

**Prenatal Exposure to NonPersistent Endocrine Disruptors and Early Childhood BMI:  
Single Pollutant and Mixture Analyses from the ECHO Program**

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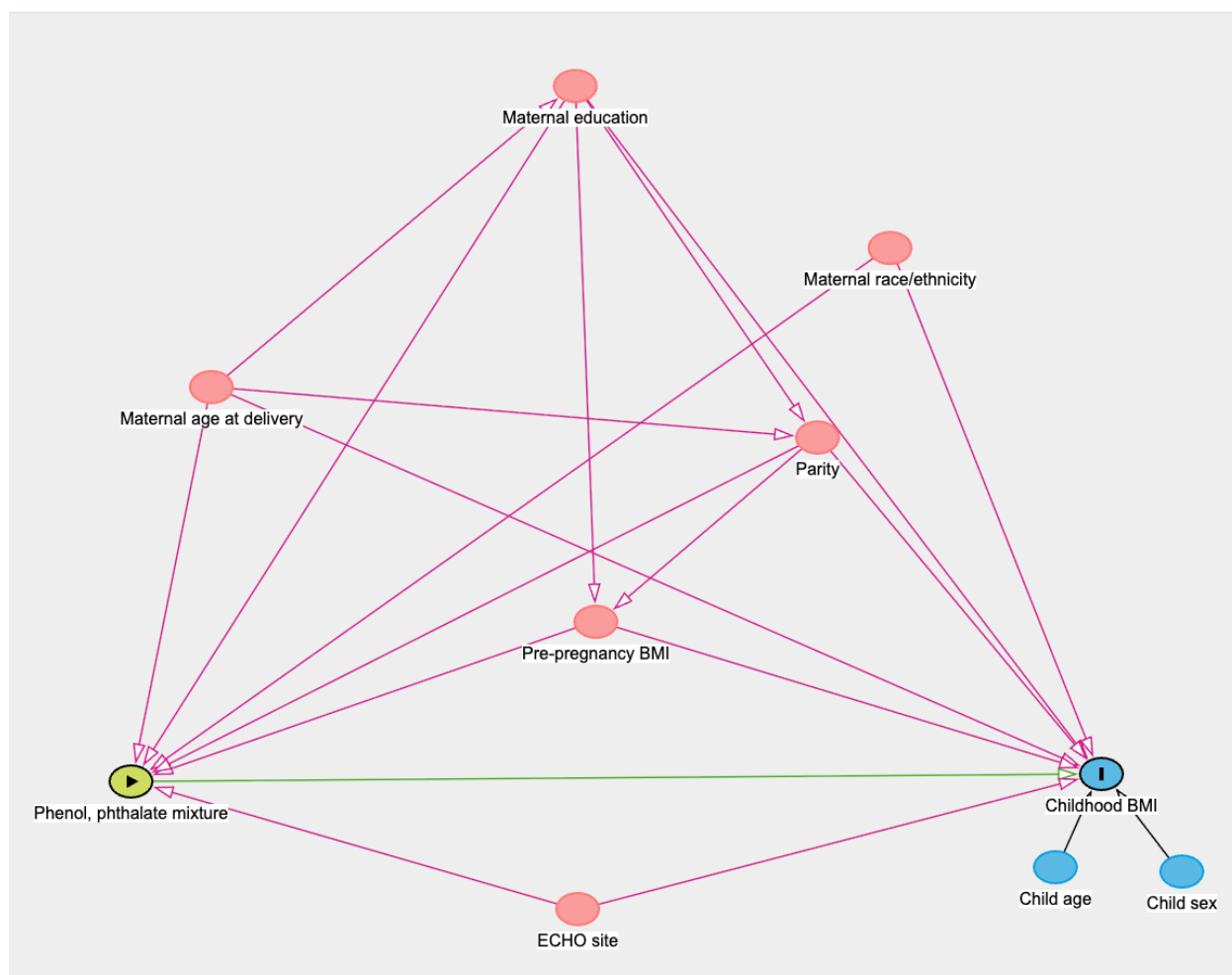
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Table S1. Characteristics of study population among selected ECHO sites

|                                                        | Inclusion criteria                                                                                                                                                                                                                                                            | N with exposure data | Recruitment site                                                      | Years of enrollment | N of urine samples and dilution measure                                                                                                                                                                                        |
|--------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|-----------------------------------------------------------------------|---------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| The PROTECT Study <sup>1</sup>                         | Age 18-40 years<br>Residence within the Northern Karst aquifer region<br>Did not use oral contraceptives within the three months prior to pregnancy<br>No use of <i>in vitro</i> fertilization to become pregnant<br>No major preexisting medical conditions (e.g., diabetes) | 569                  | Hospitals and health clinics of the north coast region of Puerto Rico | 2010 – 2018         | <ul style="list-style-type: none"> <li>• 3 spot urine samples (median collection gestation weeks (20 <math>\pm</math> 2 weeks, 24 <math>\pm</math> 2 weeks, and 28 <math>\pm</math> 2 )</li> <li>• Specific gravity</li> </ul> |
| Healthy Start <sup>2</sup>                             | Women 16 years or older and < 24 weeks gestation at first prenatal visit. Not expecting multiple births, had no previous stillbirth, pre-existing diabetes, asthma managed with steroids, cancer, or a serious psychiatric illness.                                           | 446                  | The University of Colorado obstetric clinics.                         | 2009 – 2014         | <ul style="list-style-type: none"> <li>• 1 spot urine sample between 24–32 weeks gestation (median 27 weeks).</li> <li>• Creatinine</li> </ul>                                                                                 |
| Illinois Kids Development Studies (IKIDS) <sup>3</sup> | Women between 18–40 years. Fluent in English, in a low-risk singleton pregnancy, living within a 30-minute drive of the University of Illinois campus, and not planning to move out of the area before their child's first birthday.                                          | 411                  | Two local obstetric clinics in Champaign-Urbana, Illinois.            | 2013 – 2018         | <ul style="list-style-type: none"> <li>• 5 first-morning urine samples (median 13, 17, 23, 28, and 34 weeks)</li> <li>• Specific gravity</li> </ul>                                                                            |



