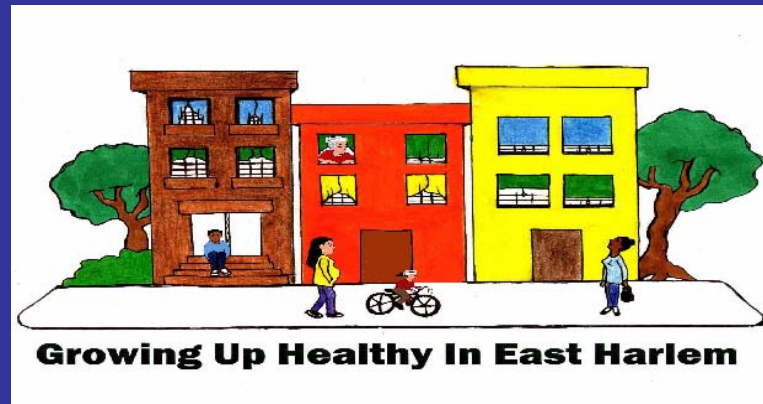


# Prenatal Phthalate Exposure and Neurodevelopmental Impairment

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The Mount Sinai Children's Environmental Health Study  
Project 2, 1998 – 2008

Stephanie M Engel, PhD  
Associate Professor, Department of Preventive Medicine  
Mount Sinai School of Medicine



# Outline

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1. **Prenatal Phthalates & Neurodevelopment: Results from the *Mount Sinai Children's Environmental Health and Disease Prevention Research Center***
2. **Strength of the evidence**
3. **Prenatal period as window of vulnerability**
4. **Strengths & limitations of prospective cohort designs for investigating prenatal environmental toxicant exposures**

# Network of NIEHS/EPA funded Centers

NIEHS/EPA Centers  
for Children's  
Environmental Health  
and Disease  
Prevention Research

## Children's Environmental Health Center Locations

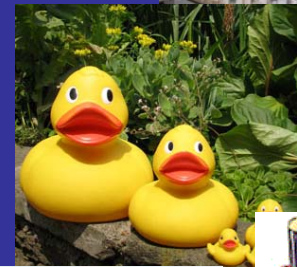
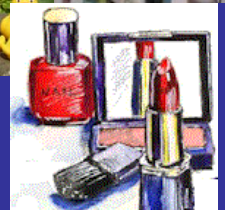
Study Sites Separate from Center Locations

- Harvard Study Site: Tar Creek, Oklahoma
- ▲ Illinois Study Site: Green Bay, Wisconsin



# Phthalates and the Environment

- Estimates of worldwide production range from 3 to 5.5 million tons per year
- Used in a wide range of consumer products
  - Plasticizers
  - Fragrance carrier
  - Solvents, adhesives, lubricants
- Ubiquitous exposure



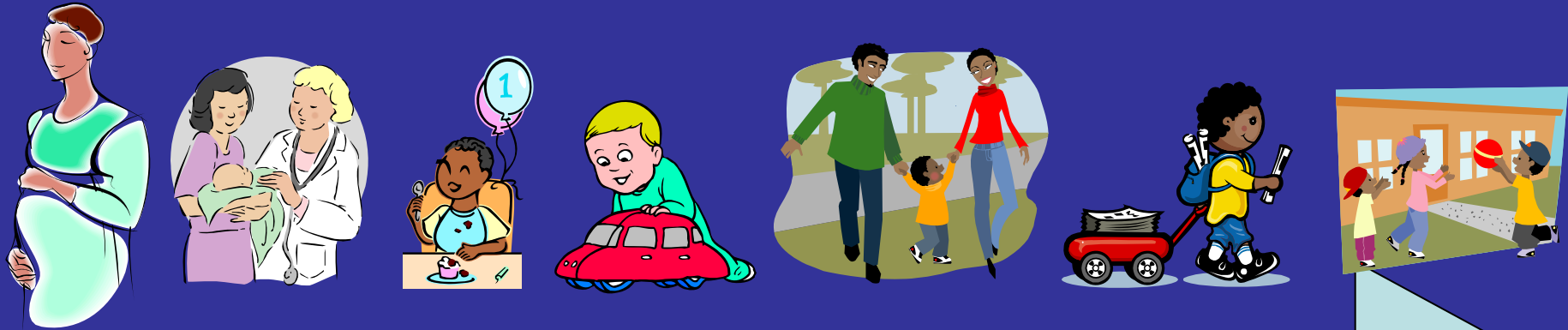


# Why Study Phthalates?

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- ✓ **Endocrine disruptors**
- ✓ **Reproductive toxicants**
- ✓ **Relevance to Neurodevelopment**
  - **In experimental animals phthalates have been shown to reduce circulating thyroid hormone**
  - **High phthalate concentrations linked with low circulating thyroid hormone in adult men and in pregnant women**

