1. ask (wake/sleep, overall quality)
2. measure it

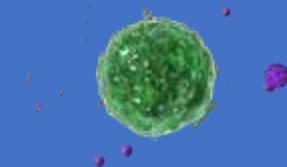


- 62% reported sleep times that differed by more than 1 hour from the one measured!
 - (39 % overestimated; 23 % underestimated)
- self reports and objective sleep duration may be related to different things
 - depression, distress about sleep
- need to know what to target



4 main gaps

1. underlying neural markers – how is prenatal sleep impacting that developing brain
2. how things would look like if we measured sleep objectively
3. mechanism underlying this association
4. offspring sex

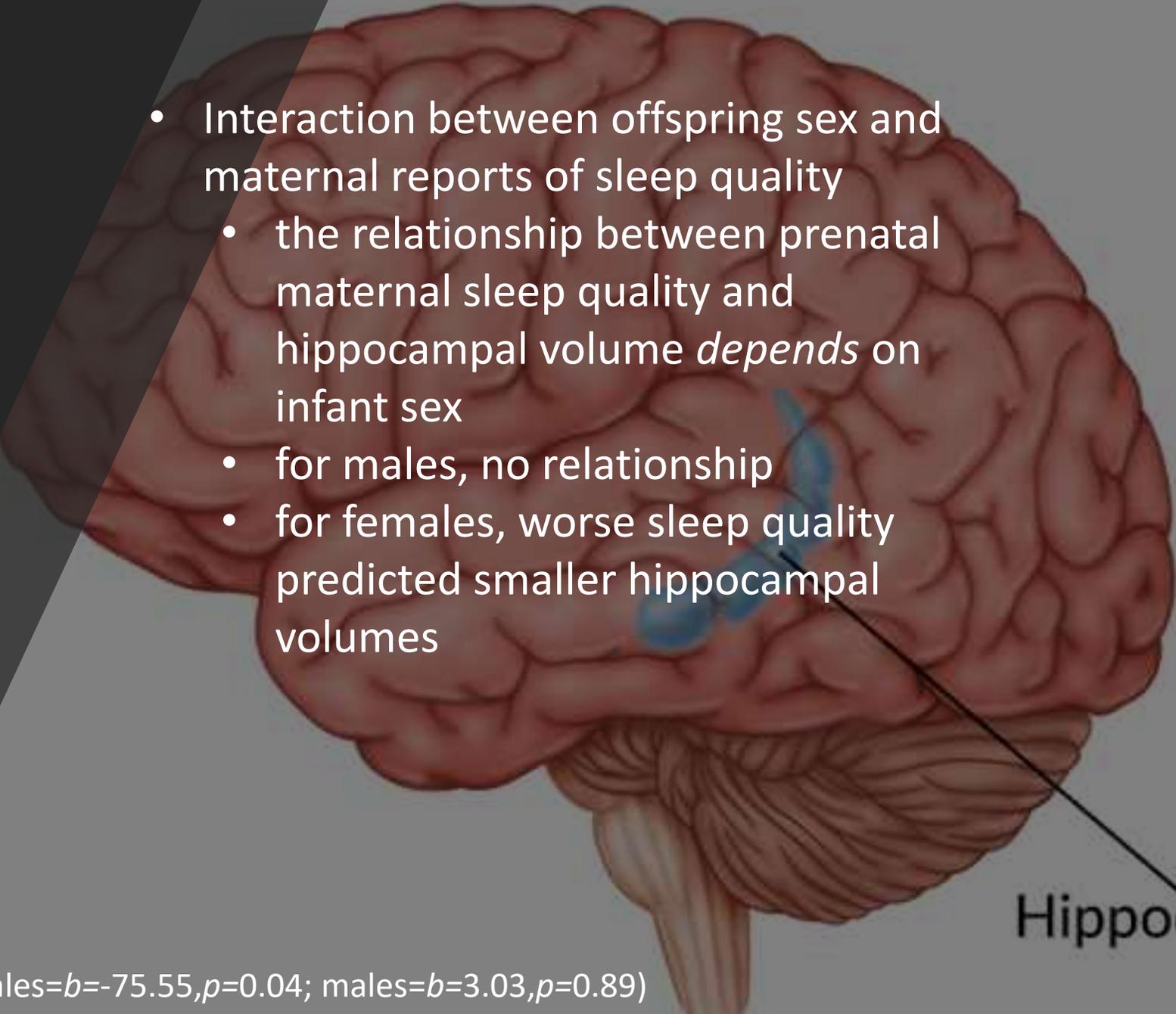


Prenatal sleep and offspring hippocampal volumes

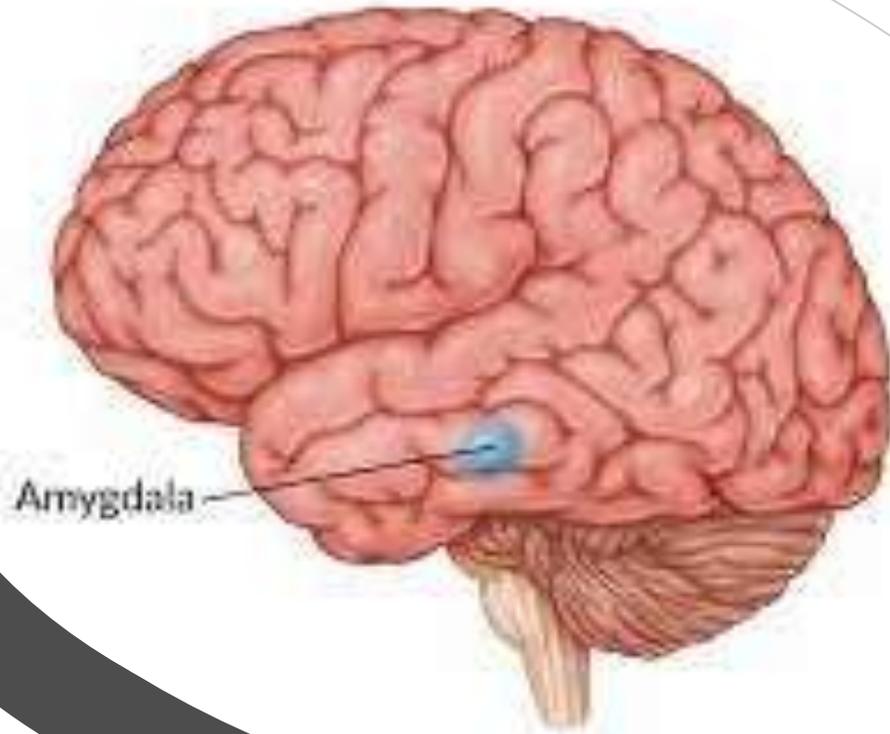
- Interaction between offspring sex and maternal reports of sleep quality
 - the relationship between prenatal maternal sleep quality and hippocampal volume *depends* on infant sex
 - for males, no relationship
 - for females, worse sleep quality predicted smaller hippocampal volumes

(females= $b=-75.55, p=0.04$; males= $b=3.03, p=0.89$)

Hippoca



Prenatal sleep and offspring amygdala volumes



- structure highly involved in emotion regulation
- worse sleep quality was associated to greater amygdala volume among males only ($b=21.91$, $p=0.03$)



Associations between prenatal sleep and children's behaviors and symptoms at 2 years

- worse sleep quality and more disturbances were associated to more sleep problems for children ($p=.01$; $p=.02$)
- shorter sleep duration was related to poorer emotion regulation, but only for males ($p=0.05$).

What about the objective sleep assessments?

- 75% are off by more than 1 hour –
underestimating sleep by ~1.17 hours
 - ($r = .43, p = .10$)
- duration is related to hippocampal volumes
- less objective sleep duration was related to smaller hippocampal volumes ($p = .04$), but sample too small to look at offspring sex effects (yet!)