**Figure S1.** Directed Acyclic Graph (DAG) for estimating the prenatal mixture effects of phenols and phthalates on childhood body mass index (BMI)

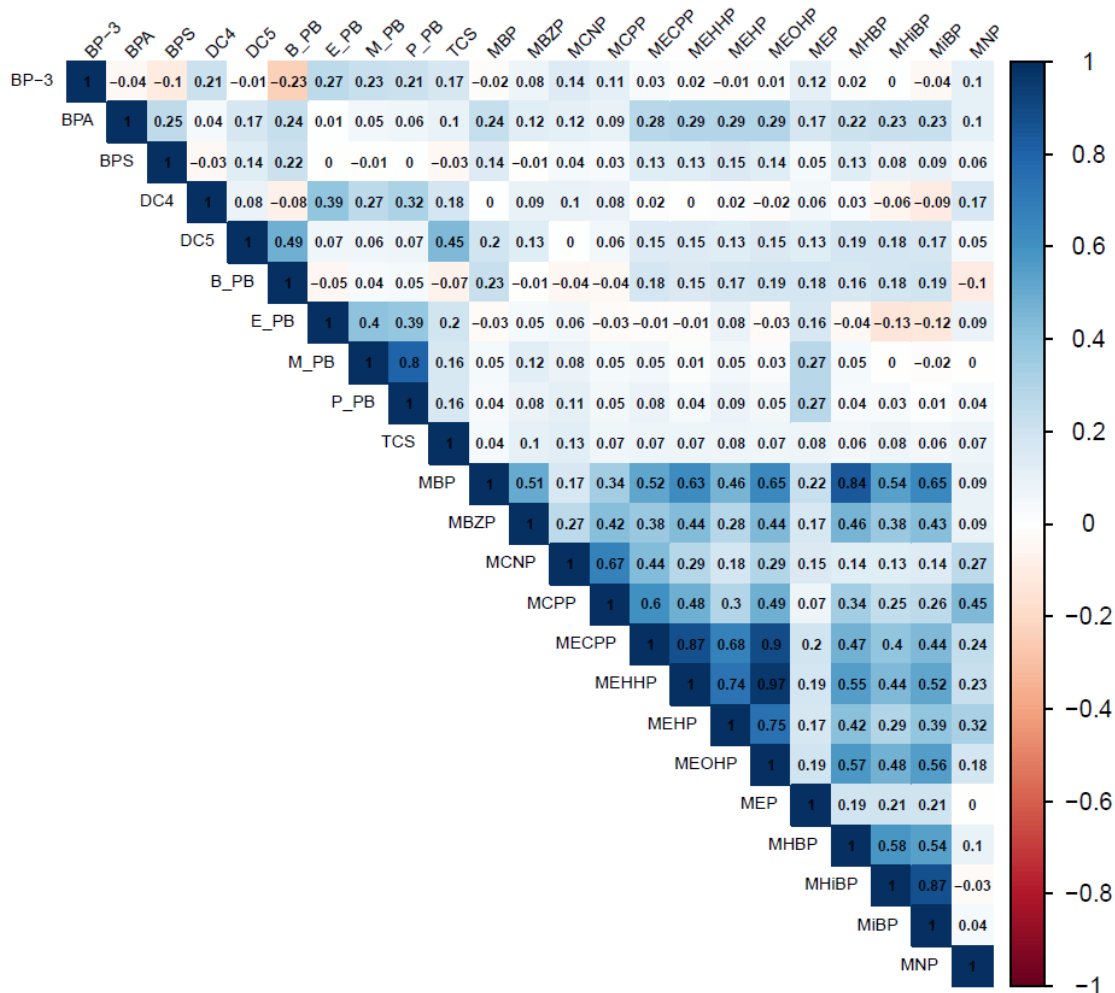


Figure S2: Spearman's correlation coefficient matrix for phenol and phthalate metabolite urinary concentrations during pregnancy among 586 participants from three ECHO cohorts.

Abbreviations: BP\_3: benzophenone-3, BPA: bisphenol A, BPS: bisphenol S, DC4: 2,4 dichlorophenol, DC5: 2,5 dichlorophenol, B\_PB: butyl paraben, E\_PB: ethyl paraben, M\_PB: methyl paraben, P\_PB: propyl paraben, TCS: triclosan, MBP: Mono-n-butyl phthalate, MBzP: Mono-benzyl phthalate ,MCNP: Mono carboxyisononyl phthalate ,MCP: Mono-3-carboxypropyl phthalate ,MECPP: Mono-2-ethyl-5-carboxypentyl phthalate ,MEHHP: Mono-2-ethyl-5-hydroxyhexyl phthalate ,MEHP: Mono-2-ethylhexyl phthalate ,MEOHP: Mono-2-ethyl-5-oxohexyl phthalate ,MEP: Mono-ethyl phthalate ,MHBP: Mono-hydroxybutyl phthalate ,MHiBP: Mono-hydroxyisobutyl phthalate ,MIBP: Mono-isobutyl phthalate ,MNP: Mono-isononyl phthalate

