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Pre-Conception Exposures and Children's Health

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Disclaimers

- I have no financial conflicts of interest related to the material being presented
- I was financially compensated as an expert witness in a lawsuit related to secondhand tobacco smoke exposures

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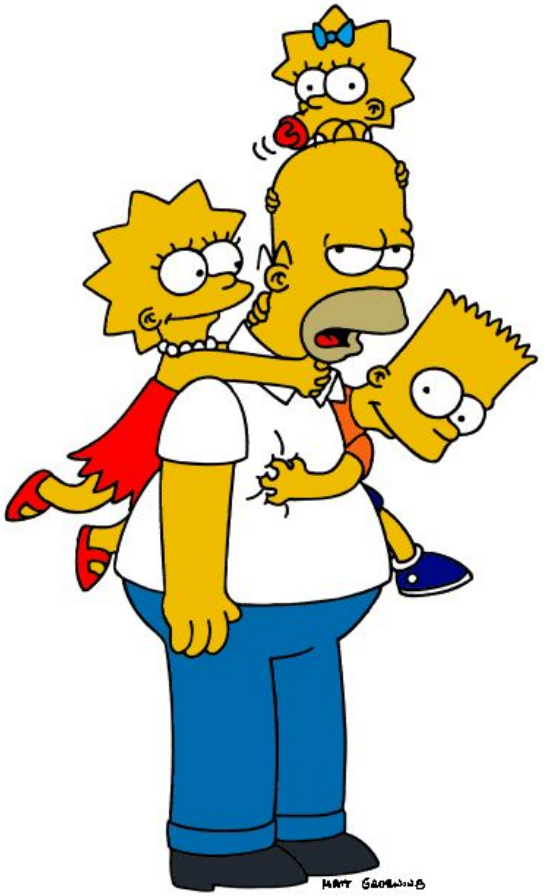
Do Dads Matter?

- I never thought of fatherhood as something that could affect a kid.

  – Homer Simpson



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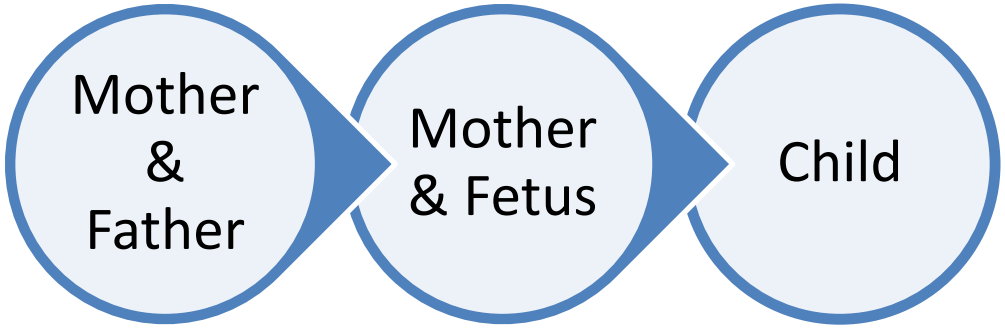
Beyond Prenatal: Preconception

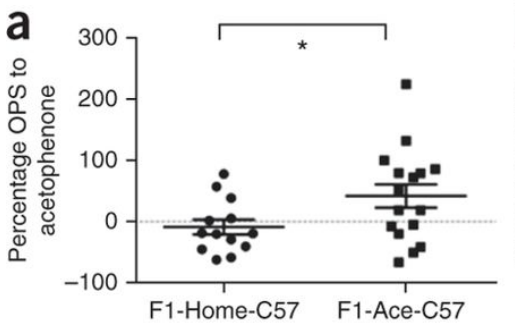
New results challenge two paradigms:

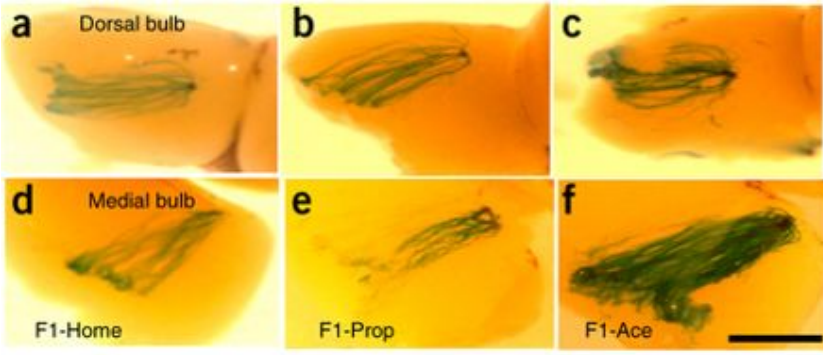
1. Gestation, infancy, and childhood are most important periods of susceptibility
2. Fathers only influence child health by Mendelian inheritance



Paternal Fear Conditioning (Diaz and Ressler, Nat Neurosci, 2014)

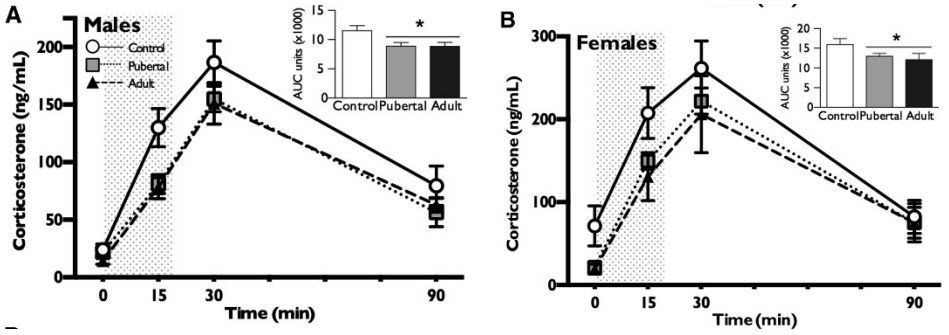
- Paternal preconception fear of acetophenone passed on to F1 & F2 male offspring
  - Neuroanatomical changes
  - DNA hypomethylation in offspring sperm

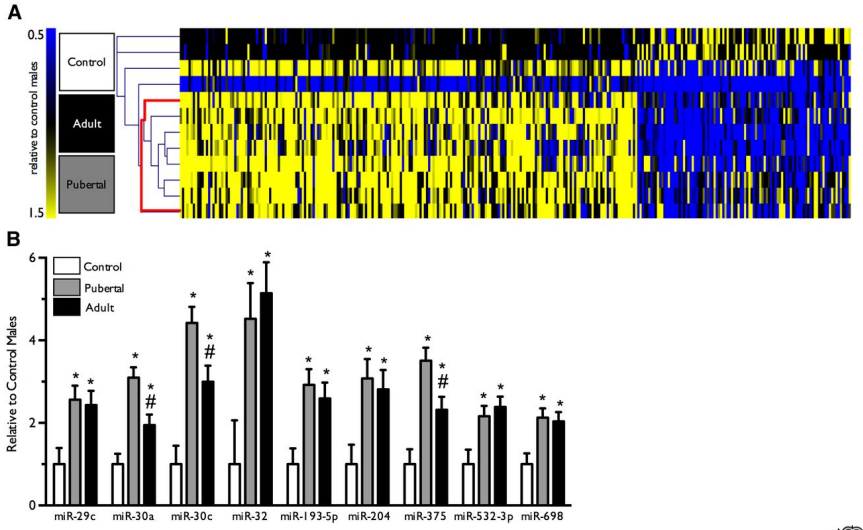




Paternal Stress and Offspring Health (Rodgers et al., 2013 and 2015)

- Paternal preconception stress caused:
  - ↓ offspring HPA axis response
  - Changes in sperm miRNA
- Sperm miRNAs recapitulated phenotype