# New York Children's Environmental Health Study



## NYCEHS Longitudinal Measures

### Prenatal

Exposure Questionnaire  
Maternal Blood  
Maternal Urine

### 1-2 year visits

Exposure Questionnaire and growth  
Child urine  
Bayley Scales of Infant Development  
Infant and Toddler Behavior Questionnaires

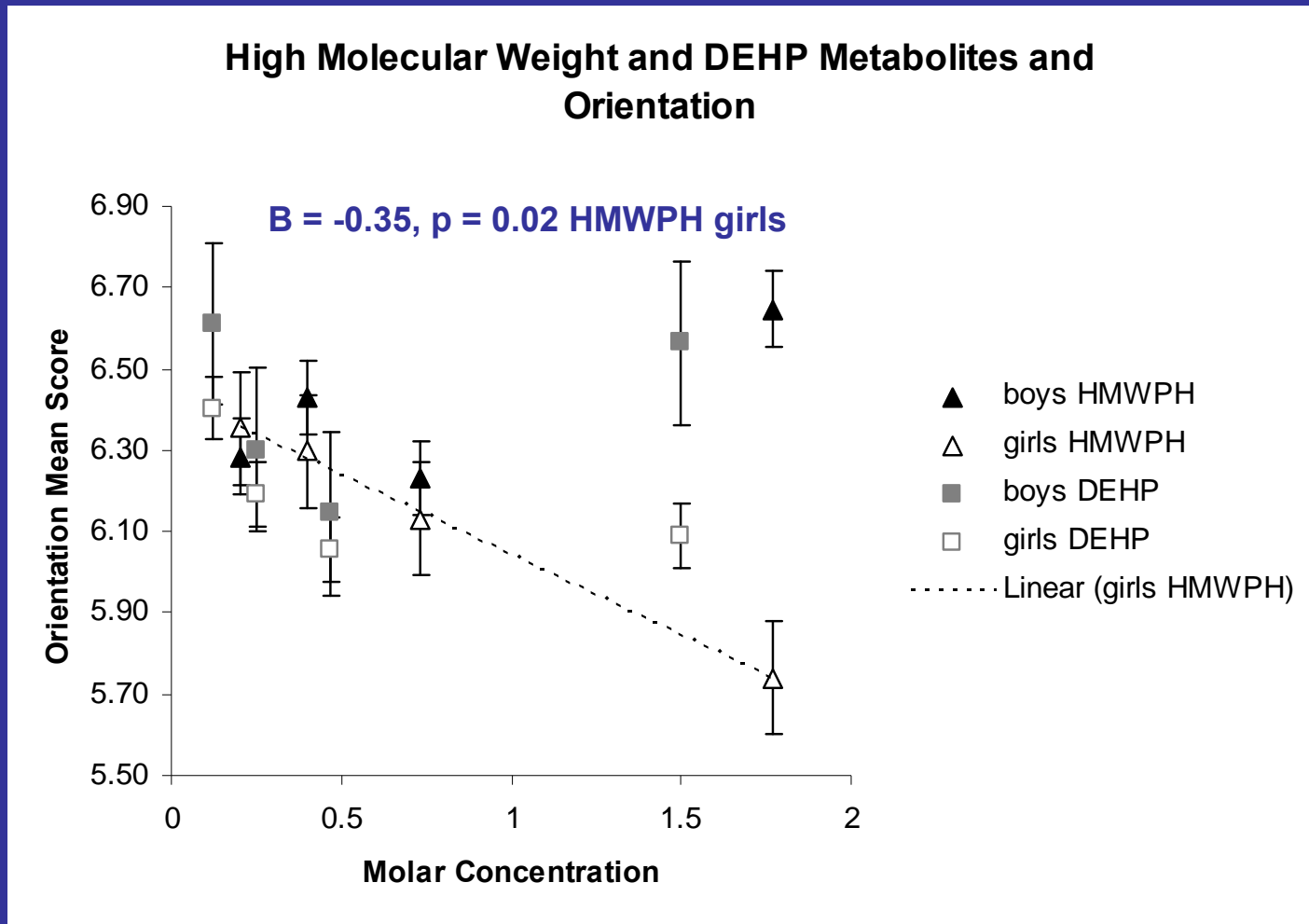
### Birth

Cord Blood  
BNBAS  
Birth size measures

### 4, 6 and 7-9 year visits

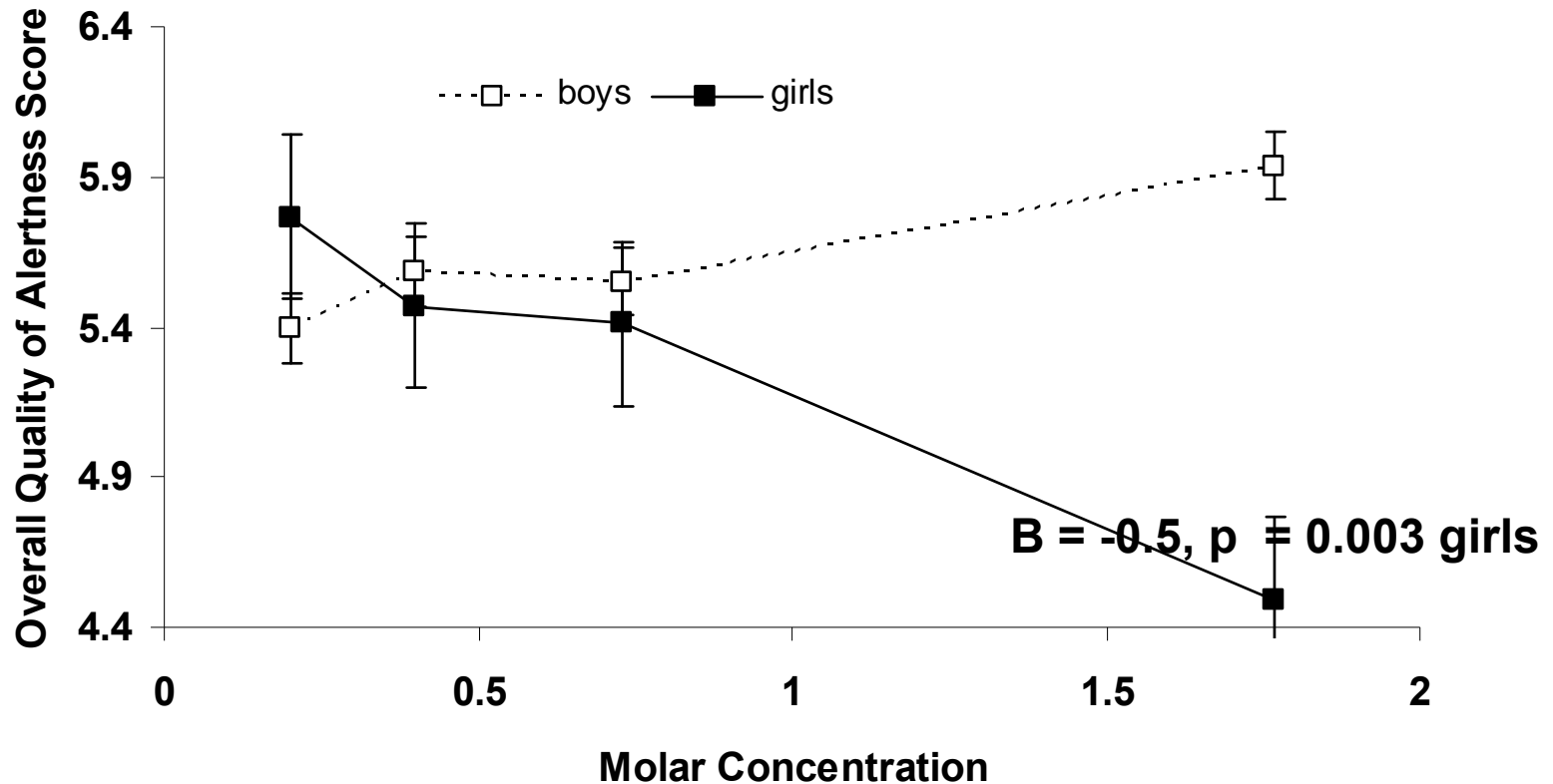
Exposure Questionnaire and growth  
Child urine and Maternal Saliva  
WISC or WPPSI  
BASC, BRIEF and SRS