Table S2: Change in child BMI z-score per interquartile range (IQR) increase in the natural log–transformed exposure concentration

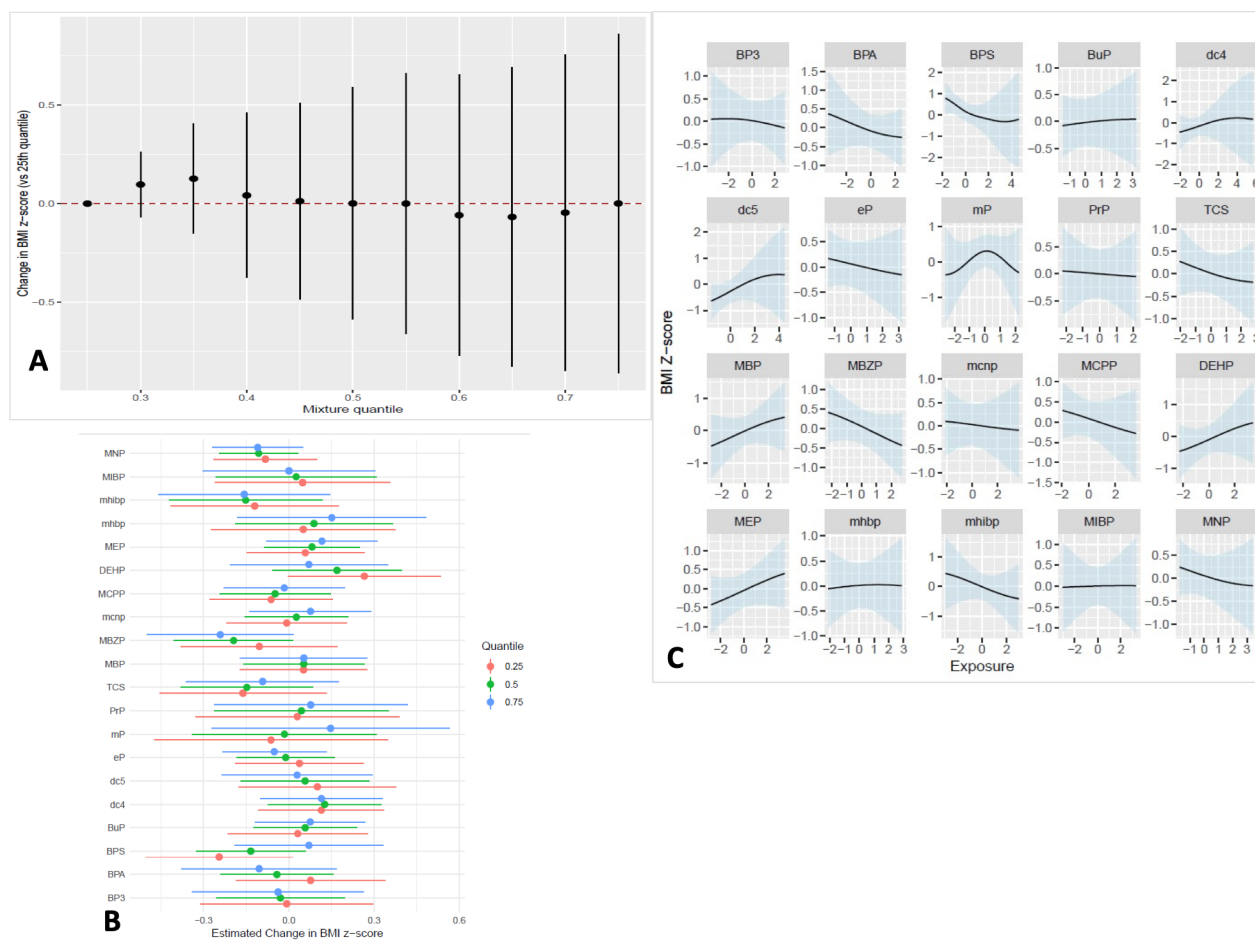
|                                | All participants    | Males               | Females             |
|--------------------------------|---------------------|---------------------|---------------------|
| Exposure                       | Estimate (95% CI)   | Estimate (95% CI)   | Estimate (95% CI)   |
| Benzophenone-3                 | −0.04 (−0.20; 0.12) | −0.12 (−0.33; 0.10) | 0.03 (−0.21; 0.27)  |
| Bisphenol-A                    | −0.03 (−0.18; 0.11) | −0.20 (−0.40; 0.00) | 0.13 (−0.08; 0.34)  |
| Bisphenol-S                    | −0.01 (−0.15; 0.12) | −0.07 (−0.26; 0.12) | −0.02 (−0.22; 0.19) |
| Butyl paraben                  | −0.03 (−0.15; 0.08) | −0.10 (−0.27; 0.07) | 0.04 (−0.13; 0.20)  |
| 2,4-Dichlorophenol             | 0.07 (−0.05; 0.18)  | 0.03 (−0.13; 0.19)  | 0.08 (−0.09; 0.25)  |
| 2,5-Dichlorophenol             | 0.10 (−0.05; 0.25)  | 0.13 (−0.08; 0.34)  | 0.06 (−0.16; 0.28)  |
| Ethyl paraben                  | −0.03 (−0.14; 0.09) | −0.08 (−0.23; 0.08) | 0.02 (−0.16; 0.20)  |
| Methyl paraben                 | 0.05 (−0.12; 0.21)  | −0.04 (−0.28; 0.20) | 0.09 (−0.14; 0.33)  |
| Propyl paraben                 | 0.07 (−0.10; 0.25)  | −0.01 (−0.27; 0.25) | 0.15 (−0.10; 0.41)  |
| Triclosan                      | −0.04 (−0.20; 0.13) | −0.15 (−0.40; 0.09) | 0.04 (−0.20; 0.27)  |
| Mono-benzyl phthalate          | 0.05 (−0.09; 0.19)  | 0.05 (−0.13; 0.24)  | 0.04 (−0.18; 0.26)  |
| Mono-benzyl phthalate          | 0.09 (−0.05; 0.24)  | 0.03 (−0.19; 0.25)  | 0.12 (−0.08; 0.32)  |
| Mono-carboxyisononyl phthalate | −0.14 (−0.28; 0.01) | −0.17 (−0.36; 0.03) | −0.08 (−0.29; 0.13) |
| Mono-3-carboxypropyl phthalate | 0.01 (−0.11; 0.14)  | −0.07 (−0.25; 0.11) | 0.05 (−0.12; 0.23)  |
| Mono-ethyl phthalate           | −0.03 (−0.16; 0.10) | −0.13 (−0.31; 0.07) | 0.01 (−0.16; 0.18)  |
| Molar sum of DEHP metabolites  | 0.07 (−0.07; 0.20)  | 0.06 (−0.13; 0.27)  | 0.07 (−0.12; 0.26)  |
| Mono-hydroxybutyl phthalate    | 0.03 (−0.12; 0.18)  | −0.04 (−0.24; 0.17) | 0.08 (−0.15; 0.30)  |
| Mono-hydroxyisobutyl phthalate | −0.03 (−0.16; 0.10) | −0.16 (−0.35; 0.02) | 0.08 (−0.11; 0.27)  |
| Mono-isobutyl phthalate        | −0.02 (−0.16; 0.12) | −0.14 (−0.34; 0.06) | 0.08 (−0.12; 0.28)  |
| Mono-isononyl phthalate        | −0.05 (−0.14; 0.03) | −0.06 (−0.17; 0.05) | −0.07 (−0.20; 0.06) |