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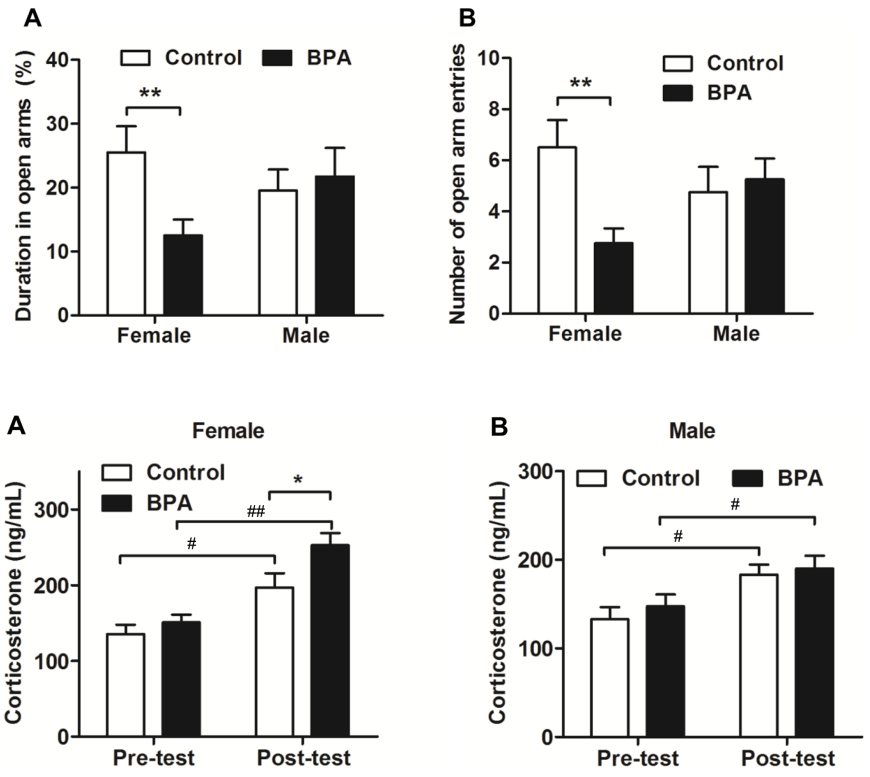
Paternal BPA and Rodent Neuro (Fan et al., PLoS ONE, 2018)

- Male rats exposed to BPA (50 μg/kg/d)
- Offspring anxiety (OFT and EPM) and corticosterone
- Exposed females displayed more signs of anxiety and had higher post-test corticosterone



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Paternal/Maternal BPA & Rodent Neuro (Harris et al., Horm & Behav, 2018)

- Male mice exposed to BPA (dose not reported)
- No effect of paternal BPA on offspring EPM and vocalizations
- Exposed males weighed less than controls
- Species-specific effects?

Epidemiological Studies of Pre-Conception Environmental Exposures

- Most epi studies of preconception exposures limited to studies of childhood cancer & birth defects
- Mostly occupational exposures
  - Paternal benzene and childhood leukemia
  - Paternal pesticides and childhood leukemia

Braun, Messerlian, and Hauser, Curr Epidem Rep, 2016; Carlos-Wallace, Am J Epidemiol, 2016; Bailey et al., Int J Cancer, 2014

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Transgenerational Effects of DES

- Grandchildren of grandmothers exposed to DES during pregnancy at increased risk of ADHD
  - OR: 1.4 (95% CI: 1.1, 1.7)
  - Strongest for 1st trimester (OR: 1.6; 95% CI: 1.2, 2.3)
  - No sex-specific effects
- Other EDCs?

Kioumourtzoglou et al., JAMA Peds, 2018

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Preconception Phthalates & Health

- Non-persistent, multifunctional class of chemicals
- Concern over toxicity
  - Anti-androgenic effects
  - Thyroid disruption
  - PPAR
- Sperm DNA methylation
  - Altered sperm DNA methylation in genes related to growth, development, and cell movement and structure

Wu et al., Human Repro, 2017

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The PEACE Study

- Preconception cohort of subfertile couples attending MGH clinic (2004-present)
- Maternal preconception and prenatal exposure, paternal preconception
- Ongoing follow-up of children at age 6-10 years (550+ eligible)
- Neurodevelopment, asthma/allergy, pubertal development, body composition, & cardiometabolic risk

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The PEACE Study

Paternal/Maternal Pre-Conception:
- Blood, urine, and hair
- Sperm (subset)
- Follicular Fluid (IVF)
- Exposure history
- Diet (FFQ)
- SES

