Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.
Study population: The two cycles included in this study provide comprehensive data on exposures and outcomes considered in this study. During these two cycles, the NHANES oversampled some individuals to better represent all ethnic groups. The NHANES utilizes standardized protocols approved by the institutional review board of the CDC to collect biological samples for laboratory analyses. All the sample collections and examinations were conducted by highly trained personnel. Since NHANES collects only a one-third subsample of all participants for phthalates analyses (https://wwwn.cdc.gov/Nchs/Nhanes/2013-2014/PHTHTE_H.htm), it is reasonable to have a large proportion of missing metabolite data.

Exposure assessment: Although different studies might have used different abbreviations for the metabolites, we followed the acronyms provided by the NHANES documentation (https://wwwn.cdc.gov/Nchs/Nhanes/2013-2014/PHTHTE_H.htm). The NHANES utilizes isotopically-labeled internal standards to increase assay precision and accuracy for measuring concentrations of metabolites in the low ng/mL range from urine samples. A very minimum number of samples (<5%) had concentrations below the limits of detection (LOD) except for MHNC and MCPP. The range of LOD of different metabolites was 0.2 to 1.2 ng/mL and instrument reading was used for concentrations below the LODs. The metabolite concentrations were categorized into tertiles to obtain sufficient number of outcomes in each category.

Outcome assessment: The NHANES implements quality assurance and control protocols for ensuring high accuracy and precision. Serum samples were collected, appropriately stored, and analyzed using the standard protocols for measuring androgen concentrations. Details of sample processing, method performance, quality control assessment, and analytical and result interpretation are reported by the CDC. The LOD was 0.7475 for TT and 0.800 nmol/L for SHBG.
As per the National Cholesterol Education Program (NCEP)’s Adult Treatment Panel III, MS is the presence of three or more abnormal levels of cardiometabolic symptoms including glucose (FG) or hemoglobin A1c (HbA1c), waist circumference (WC), triglyceride (TG), high-density lipoprotein (HDL) cholesterol, and systolic and diastolic blood pressures (SBP and DBP). We defined MS using the NCEP criteria and considered MS if individuals were present with at least 3 symptoms of the following: FG level at least 100 mg/dL or HbA1c> 6 or taking diabetes medications, WC> 88 cm, TG> 150 mg/dL, HDL<50 mg/dL, and SBP ≥130 or DBP ≥85 or taking hypertension medications.

**Statistical analysis:** We described the distribution of metabolite concentrations using centiles. Mean with standard deviation (SD) or median with interquartile range (IQR) was used to describe continuous outcome data while categorical variables were summarized with proportions. Based on previous studies and clinical applications, the primary analyses were carried out using categorized forms of metabolites whereas sensitivity analyses were performed on continuous forms of phthalate metabolites with continuous and categorized forms of sex hormones. The cutoffs were established for androgen markers according to age groups. Since most studies consider age 50-51 years as the reference category for menopause, women with age≥ 50 years were considered postmenopausal and women with age < 50 years were considered premenopausal.

Data-driven clustering among considered metabolites of phthalates and related standardized coefficients were used to create a composite score for each group. Furthermore, the grouping of phthalate metabolites was also done based on the molecular weight of metabolites or phthalate compounds. After obtaining grouping among metabolites and the composite exposure score for each group, the multivariable associations of log-transformed composite scores with TT, SHBG, obesity, and MS were examined using a survey weight-adjusted linear or Poisson regression.
analyses. The log transformation was made to improve the normality of continuous skewed phthalate metabolites and sex hormones data. The results were summarized using relative risk (RR) or regression coefficient (RC) along with a 95% confidence interval (CI) and p-value. In view of the analysis of multiple related outcomes, results from primary analysis were considered statistically significant at a 1% level of significance after adjusting for multiple comparisons.
**eAppendix. Supplemental Results**