# Prenatal Phthalate Exposure and Orientation



**Linear decline in mean orientation score with increasing concentrations of high molecular weight phthalates among girls. Boys and girls similar below 1 uM. Adjusted for Race, examiner, urinary creatinine**

# High Molecular Weight Phthalate Exposure and Quality of Alertness

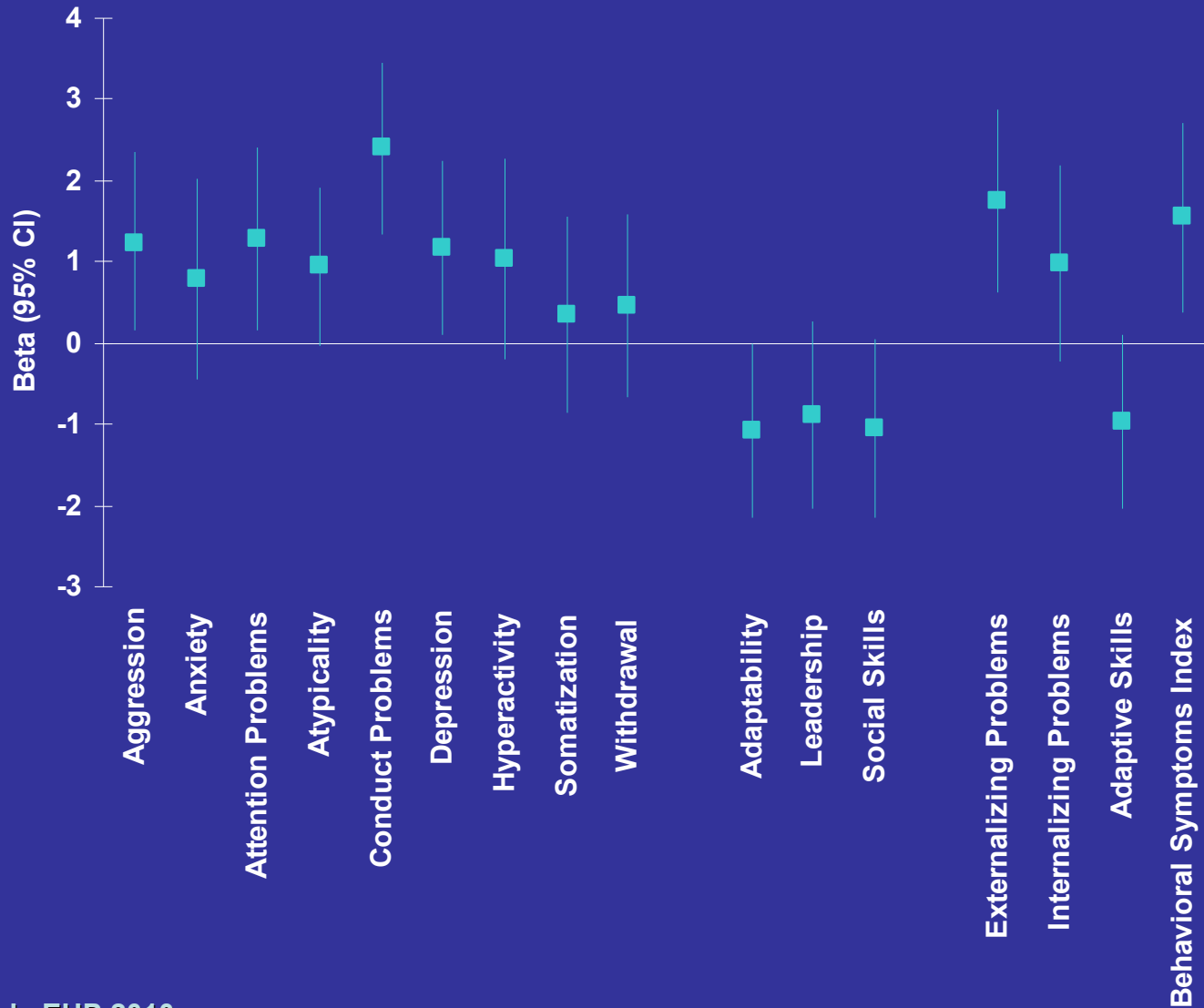


*Quality of Alertness, overall quality of the infant's responsiveness*  
*Adjusted for Race, examiner, urinary creatinine*