Adjustment factors: child sex, child age at BMI assessment, maternal age at delivery, maternal pre-pregnancy BMI, parity, maternal race, maternal education level and ECHO site.

Table S3: Differences in BMI z-score per tertile of prenatal phthalate metabolite exposure, relative to the reference category (Tertile 1)

| Exposure                | Tertile   | All participants     | Males                | Females             |
|-------------------------|-----------|----------------------|----------------------|---------------------|
|                         |           | Estimate (95%)       | Estimate (95%)       | Estimate (95%)      |
| Benzophenone-3          | Tertile 2 | 0.10 (-0.17; 0.37)   | 0.05 (-0.33; 0.43)   | 0.14 (-0.25; 0.54)  |
|                         | Tertile 3 | -0.02 (-0.31; 0.26)  | -0.02 (-0.43; 0.38)  | -0.01 (-0.43; 0.40) |
| Bisphenol-A             | Tertile 2 | 0.03 (-0.23; 0.28)   | -0.11 (-0.45; 0.23)  | 0.14 (-0.25; 0.53)  |
|                         | Tertile 3 | -0.10 (-0.36; 0.17)  | -0.32 (-0.68; 0.04)  | 0.12 (-0.28; 0.53)  |
| Bisphenol-S             | Tertile 2 | -0.01 (-0.26; 0.25)  | -0.24 (-0.61; 0.12)  | 0.13 (-0.26; 0.52)  |
|                         | Tertile 3 | -0.01 (-0.27; 0.26)  | -0.09 (-0.44; 0.26)  | 0.00 (-0.41; 0.42)  |
| Butyl paraben           | Tertile 2 | 0.13 (-0.14; 0.40)   | -0.14 (-0.50; 0.22)  | 0.39 (0.00; 0.79)   |
|                         | Tertile 3 | 0.03 (-0.24; 0.30)   | -0.11 (-0.48; 0.26)  | 0.24 (-0.16; 0.64)  |
| 2,4-Dichlorophenol      | Tertile 2 | 0.09 (-0.17; 0.35)   | 0.18 (-0.17; 0.53)   | 0.01 (-0.38; 0.40)  |
|                         | Tertile 3 | 0.19 (-0.07; 0.46)   | 0.15 (-0.20; 0.50)   | 0.21 (-0.20; 0.61)  |
| 2,5-Dichlorophenol      | Tertile 2 | 0.07 (-0.20; 0.34)   | 0.04 (-0.33; 0.41)   | 0.08 (-0.32; 0.48)  |
|                         | Tertile 3 | 0.25 (-0.06; 0.55)   | 0.29 (-0.13; 0.70)   | 0.13 (-0.34; 0.59)  |
| Ethyl paraben           | Tertile 2 | 0.02 (-0.25; 0.29)   | 0.00 (-0.37; 0.36)   | 0.04 (-0.35; 0.43)  |
|                         | Tertile 3 | -0.03 (-0.30; 0.23)  | -0.15 (-0.50; 0.21)  | 0.10 (-0.30; 0.51)  |
| Methyl paraben          | Tertile 2 | -0.01 (-0.27; 0.25)  | 0.06 (-0.30; 0.42)   | -0.08 (-0.48; 0.31) |
|                         | Tertile 3 | 0.06 (-0.22; 0.33)   | 0.00 (-0.39; 0.38)   | 0.09 (-0.32; 0.50)  |
| Propyl paraben          | Tertile 2 | 0.03 (-0.23; 0.30)   | 0.04 (-0.33; 0.41)   | 0.01 (-0.38; 0.40)  |
|                         | Tertile 3 | 0.17 (-0.10; 0.44)   | 0.04 (-0.35; 0.43)   | 0.31 (-0.09; 0.70)  |
| Triclosan               | Tertile 2 | -0.04 (-0.31; 0.23)  | -0.20 (-0.55; 0.15)  | 0.13 (-0.29; 0.54)  |
|                         | Tertile 3 | -0.04 (-0.31; 0.22)  | -0.20 (-0.58; 0.17)  | 0.08 (-0.30; 0.47)  |
| Mono-n-butyl phthalate  | Tertile 2 | 0.07 (-0.19; 0.32)   | 0.45 (0.11; 0.79)    | -0.26 (-0.64; 0.12) |
|                         | Tertile 3 | 0.03 (-0.24; 0.30)   | 0.02 (-0.34; 0.38)   | 0.01 (-0.38; 0.41)  |
| Mono-benzyl phthalate   | Tertile 2 | 0.00 (-0.27; 0.26)   | 0.11 (-0.25; 0.47)   | -0.06 (-0.47; 0.35) |
|                         | Tertile 3 | -0.36 (-0.63; -0.08) | -0.39 (-0.76; -0.01) | -0.30 (-0.72; 0.12) |
| Mono-carboxyisononyl    | Tertile 2 | 0.11 (-0.16; 0.39)   | 0.00 (-0.36; 0.36)   | 0.12 (-0.30; 0.54)  |
|                         | Tertile 3 | -0.05 (-0.32; 0.22)  | -0.24 (-0.62; 0.14)  | 0.08 (-0.31; 0.47)  |
| Mono-3-carboxypropyl    | Tertile 2 | -0.09 (-0.35; 0.18)  | -0.21 (-0.57; 0.14)  | 0.03 (-0.38; 0.45)  |
|                         | Tertile 3 | -0.06 (-0.33; 0.21)  | -0.25 (-0.62; 0.13)  | 0.06 (-0.33; 0.46)  |
| Mono-ethyl phthalate    | Tertile 2 | 0.27 (0.01; 0.53)    | 0.04 (-0.32; 0.40)   | 0.43 (0.04; 0.81)   |
|                         | Tertile 3 | 0.14 (-0.12; 0.41)   | 0.03 (-0.33; 0.40)   | 0.18 (-0.22; 0.57)  |
| Molar sum of DEHP       | Tertile 2 | 0.07 (-0.19; 0.32)   | -0.05 (-0.40; 0.29)  | 0.22 (-0.17; 0.62)  |
|                         | Tertile 3 | 0.02 (-0.25; 0.29)   | 0.05 (-0.32; 0.41)   | 0.03 (-0.36; 0.42)  |
| Mono-hydroxybutyl       | Tertile 2 | -0.14 (-0.40; 0.12)  | 0.00 (-0.35; 0.35)   | -0.29 (-0.68; 0.10) |
|                         | Tertile 3 | 0.02 (-0.24; 0.28)   | -0.10 (-0.45; 0.26)  | 0.09 (-0.30; 0.47)  |
| Mono-hydroxyisobutyl    | Tertile 2 | -0.07 (-0.33; 0.19)  | 0.01 (-0.34; 0.35)   | -0.08 (-0.48; 0.32) |
|                         | Tertile 3 | -0.05 (-0.31; 0.21)  | -0.18 (-0.53; 0.17)  | 0.05 (-0.36; 0.45)  |
| Mono-isobutyl phthalate | Tertile 2 | 0.12 (-0.13; 0.38)   | -0.08 (-0.43; 0.27)  | 0.31 (-0.08; 0.70)  |
|                         | Tertile 3 | 0.09 (-0.17; 0.35)   | -0.10 (-0.47; 0.27)  | 0.24 (-0.14; 0.62)  |
| Mono-isononyl phthalate | Tertile 2 | -0.18 (-0.45; 0.10)  | -0.05 (-0.41; 0.32)  | -0.35 (-0.76; 0.07) |
|                         | Tertile 3 | -0.21 (-0.46; 0.05)  | -0.17 (-0.52; 0.17)  | -0.32 (-0.70; 0.07) |

Adjustment factors: child sex, child age at BMI assessment, maternal age at delivery, maternal pre-pregnancy BMI, parity, maternal race, maternal education level and ECHO site



**S3.** Association between BMI z-scores and prenatal exposure to phenol and phthalate mixtures using Bayesian Kernel Machine Regression (BKMR) in males only.

