Prenatal phthalate exposures and body mass index among 4 to 7 year old children: A pooled analysis

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PPTOX IV
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Phthalates

• Low molecular weight
  – Adhesives, paints, personal care products (e.g., cosmetics, lotions, fragrances)

• High molecular weight
  – Plastics (e.g. food packaging, building materials, toys)

• All exposure routes

• Elimination half lives of less than 24 hours

• Ubiquitous exposure

Koch et al. Arch Toxicol 2005; Silva et al. EHP 2004

Di-(2-ethylhexyl) phthalate (DEHP)
Obesogen hypothesis

Early life phthalate exposures

- peroxisome proliferator-activated receptors (PPARs)
- thyroid hormones
- androgen activity

-> adipogenesis, insulin sensitivity, leptin
-> energy balance, metabolism
-> muscle and fat development

-> Obesity

Objective

To assess the relationship between prenatal phthalate exposures and BMI in early childhood
Challenge

• Limited power in birth cohorts with longitudinal follow-up

• Solution: Pooled analysis of three U.S. birth cohorts
  – Mount Sinai School of Medicine Children’s Environmental Health Center (MSSM), New York, NY
  – Columbia Center for Children’s Environmental Health (CCEH), New York, NY
  – Health Outcomes and Measures of the Environment Study (HOME), five Ohio counties

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<tbody>
<tr>
<td>MSSM</td>
<td>Enrollment</td>
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<td>Enrollment</td>
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<td>HOME</td>
<td>Enrollment</td>
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Study sample

MSSM  N = 404
CCEH  N = 727
HOME  N = 389

N = 1520

Exclusions:
- <32 weeks gestation or <1,500 grams
- Urinary creatinine < 10 mg/dL
- Urinary phthalate concentrations not measured during pregnancy

N = 1143

Restricted to children with measured weight and height collected at ≥1 follow-up visit occurring between 4 and 7 years of age

N = 707, 1416 visits
Phthalate metabolite concentrations
Outcomes

- Calculated age- and sex-standardized BMI percentiles and z-scores using CDC growth charts.

- Overweight or obese = age- and sex-standardized BMI percentile >85.

- Assessed BMI z-score as a continuous outcome.
Statistical analysis

• Bayesian modeling framework
  – Linear and logistic mixed effects regression models
  – Adjusted for a large set of potential confounders
  – Multiply imputed missing covariate data
  – Assessed heterogeneity by child’s sex
  – Multiple metabolite models

<table>
<thead>
<tr>
<th></th>
<th>MEP</th>
<th>MnBP</th>
<th>MiBP</th>
<th>MCPP</th>
<th>MBzP</th>
<th>ΣDEHP</th>
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<td>MnBP</td>
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<td>MiBP</td>
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<td>0.8</td>
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<td>MCPP</td>
<td>0.4</td>
<td>0.7</td>
<td>0.6</td>
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<td>MBzP</td>
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<td>0.7</td>
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# Characteristics by cohort, n (%)

<table>
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<tr>
<th>Characteristic</th>
<th>MSSM</th>
<th>CCEH</th>
<th>HOME</th>
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<tr>
<td><strong>Total (N)</strong></td>
<td>151</td>
<td>339</td>
<td>217</td>
<td>707</td>
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<td><strong>Maternal age at delivery (years)</strong></td>
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<tr>
<td>&lt; 20</td>
<td>42</td>
<td>47</td>
<td>13</td>
<td>102</td>
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<tr>
<td>20–24</td>
<td>53</td>
<td>121</td>
<td>37</td>
<td>211</td>
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<td>25–29</td>
<td>21</td>
<td>100</td>
<td>62</td>
<td>183</td>
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<td>≥ 30</td>
<td>35</td>
<td>71</td>
<td>105</td>
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<td>Non-Hispanic white</td>
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<td>135</td>
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<tr>
<td>Non-Hispanic black</td>
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<td>Hispanic</td>
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<td>Other</td>
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<td><strong>Maternal education</strong></td>
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<td>&lt;High school</td>
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<td>159</td>
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<td><strong>Mother worked during pregnancy</strong></td>
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<td>0 (0)</td>
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<td>199</td>
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<td>472</td>
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<td><strong>Parity (multiparous)</strong></td>
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<td>305</td>
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<td><strong>Maternal smoking during pregnancy</strong></td>
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Odds ratio per SD increase in natural log phthalate metabolite concentrations estimated in a multiple metabolite logistic mixed effects model, adjusted for cohort; urine dilution and collection date; maternal race/ethnicity, age, education, work status, parity, height, and pre-pregnancy body mass index; gestational weight gain; gestational tobacco exposure; breastfeeding; child’s sex; and child’s age (months) at follow-up
Overweight/obesity by child’s sex

Odds ratio per SD increase in natural log phthalate metabolite concentrations estimated in a multiple metabolite logistic mixed effects model, adjusted for cohort; urine dilution and collection date; maternal race/ethnicity, age, education, work status, parity, height, and pre-pregnancy body mass index; gestational weight gain; gestational tobacco exposure; breastfeeding; and child’s age (months) at follow-up.
Beta per SD increase in natural log phthalate metabolite concentrations estimated in a multiple metabolite linear mixed effects model, adjusted for cohort; urine dilution and collection date; maternal race/ethnicity, age, education, work status, parity, height, and pre-pregnancy body mass index; gestational weight gain; gestational tobacco exposure; breastfeeding; child’s sex; and child’s age (months) at follow-up.
Beta per SD increase in natural log phthalate metabolite concentrations estimated in a multiple metabolite linear mixed effects model, adjusted for cohort; urine dilution and collection date; maternal race/ethnicity, age, education, work status, parity, height, and pre-pregnancy body mass index; gestational weight gain; gestational tobacco exposure; breastfeeding; and child’s age (months) at follow-up.
Conclusions

• MCPP may be an environmental obesogen
  – Associated with overweight/obesity but not BMI z-scores
  – Confounding by diet?
  – Associated with increased odds of high cord blood leptin levels in male infants (Ashley-Martin et al. Environ Health in press)

• MEP associated with lower BMI z-scores in girls
  – No evidence of obesogenic effects, may interfere with other processes related to physical development
Future directions

• Other susceptible windows
  – Phthalate exposures during childhood
  – Body size at other developmental stages (e.g., puberty)

• Co-exposures to other environmental obesogens
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