Maternal/Infant Pregnancy:
- Blood, urine, and hair
- Exposure history
- Labor & Delivery

Children:
- Blood, urine, and hair
- IQ
- Behavior
- Executive function
- Body composition
- Metabolism
- Eating behaviors

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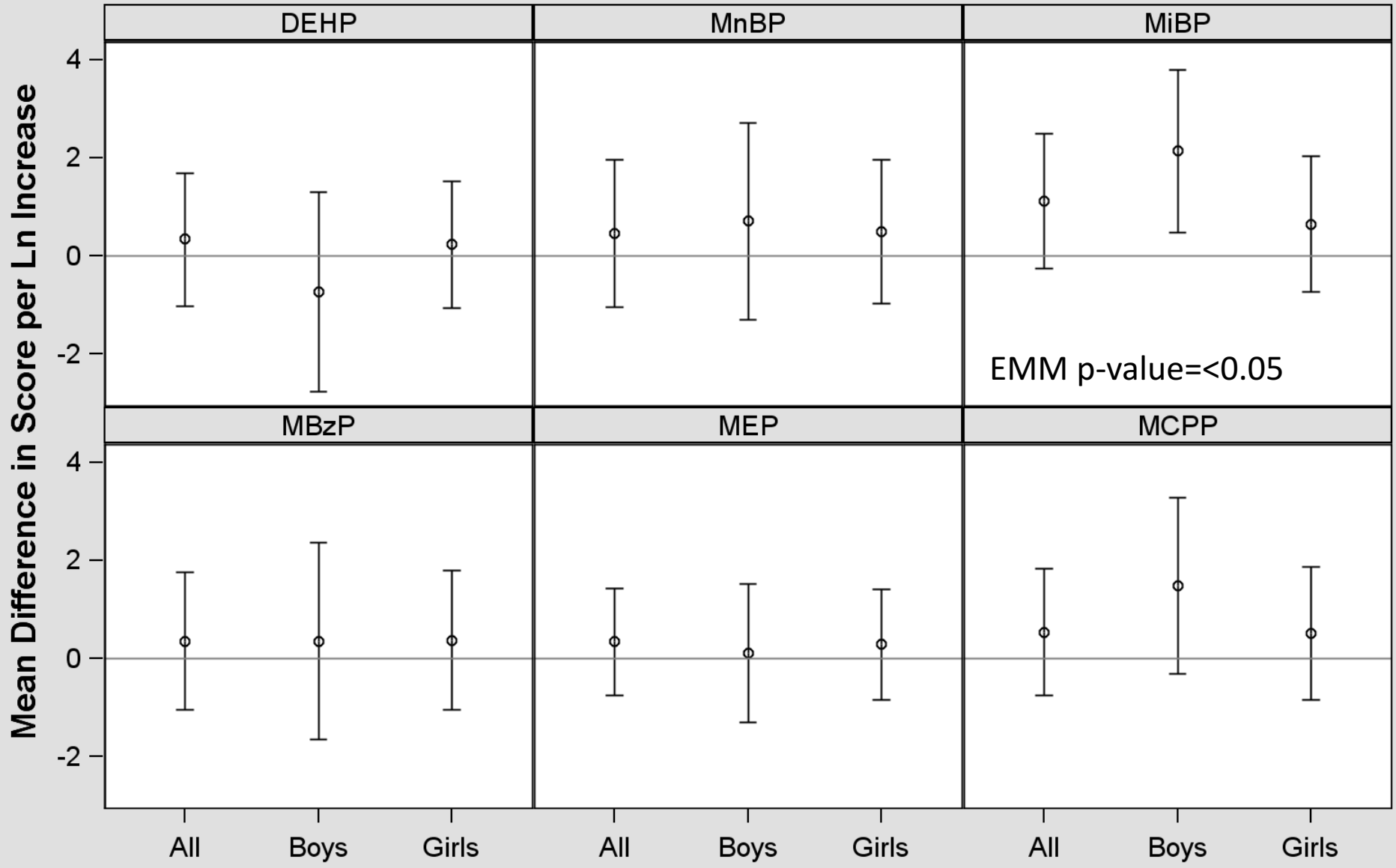