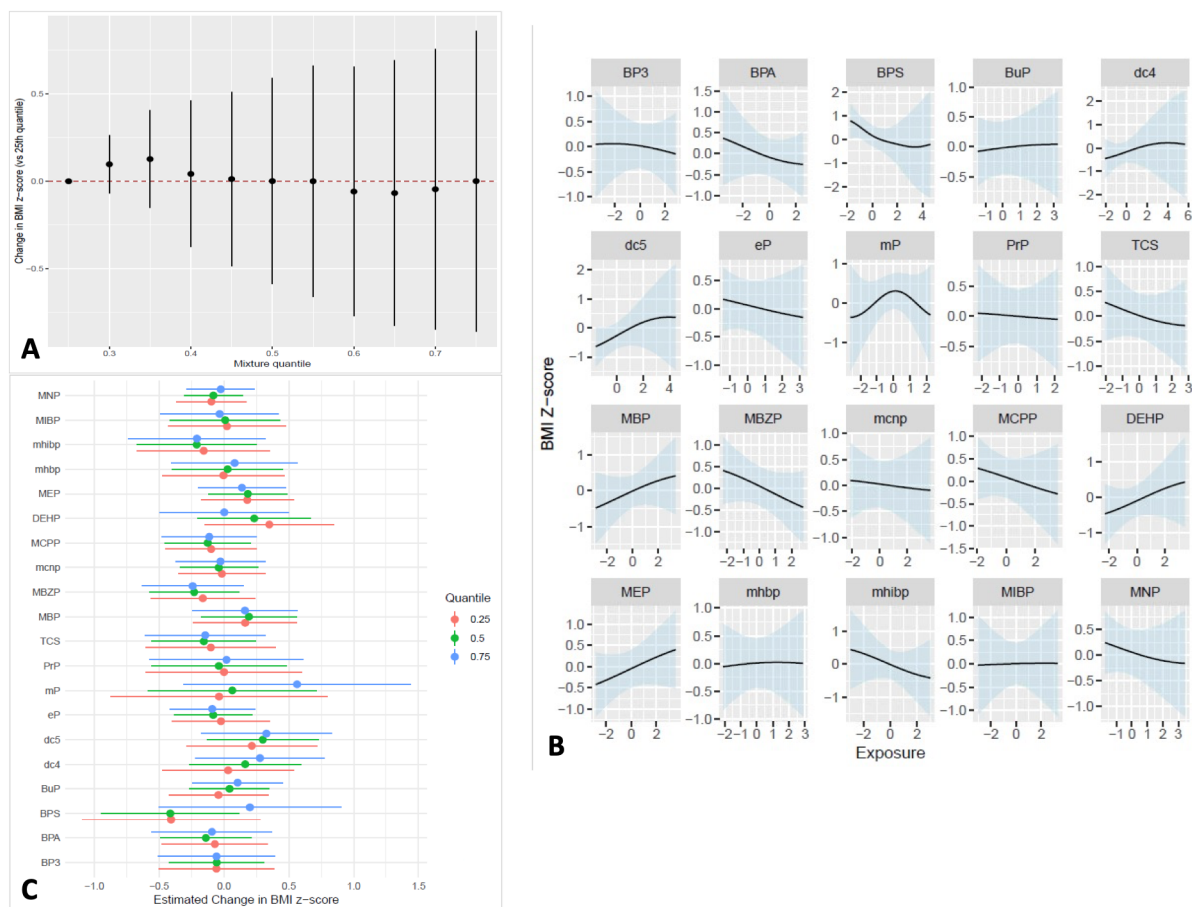
**A:** Overall mixture effect estimate with 95% credible intervals.

**B:** Single-exposure effects of each compound on BMI z-scores while fixing all other exposures at the 25th (red), 50th (green), and 75th (blue) percentiles.

**C:** Univariate exposure-response functions for each compound (95% CI), holding all other exposures at their median values.

Adjustment factors: child sex, child age at BMI assessment, maternal age at delivery, maternal pre-pregnancy BMI, parity, maternal race, maternal education level and ECHO site.

Abbreviations: BP3: Benzophenone-3, BPA: Bisphenol A, BPS: Bisphenol S, BuP: Butyl Paraben, DC4: 2,4-Dichlorophenol, DC5: 2,5-Dichlorophenol, eP: Ethyl Paraben, mP: Methyl Paraben, PrP: Propyl Paraben, TCS: Triclosan, MBP: Mono-n-butyl phthalate (metabolite of DBP), MEP: Mono-ethyl phthalate (metabolite of DEP), MBZP: Mono-benzyl phthalate (metabolite of BBzP), MCnP: Mono-carboxyisononyl phthalate (metabolite of DINP), MCPP: Mono-3-carboxypropyl phthalate, MHBP: Mono-hydroxybutyl phthalate, MHiBP: Mono-hydroxyisobutyl phthalate, MIBP: Mono-isobutyl phthalate, MNP: Mono-nonyl phthalate.



**Figure S4.** Association between BMI z-scores and prenatal exposure to phenol and phthalate mixtures using Bayesian Kernel Machine Regression (BKMR) in females only.

**A:** Overall mixture effect estimate with 95% credible intervals.

**B:** Single-exposure effects of each compound on BMI z-scores while fixing all other exposures at the 25th (red), 50th (green), and 75th (blue) percentiles.

**C:** Univariate exposure-response functions for each compound (95% CI), holding all other exposures at their median values.

Adjustment factors: child sex, child age at BMI assessment, maternal age at delivery, maternal pre-pregnancy BMI, parity, maternal race and ethnicity, maternal education level and ECHO stie.