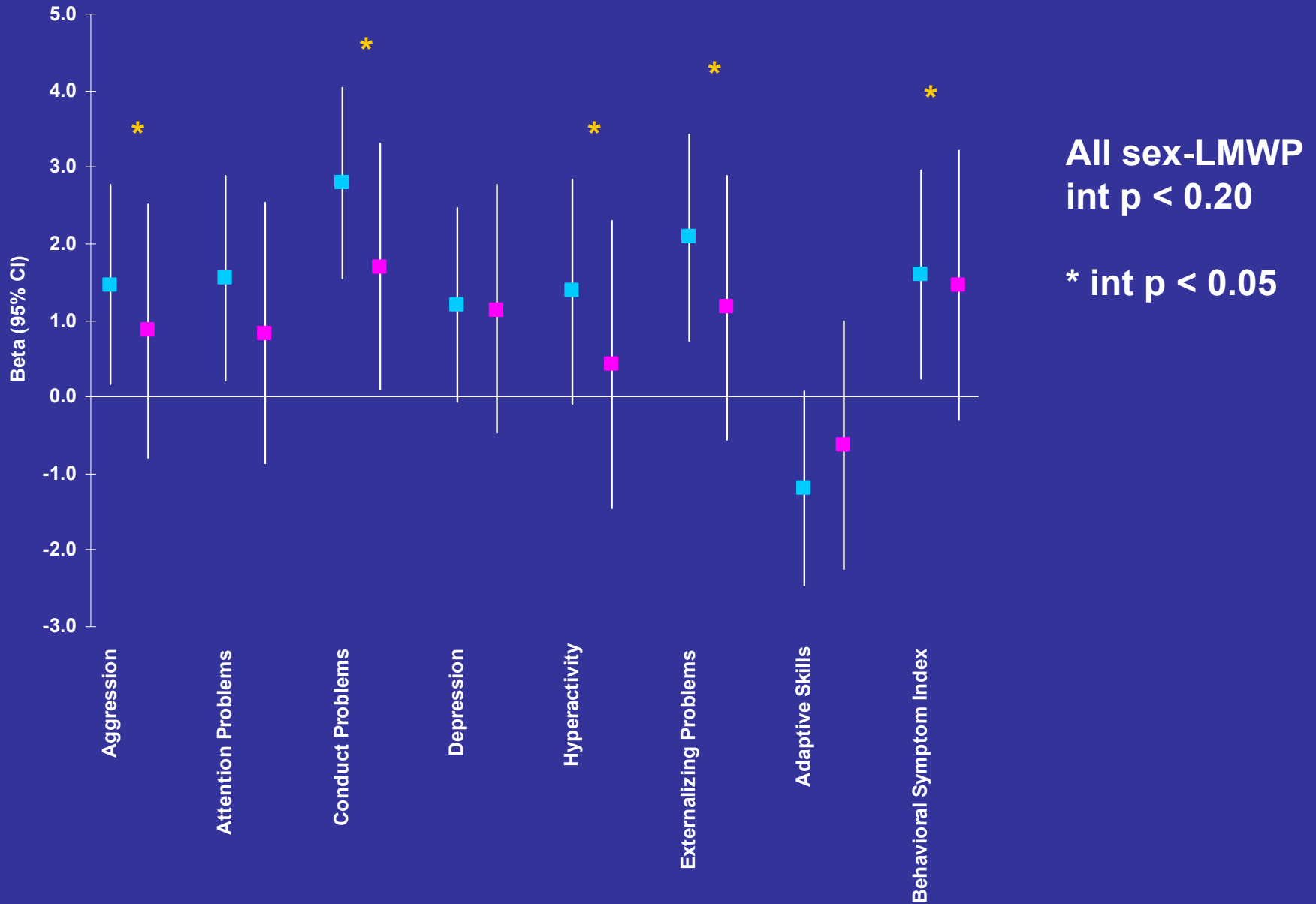


# Prenatal LMWP and BASC-PRS Scales

## Overall Effects of LMWP on Behavior



# Prenatal LMWP, Sex, and BASC-PRS Scales



<b>BASC Domain</b>	<b>LMWP p-value</b>	<b>At-Risk or Clinically Significant Scales by Childhood Clinical Groups</b>	
		<b>Conduct Disorder</b>	<b>ADHD</b>
<b><i>Clinical Scales</i></b>			
Aggression	**	✓	✓
Anxiety			
Attention Problems	**		✓
Atypicality	*		
Conduct Problems	***	✓	✓
Depression	**	✓	✓
Hyperactivity	*	✓	✓
Somatization			
Withdrawal			
<b><i>Adaptive Scales</i></b>			
Adaptability	**	✓	✓
Leadership			
Social Skills	*		
<b><i>Composite Scales</i></b>			
Externalizing Problems	***	✓	✓
Internalizing Problems			
Adaptive Skills	*	✓	✓
Behavioral Symptom Index	***	✓	✓