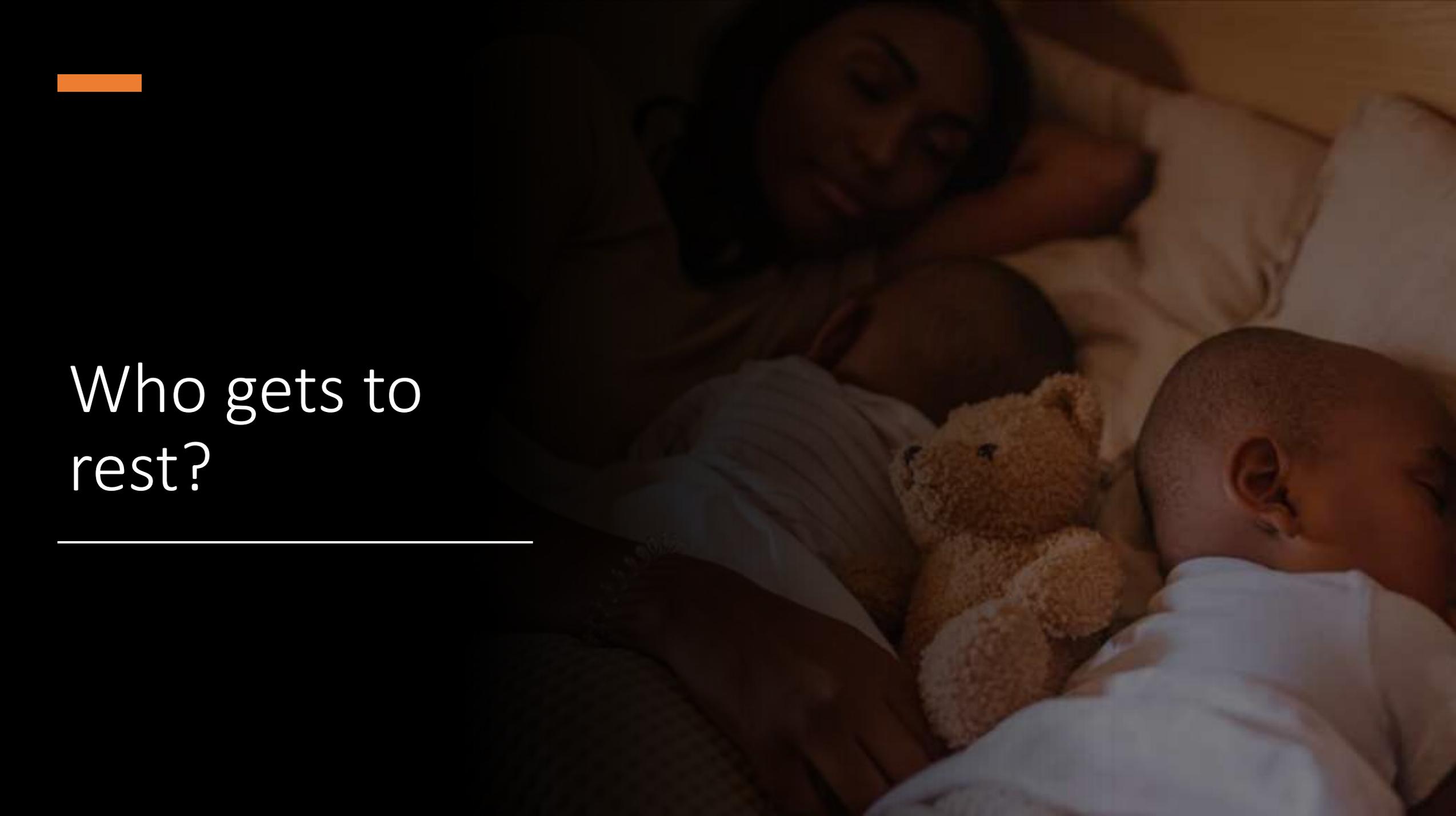
Summary

- Prenatal maternal sleep may impact *in utero* neurodevelopment in sex-specific ways.
- It is possible that males are more affected in ER abilities, which are associated to amygdala structure and function and a significant area of impairment in ADHD.
- Females may be at risk for sleep difficulties, which may carry subsequent risk for negative mental health outcomes later in life, including depression and anxiety.



- Mechanisms
 - Underlying sex differences
- What happens as children age?
 - Their own sleep
- Trimester-specific effects
- Implement interventions
 - CBT-I

Next steps