Abbreviations: BP3: Benzophenone-3, BPA: Bisphenol A, BPS: Bisphenol S, BuP: Butyl Paraben, DC4: 2,4-Dichlorophenol, DC5: 2,5-Dichlorophenol, eP: Ethyl Paraben, mP: Methyl Paraben, PrP: Propyl Paraben, TCS: Triclosan, MBP: Mono-n-butyl phthalate (metabolite of DBP), MEP: Mono-ethyl phthalate (metabolite of DEP), MBzP: Mono-benzyl phthalate (metabolite of BBzP), MCnP: Mono-carboxyisononyl phthalate (metabolite of DINP), MCPP: Mono-3-carboxypropyl phthalate, MHPB: Mono-hydroxybutyl phthalate, MHiBP: Mono-hydroxyisobutyl phthalate, MIBP: Mono-isobutyl phthalate, MNP: Mono-nonyl phthalat

Table S4: Change in BMI z-score associated with a One-Tertile Increase in the phenol–phthalate Mixture Index

|                                                                | <b>Beta</b> | <b>Credible interval [25<sup>th</sup> , 97.5<sup>th</sup>]</b> |
|----------------------------------------------------------------|-------------|----------------------------------------------------------------|
| All participants                                               | -0.06       | [-0.36, 1.97]                                                  |
| Males                                                          | -0.024      | [-0.64, 0.17]                                                  |
| Females                                                        | 0.07        | [-0.36, 0.55]                                                  |
| <b>Restricted to sites with repeated exposure measurements</b> |             |                                                                |
| All participants                                               | -0.02       | [-0.45, 0.42]                                                  |

Adjustment factors: child sex, child age at BMI assessment, maternal age at delivery, maternal pre-pregnancy BMI, parity, maternal race, maternal education level and study site.

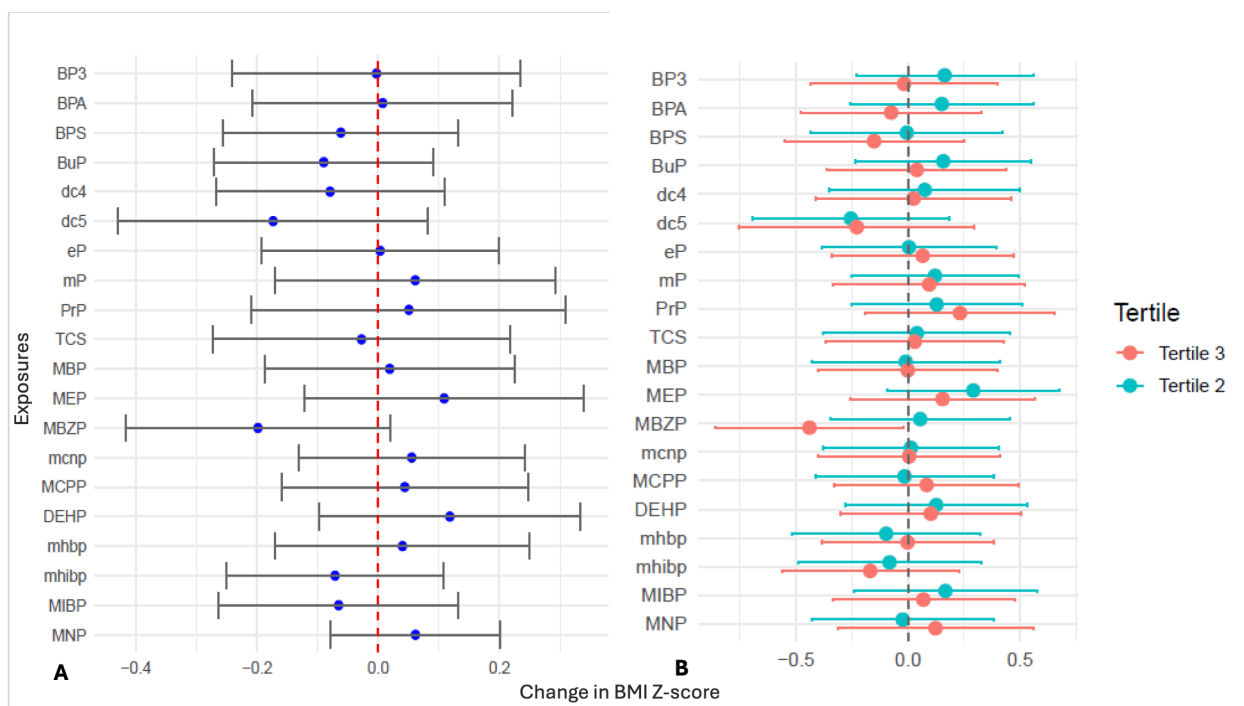
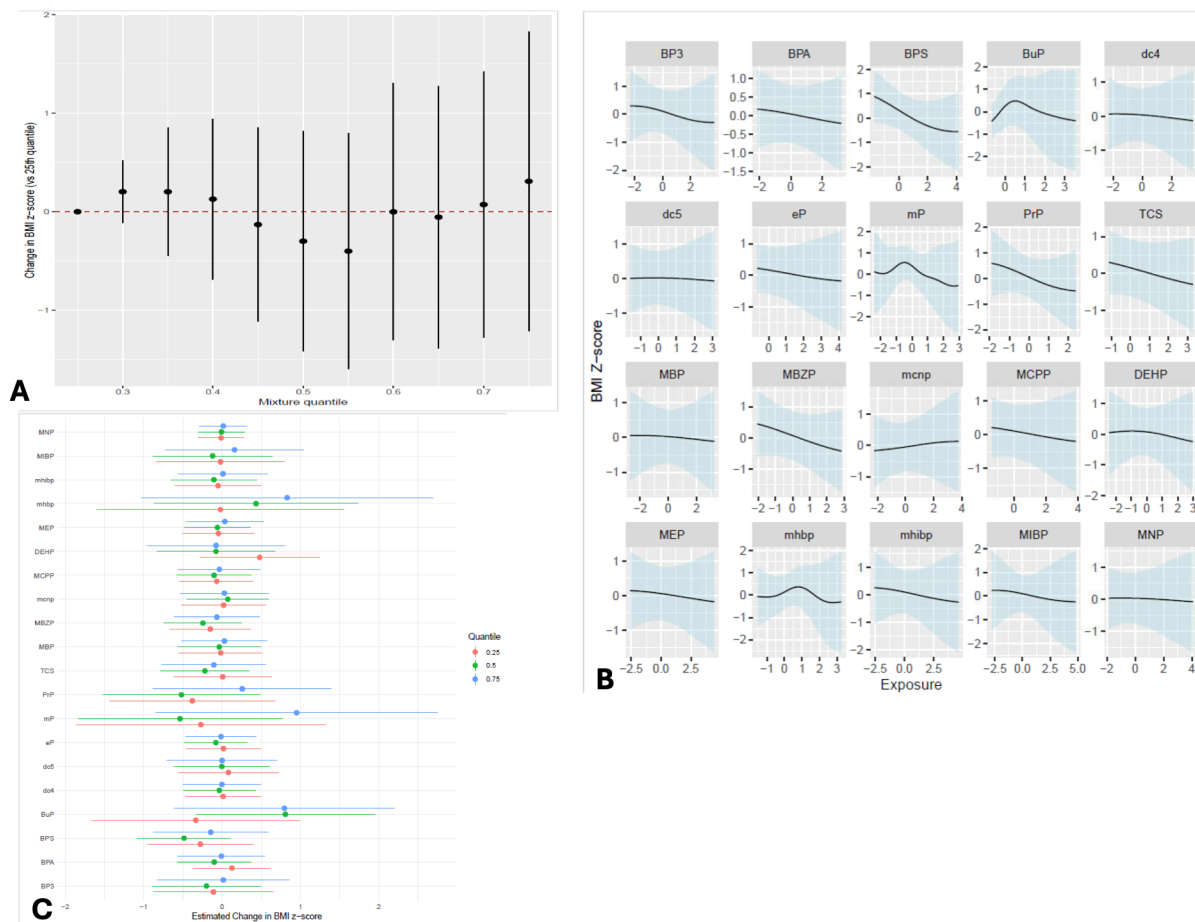