\*\*\* p < 0.01

\*\* p < 0.05

\* p < 0.1

# Prenatal LMWP and the Social Responsiveness Scale

**SRS** measures a range of social impairments present in the general population, and consistent with a number of child psychiatric conditions, including Autism Spectrum Disorders, PDD-NOS, ADHD and schizoid personality disorder of childhood.

## Subscales include:

- **Social Awareness**: Ability to pick up on social cues
- **Social Cognition**: Ability to interpret social cues
- **Social Communication**: Motoric aspects of reciprocal social behavior
- **Social Motivation**: Motivation to engage in social-interpersonal behavior
- **Autistic Mannerisms**: Stereotypical behaviors or restricted interests

LMWP Biomarker (log)	Beta	95% CI
Total Score	1.53	0.25, 2.82
Awareness	1.25	0.59, 2.13
Cognition	1.40	0.07, 2.74
Communication	1.86	0.48, 3.24
Motivation	0.83	-0.35, 2.02
Mannerisms	0.88	-0.50, 2.26

# Evaluating the evidence for phthalates and neurodevelopment-- strengths

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## 1. Biological Plausibility

- Disruption of maternal prenatal thyroid hormone a potential mechanism
- Consequences of severe hypothyroxinemia during pregnancy include significant neurodevelopmental impairment
- Evidence emerging that subclinical hypothyroxenima is also a threat to neurodevelopment

## 2. Dose-Response

- Both our examination of the BNBAS and the Behavioral screening instruments indicate that higher exposure was associated with more symptoms

## 3. Temporality

- Biomarker of exposure in the prenatal period very clearly preceded the outcome and was well aligned with a vulnerable window of development.

# Evaluating the evidence for phthalates and neurodevelopment-- weaknesses

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## 1. Replication

- No published replication with prenatal markers of exposure, but multiple studies underway

## 2. Experimental evidence

- We cannot randomize people to exposures

### Examples

- People choose to apply pesticides in their home
  - People choose to use scented products or cosmetics
  - People eat seafood containing contaminants
- 
- No published animal studies that have investigated phthalates with attention



# Prenatal Period as Window of Vulnerability

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**“Susceptibility to teratogens varies with the developmental stage at the time of exposure”**

## **Example: Congenital Rubella Syndrome**

- **≤12 weeks: Severe congenital anomalies: cataracts, deafness, cardiac, neurological**
- **13-16 weeks: Milder: deafness, mild neurological problems**
- **> 16 weeks: no symptoms at birth, impaired development**

**Other toxicants with epidemiological data supporting long-term impacts of prenatal exposure:**

- **Alcohol, cocaine, tobacco smoke, DES, valproic acid, thalidomide, methylmercury, lead, organophosphates...**



# Lessons Learned from the NIEHS/EPA Children's Environmental Health Centers

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- It may not be possible to accurately measure historical exposure from specimens or data collected after the outcome occurs

Regulatory changes in environmental chemicals  
Persistence of biomarker over time  
Accuracy of recall

- Context is key

**The same magnitude of exposure may impact two individuals differently**

Genetic Susceptibility  
Sex-specific effects

Parenting & home environment  
Lifestyle factors, diet or obesity



Difficult to assess  
without prospectively  
collected data



# The Promise & the Burden of Prospective Birth Cohorts

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- Required to obtain specimens from critical windows of development
- More accurately reflect the context of exposure during critical windows
- Other approaches may be preferable for rare disease & rare exposures
- Bio & Data repositories from prospective cohorts are costly and burdensome to assemble & maintain
- Provide the greatest flexibility to pursue other outcomes and exposures of interest in the future, perhaps not originally considered

## ***Project 2 contributors***

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***CEH: Grant Support NIEHS (ES009584), EPA (R827039 and RD831711), ATSDR, and The New York Community Trust***