A photograph of a woman, a man, and a baby sleeping in a bed. The woman is at the top, the man is in the middle, and the baby is at the bottom right. A teddy bear is lying between the man and the baby. The scene is dimly lit, suggesting a nighttime setting. An orange horizontal bar is located in the top left corner of the image.

Who gets to
rest?

Sleep is not distributed equally

- significant differences (disparities)
 - minoritized ethnic and racial groups appear to get less and poorer sleep
 - reasons may be multiple and complex, but several studies have found that experiences of racism and discrimination are related to worse sleep health



the social
epidemiology
of sleep

EDITED BY

DUSTIN T. DUNCAN

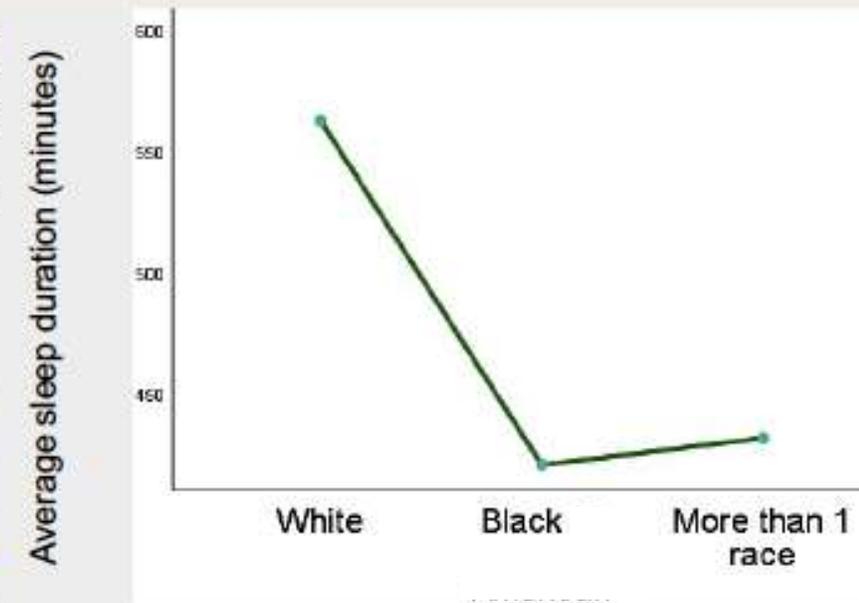
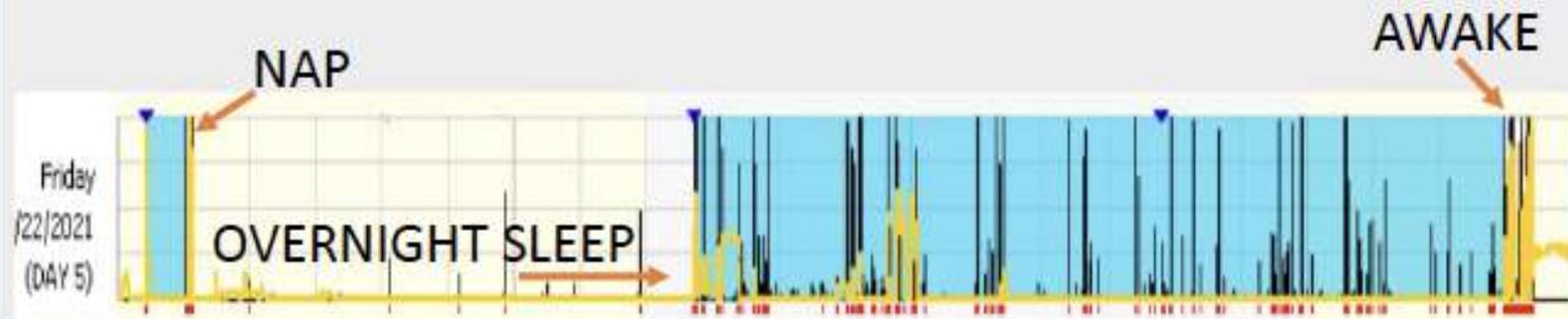
ICHIRO SAWASHI

