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

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Road Map

- Prenatal origins of health and disease
- Studies on early origins of ADHD
- Prenatal sleep
- Who gets to sleep
- Thinking about ADHD intergenerationally
Terms

prenatal

postnatal

in utero

perinatal
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

Barker, 2004
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

Schulz, 2010, PNAS
Risk disorder
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)
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?
Prenatal Sleep

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

Radhakrishnan, 2015; Zhao, 2014; 2015
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

Anand, 2021; Gross 2015
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

Hoogman et al., 2017
# Prenatal sleep and ADHD: Human studies

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted</th>
<th>Model 1</th>
<th>Model 2</th>
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<tbody>
<tr>
<td></td>
<td>% difference in number of symptoms (95% CI)*</td>
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<tr>
<td><strong>ADHD-I</strong></td>
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<tr>
<td>Anxiety</td>
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<tr>
<td>Never</td>
<td>0 (Ref)</td>
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<tr>
<td>Lifetime diagnosis</td>
<td>16.8 (8.0–26.2)</td>
<td>14.6 (6.1–23.8)</td>
<td>13.5 (4.8–22.8)</td>
</tr>
<tr>
<td>Pre-pregnancy</td>
<td>2.3 (–11.1–17.7)</td>
<td>0.7 (–12.4–15.6)</td>
<td>1.2 (–12.0–14.4)</td>
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<tr>
<td>During pregnancy</td>
<td>23.2 (12.5–34.9)</td>
<td>20.9 (10.4–33.3)</td>
<td>19.2 (8.6–31.0)</td>
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<tr>
<td>Sleep disorder</td>
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<tr>
<td>Never</td>
<td>0 (Ref)</td>
<td>0 (Ref)</td>
<td>0 (Ref)</td>
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<tr>
<td>Lifetime diagnosis</td>
<td>30.3 (9.3–51.4)</td>
<td>32.1 (10.7–57.6)</td>
<td>29.8 (8.1–50.9)</td>
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<tr>
<td>Pre-pregnancy</td>
<td>11.0 (–18.1–39.4)</td>
<td>11.9 (–17.0–50.8)</td>
<td>12.6 (–17.2–32.0)</td>
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<tr>
<td>During pregnancy</td>
<td>41.2 (13.9–67.5)</td>
<td>44.2 (16.0–79.2)</td>
<td>40.3 (11.8–69.1)</td>
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<tr>
<td>Depression</td>
<td></td>
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<tr>
<td>Never</td>
<td>0 (Ref)</td>
<td>0 (Ref)</td>
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<tr>
<td>Lifetime diagnosis</td>
<td>15.3 (2.6–29.1)</td>
<td>12.8 (0.6–26.9)</td>
<td>11.9 (–0.5–29.8)</td>
</tr>
<tr>
<td>Pre-pregnancy</td>
<td>15.3 (–1.7–35.3)</td>
<td>11.3 (–5.2–30.7)</td>
<td>10.5 (–6.0–30.0)</td>
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*Negative values indicate a relative decrease in the number of ADHD subscale symptoms.

Vizzini 2018, Lahti-Pulkkinen, 2019
• 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

Rosenberg, 2018
Neonatal neuroimaging (MRI)

- 2-4 weeks (naturally sleeping)
- Understand prenatal risk independent from postnatal exposures
- Significantly minimizing exposure to the postnatal world
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

Rosenberg, 2018
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

Herring, 2013; Matthews 2018; Cudney 2021
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

Rosenberg, 2018
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=$b=3.03, p=0.89$)
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!)

$n=15$
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.
Next steps

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

Jackson et. al., 2020
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

Average sleep duration (minutes)

- White
- Black
- More than 1 race

n = 16 (p = .017)
Discrimination and prenatal maternal sleep

Sleep latency (minutes it takes to fall asleep)

Maternal Race

- Black
- Mixed (trigueña, morena & ja

Poor sleep quality

- High Levels of Discrimination
- Low/No Discrimination

Maternal reports of perceived interpersonal discrimination
Structural manifestations of racism and discrimination (SRD)

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

Food Security

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

Self-reported sleep duration

Results displayed control for income and education

Error bars: +/- 2 SE
The impact of structural racism and discrimination may extend well beyond the exposed individual, reaching the next generation.
Next steps

- Mechanisms
- Which domains are most important?
- Foster resilience
- Structural interventions
Fetal origins of ADHD

- Academic achievement
- Relationships (bulling/bullied)
- Self-esteem/perceptions of self

Impairment

Childhood
- Injuries
- Substance abuse/smoking
- Risk taking
- Driving accidents

Adolescence
- Occupational under-attainment
- Social isolation (divorce)
- Health behaviors (overeating)

Adulthood

• how to identify children at need and prevent this cascade

Lamberg 2003; Brod 2012; Doshi 2012
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

Lugo-Candelas et al., 2021
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
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Families in all studies
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