Figure S5: Adjusted Linear regression results of associations between prenatal exposure to phenols and phthalates and childhood BMI z-Scores (A, Continuous and B, Tertile Models, restricted to participants from the PROTECT and IKIDS study sites).

Adjustment factors: child age at BMI assessment, maternal age at delivery, maternal pre-pregnancy BMI, parity, maternal race, maternal education level and study site (cohort).

Abbreviations: BP3: Benzophenone-3, BPA: Bisphenol A, BPS: Bisphenol S, BuP: Butyl Paraben, DC4: 2,4-Dichlorophenol, DC5: 2,5-Dichlorophenol, eP: Ethyl Paraben, mP: Methyl Paraben, PrP: Propyl Paraben, TCS: Triclosan, MBP: Mono-n-butyl phthalate (metabolite of DBP), MEP: Mono-ethyl phthalate (metabolite of DEP), MBZP: Mono-benzyl phthalate (metabolite of BBZP), MCnP: Mono-carboxyisononyl phthalate (metabolite of DINP), MCP: Mono-3-carboxypropyl phthalate, MHBP: Mono-hydroxybutyl phthalate, MHiBP: Mono-hydroxyisobutyl phthalate, MIBP: Mono-isobutyl phthalate, MNP: Mono-nonyl phthalate.



**Figure S6.** Association between BMI z-scores and prenatal exposure to phenol and phthalate mixtures using BKMR (Restricted to participants from the PROTECT and IKIDS study sites).

**A:** Overall mixture effect estimate with 95% credible intervals.

**B:** Single-exposure effects of each compound on BMI z-scores while fixing all other exposures at the 25th (red), 50th (green), and 75th (blue) percentiles.

**C:** Univariate exposure-response functions for each compound (95% CI), holding all other exposures at their median values.

Adjustment factors: child sex, child age at BMI assessment, maternal age at delivery, maternal pre-pregnancy BMI, parity, maternal race and ethnicity, maternal education level, and ECHO site.

Abbreviations: BP3: Benzophenone-3, BPA: Bisphenol A, BPS: Bisphenol S, BuP: Butyl Paraben, DC4: 2,4-Dichlorophenol, DC5: 2,5-Dichlorophenol, eP: Ethyl Paraben, mP: Methyl Paraben, PrP: Propyl Paraben, TCS: Triclosan, MBP: Mono-n-butyl phthalate (metabolite of DBP), MEP: Mono-ethyl phthalate (metabolite of DEP), MBZP: Mono-benzyl phthalate (metabolite of BBzP), MCnP: Mono-carboxyisononyl phthalate (metabolite of DINP), MCPP: Mono-3-carboxypropyl phthalate, MHBP: Mono-hydroxybutyl phthalate, MHiBP: Mono-hydroxyisobutyl phthalate, MIBP: Mono-isobutyl phthalate, MNP: Mono-nonyl phthalate

## REFERENCES

1. Meeker JD et al. Distribution, variability, and predictors of urinary concentrations of phenols and parabens among pregnant women in Puerto Rico. *Environmental science & technology* 2013;47:3439–47.
2. Polinski KJ et al. Distribution and predictors of urinary concentrations of phthalate metabolites and phenols among pregnant women in the Healthy Start Study. *Environ Res* 2018;162:308–17.
3. Pacyga DC et al. Identification of profiles and determinants of maternal pregnancy urinary biomarkers of phthalates and replacements in the Illinois Kids Development Study. *Environ Int* 2022;162:107150.