SUSAN REDLINE

Race disparities in prenatal sleep among Puerto Rican women

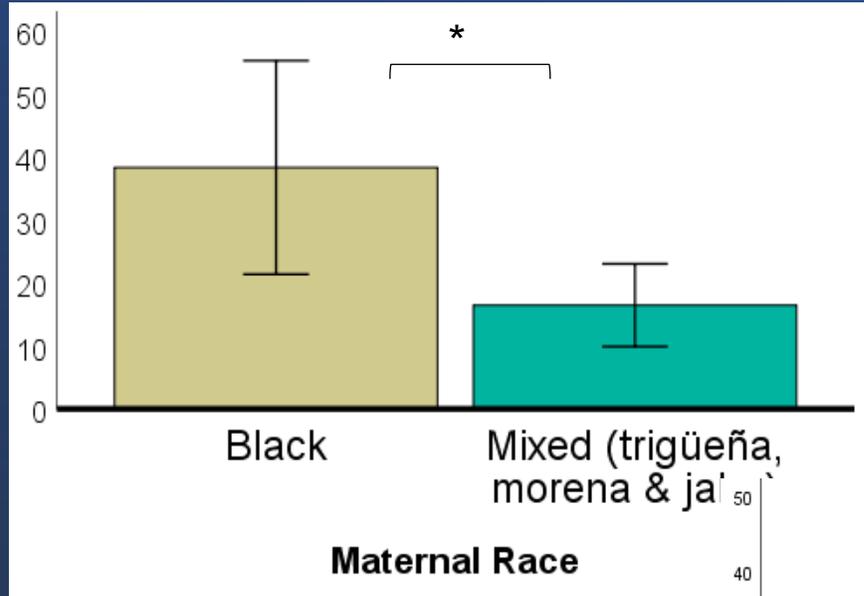
- Within a sample of pregnant Puerto Rican women

Figure 3a. Pilot actigraphy data. Blue shading indicates rest intervals (i.e., sleep), back lines and red underline index activity counts, and yellow lines index light levels. **Figure 3a.** Prenatal sleep duration and race