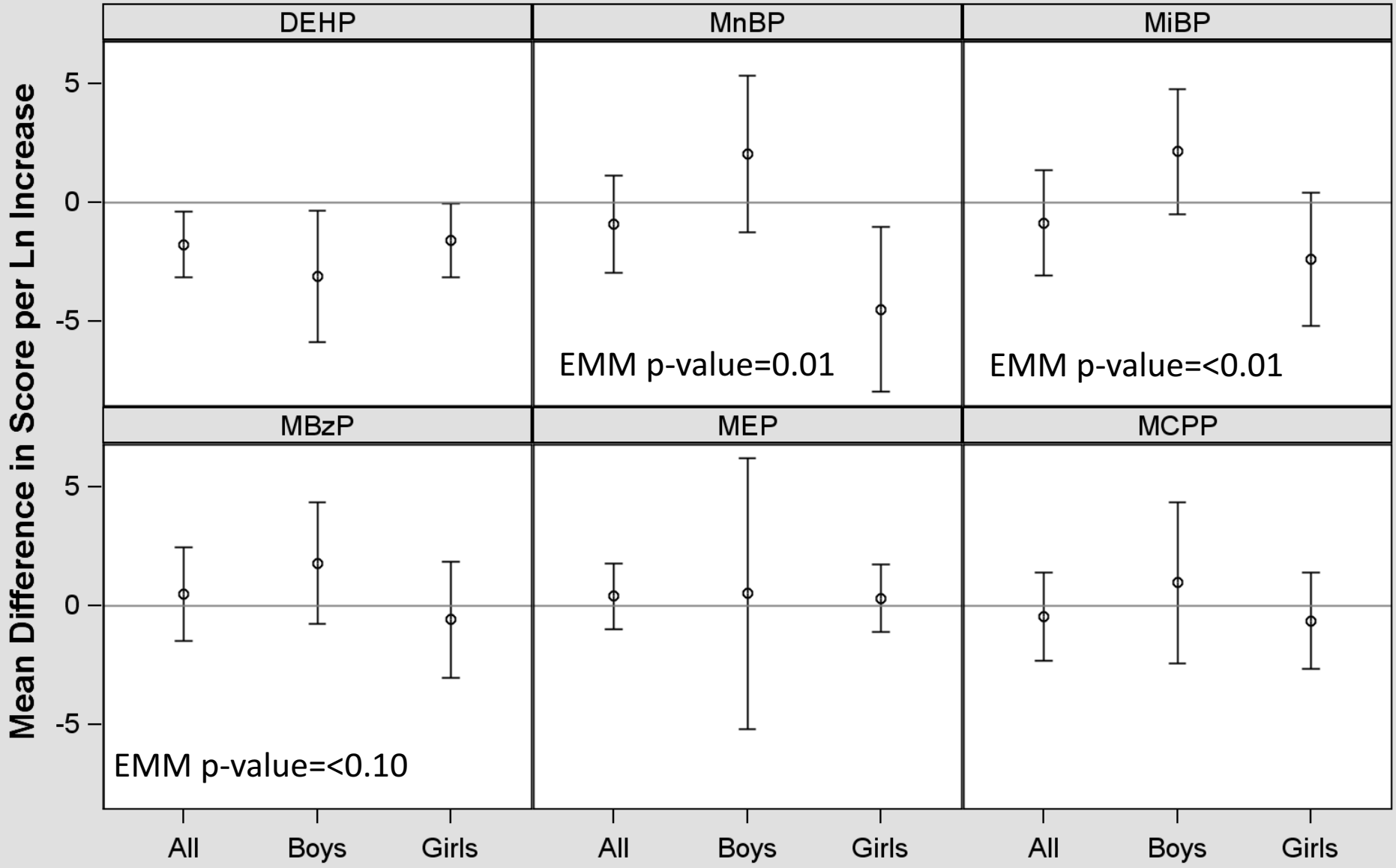
Maternal Preconception Urinary Phthalate Concentrations and Child Externalizing Behaviors (n=148)



Messerlian et al., Environ Res, 2017

Paternal Preconception Urinary Phthalate Concentrations and Child Internalizing Behaviors (n=105)