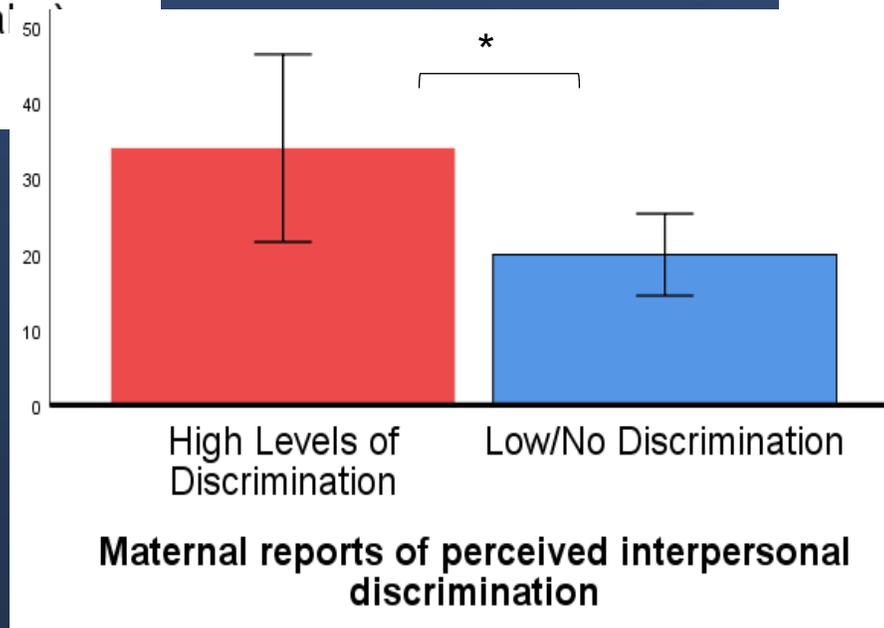
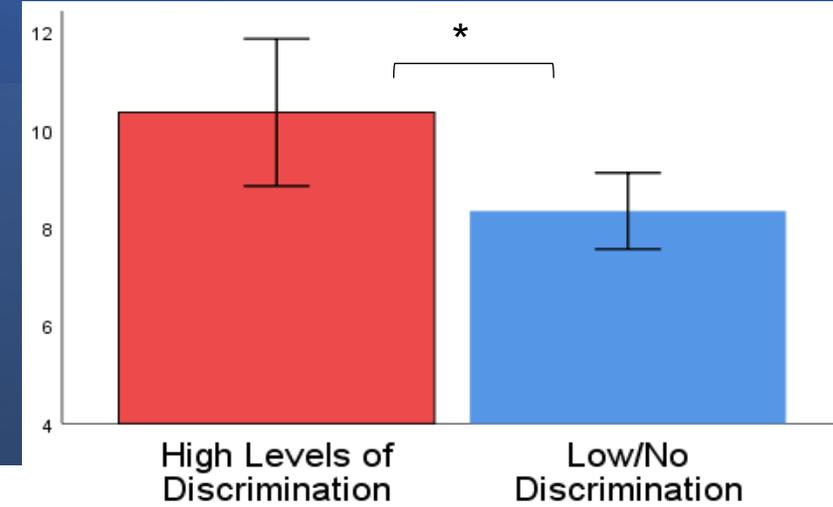


Discrimination and prenatal maternal sleep

Sleep latency (minutes it takes to fall asleep)

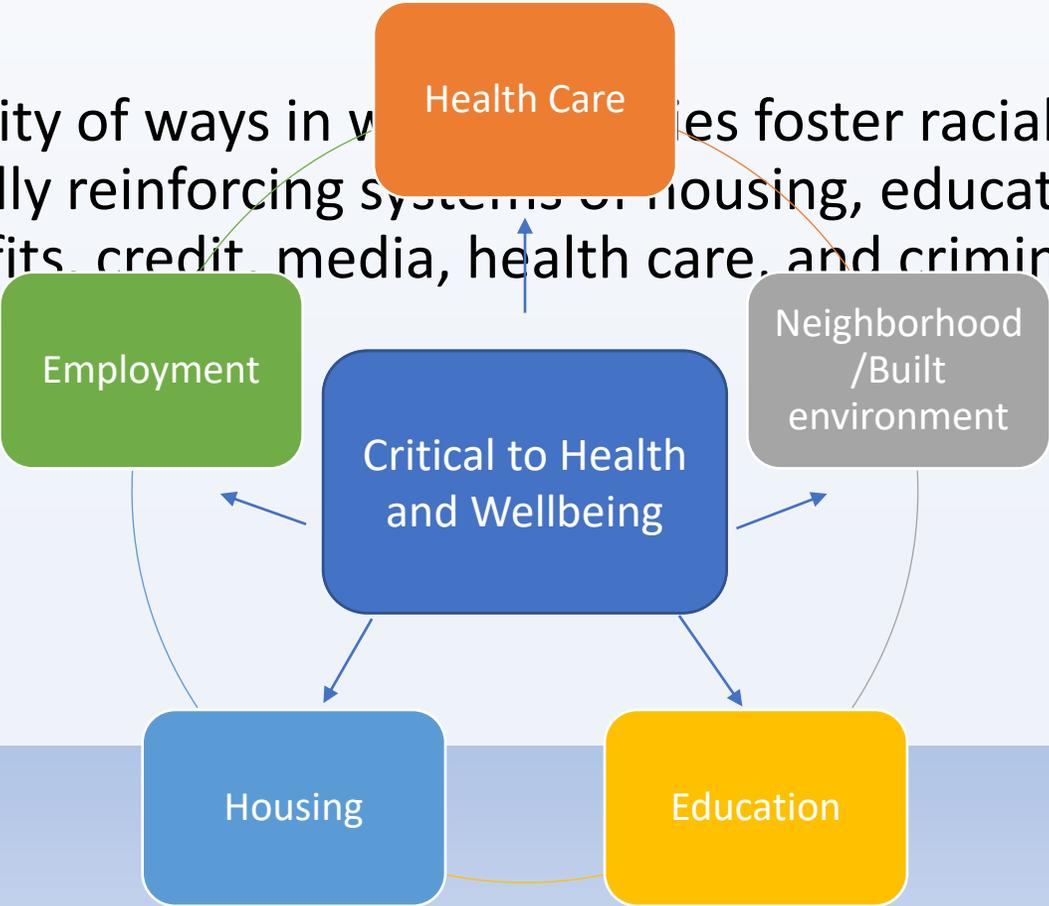


Poor sleep quality



Structural manifestations of racism and discrimination (SRD)

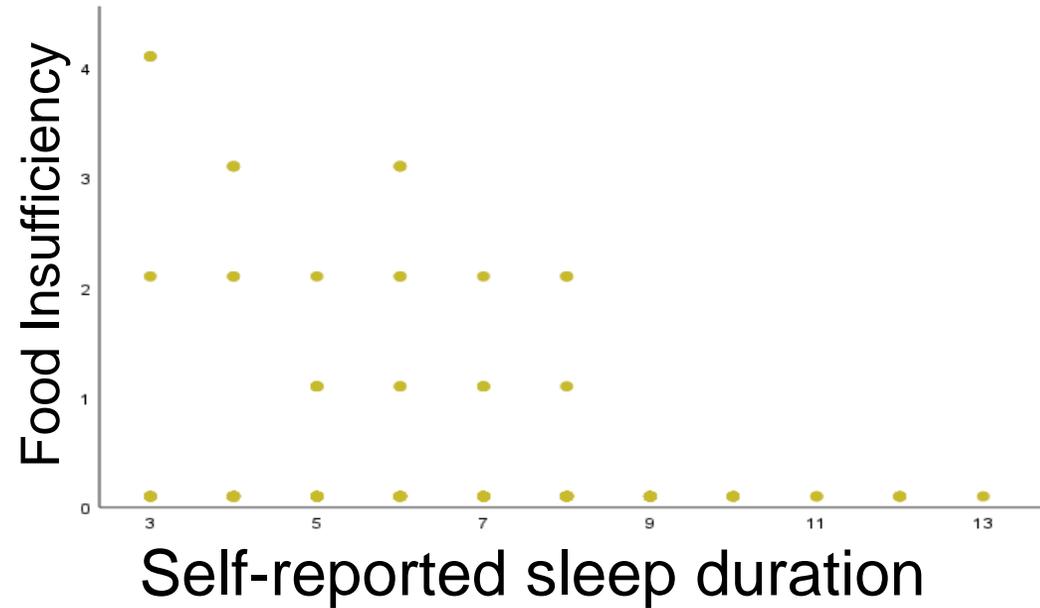
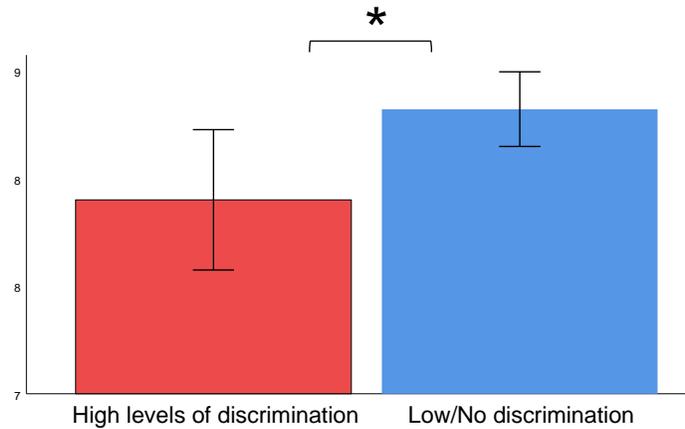
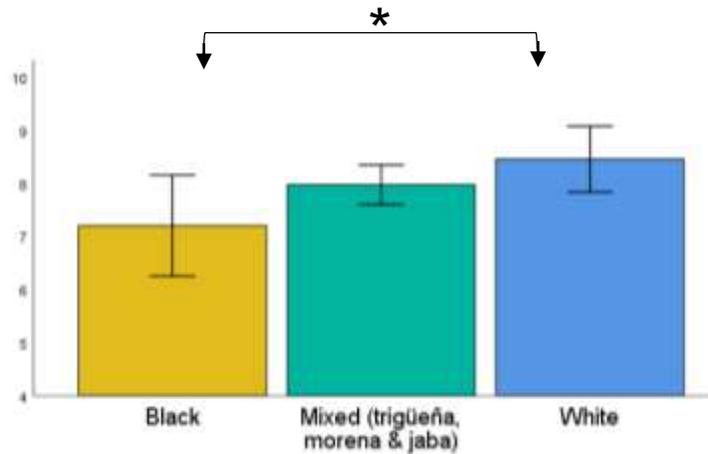
- Going beyond perceived or interpersonal discrimination
 - structural
- SRD = The totality of ways in which societal systems foster racial discrimination through mutually reinforcing systems of housing, education, employment, earnings, benefits, credit, media, health care, and criminal justice. (Bailey et al., 2017, Lar...