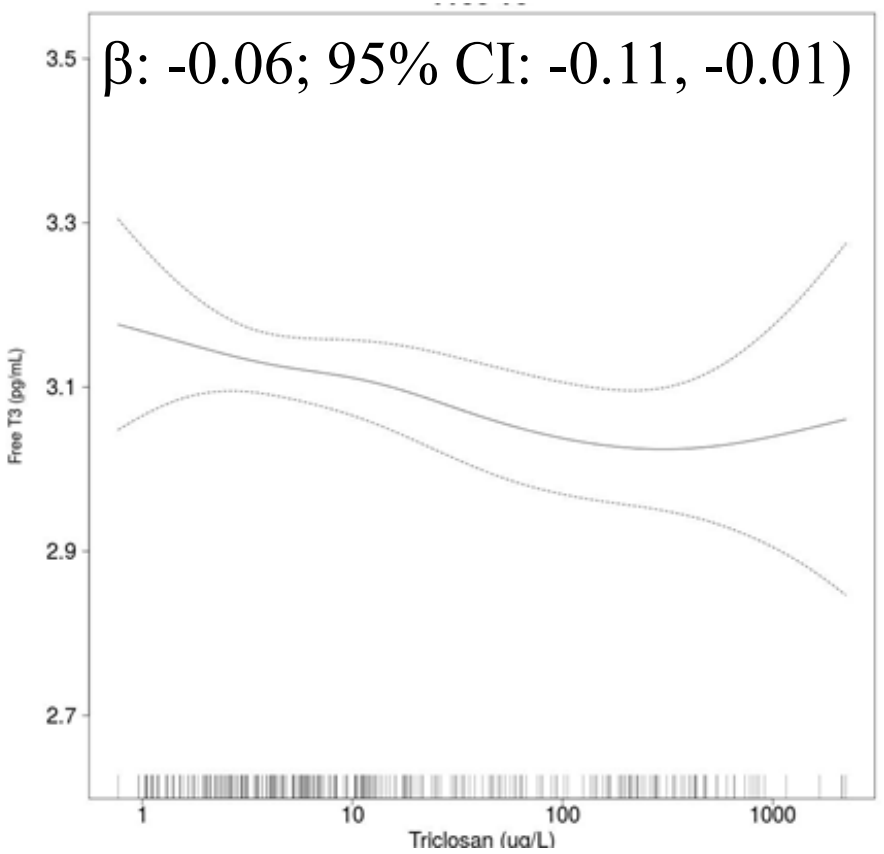
Messerlian et al., Environ Res, 2017

Pre-Conception Exposures and Birth Weight

- Messerlian, et al., Environ Int, 2017
  - Paternal DEHP associated with lower BW in 195 father-infant
  - Association stronger among babies conceived via IVF ($p<0.05$)
    - 90 gram decrease in BW with increasing DEHP (95% CI: -165, -15)
  - Association stronger after adjustment for maternal prenatal levels
- Mustieles et al., Human Reproduction, 2018
  - Maternal preconception BPA associated with reduced BW
    - 119 gram decrease in BW with increasing BPA (95% CI: -212, -27)
  - Association remained after adjusting for prenatal exposure

Preconception Triclosan and Thyroid

- EARTH Study
- Preconception urinary triclosan associated with decreased fT3 in women
  - N=317



Skarha et al., Environ Int, Under Review

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Challenges to Epidemiological Studies of Preconception Exposures

Challenges

- Enrolling couples at risk of becoming pregnant
  - ~10% of US women become pregnant each year and ~63% are intended pregnancies
- Potential for loss to follow-up and censoring
  - Conceiving, live-birth, and continued follow-up
- Generalizability

Solutions

- Fertility clinic enrollment, targeted internet advertising, and brute-force
  - LIFE, EARTH, and PRESTO Studies
- Large sample sizes or retrospective assessment
- Scientific validity

Braun, Messerlian, and Hauser; Curr Epidem Rep; 2016

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Concluding Remarks

- Potential for preconception environmental exposures to affect children's health
- Fathers matter
- Public health implications

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THANK YOU!!!