SRD and poor prenatal sleep

Food Security

Food Insecurity (lower scores indicate lower food availability/security)



Discriminatory policies and systems

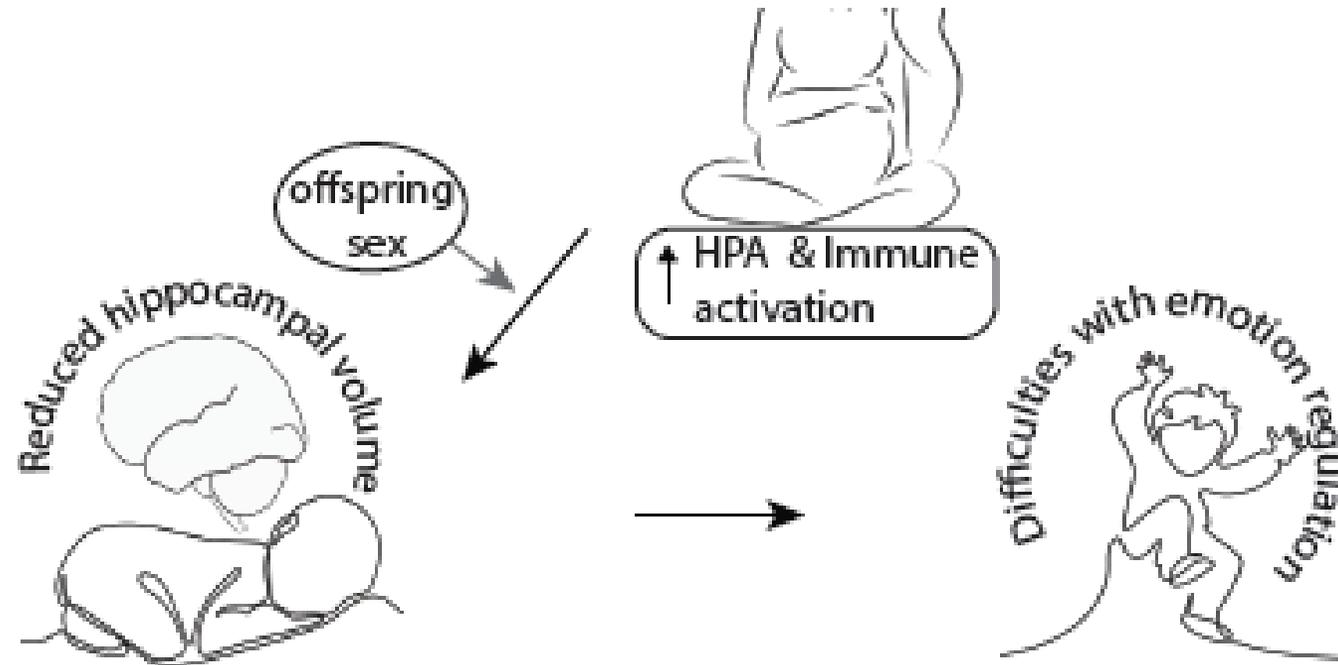
Redlining, unequal distribution of employment, educational, and health resources, biased legal system, environmental exposures (e.g., light, noise, air pollution).

Reduction of resources & services needed for maternal & infant health
Increases in maternal stress, allostatic load, autonomic arousal

Impact on pregnant parents

The impact of structural racism and discrimination may extend well beyond the exposed individual, reaching the next generation.

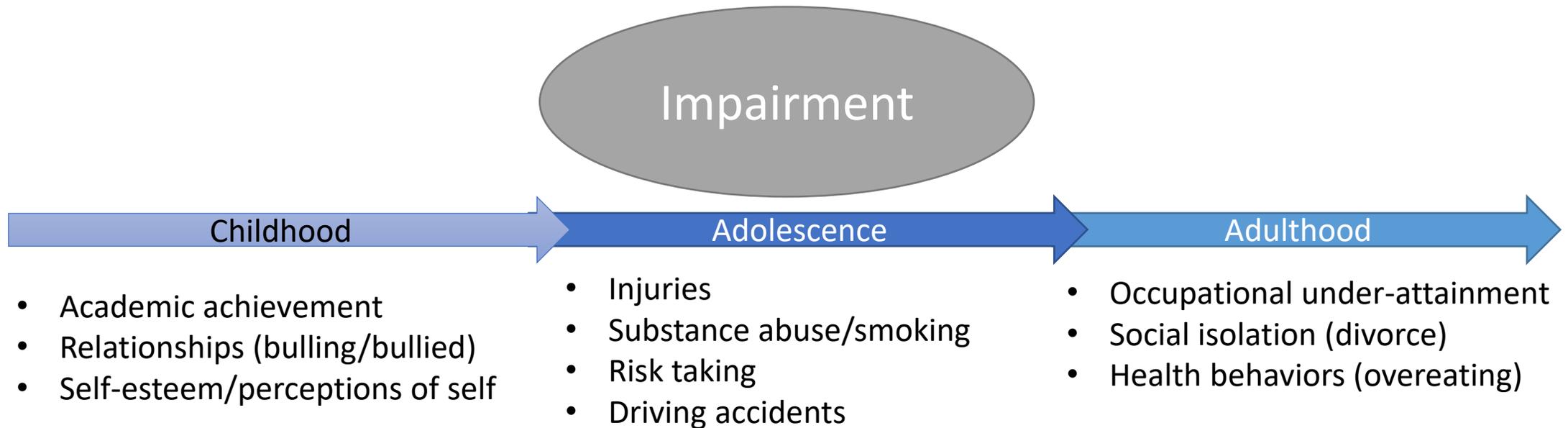
Impact on offspring



- Mechanisms
- Which domains are most important?
- Foster resilience
- Structural interventions

Next steps

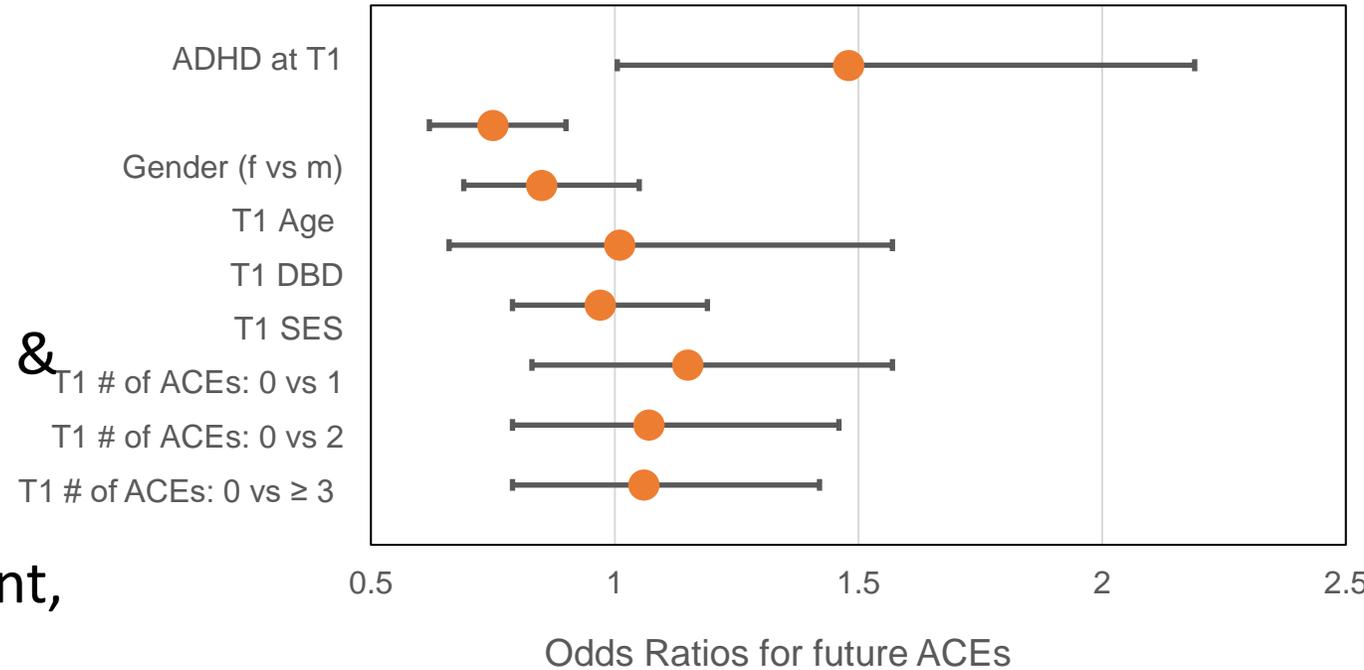
Fetal origins of ADHD



- how to identify children at need and prevent this cascade

ADHD and future adversity

- intergenerational study of Puerto Rican families
 - (Drs. Duarte & Canino)
- children & parents for ~3 years
- ADHD & ACEs
 - maltreatment, parent maladjustment & parental separation
- cycles and developmental trajectories
- highlights need for intervention, treatment, and support – for entire family



Summary

- Poor prenatal maternal sleep health may be an important risk factor for ADHD
 - need to understand mechanisms
 - call to increase perinatal support for families
- SRD may determine who gets to sleep
 - critical to designing and implementing interventions aimed at achieving sleep equity and stopping the effects of discrimination on mother's and children's health



Acknowledgements

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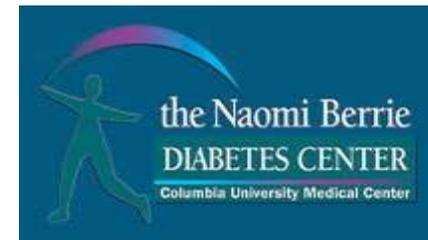
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- Dr. Estelle Bender
- Dr. Cristiane Duarte
- Dr. Catherine Monk
- Dr. William Fifer
- Dr. Maristella Lucchini

Families in all studies



Summary

- Poor prenatal maternal sleep health may be an important risk factor for ADHD
 - need to understand mechanisms
 - call to increase perinatal support for families
- SRD may determine who gets to sleep
 - critical to designing and implementing interventions aimed at achieving sleep equity and stopping the effects of discrimination on mother's and children's health