In the adjusted analyses of combined phthalate metabolites, the composite score of group 4 was positively associated with TT concentrations among postmenopausal women whereas other HMW was inversely associated with TT concentrations among premenopausal women (eTable 5). However, composite scores of group 2 (RC, -0.08 [95%CI, -0.12,-0.04]) or DNP-HMW score (RC, -0.06 [95%CI, -0.10,-0.03]) and group 4 (RC,-0.05 [95%CI, -0.08,-0.03]) or other HMW score (RC,-0.06 [95%CI, -0.10,-0.02]) were associated with lower SHBG concentrations to a greater extent among premenopausal women than among postmenopausal women (eTable 5). A combined score of all HMW metabolites was significantly associated with lower SHBG concentrations among premenopausal (RC,-0.10 [95%CI, -0.16, -0.05]) and postmenopausal (RC, -0.07 [95%CI,-0.13, -0.01]) women (eTable 5). However, obesity was positively associated with composite scores of group 2 (RR, 1.08 [95%CI, 1.02, 1.14]) and group 3 (RR, 1.09 [95%CI, 1.01, 1.17]) which were more pronounced among postmenopausal women than among premenopausal women. Composite scores of all HMW metabolites (RR, 1.12 [95%CI, 1.03, 1.23]) and other HMW metabolites (RR, 1.18 [95%CI, 1.05, 1.33]) were positively associated with obesity among premenopausal women while DNP related HMW metabolites (RR, 1.10 [95%CI, 1.00, 1.22]) was associated with obesity among postmenopausal women (eTable 6).
### eTable 1. Distribution of Exposure to Phthalate Metabolites

| Phthalate metabolites | 5th Percentile | 25th Percentile | 50th Percentile | 75th Percentile | 95th Percentile | T1 (range) | T2 (range) | T3 (range) |
|-----------------------|----------------|-----------------|----------------|----------------|----------------|------------|------------|------------|
| MCNP                  | 0.3            | 0.9             | 1.8            | 3.7            | 13.0           | 0.1-1.2    | 1.3-2.8    | 2.8-876.4  |
| MCOP                  | 1.3            | 4.2             | 9.9            | 28.6           | 147.4          | 0.2-6.1    | 6.2-20.7   | 20.7-1019.8|
| MECPP                 | 1.6            | 4.2             | 8.3            | 16.8           | 41.1           | 0.3-6.3    | 6.4-14.6   | 14.6-1421.9|
| MBP                   | 1.1            | 4.3             | 9.8            | 18.4           | 48.6           | 0.3-6.8    | 6.9-16.5   | 16.6-1239.4|
| MCPP                  | 0.3            | 0.5             | 1.2            | 2.9            | 12.5           | 0.3-0.7    | 0.8-2.0    | 2.0-449.5  |
| MEP                   | 3.6            | 12.9            | 33.6           | 97.4           | 521.5          | 0.9-21.4   | 21.5-75.2 | 75.2-22983 |
| MEHHP                 | 0.9            | 2.6             | 5.2            | 10.7           | 27.8           | 0.3-3.8    | 3.9-9.3    | 9.3-1029.7 |
| MEHP                  | 0.6            | 0.6             | 0.9            | 2.1            | 6.2            | 0.6-0.6    | 0.6-1.7    | 1.7-152.3  |
| MiBP                  | 0.9            | 3.3             | 7.3            | 15.1           | 43.1           | 0.6-5.2    | 5.3-13.2   | 13.2-555.2 |
| MNP                   | 0.6            | 0.6             | 0.6            | 1.1            | 8.2            | 0.6-0.6    | 0.6-0.6    | 0.7-875.4  |
| MEOHP                 | 0.6            | 1.7             | 3.5            | 7.1            | 17.6           | 0.1-2.5    | 2.6-6.2    | 6.2-585.2  |
| MBzP                  | 0.4            | 1.5             | 3.8            | 9.1            | 34.0           | 0.2-2.2    | 2.3-6.8    | 6.8-340.1  |
| MHNCH                 | 0.3            | 0.3             | 0.3            | 0.7            | 3.3            | 0.3-0.3    | 0.3-0.5    | 0.5-151.7  |

Abbreviations: MBP, mono-n-butyl phthalate (ng/mL); MBzP, mono-benzyl phthalate (ng/mL); MCNP, mono(carboxynonyl) phthalate (ng/mL); MCOP, mono(carboxyoctyl) phthalate (ng/mL); MCPP, mono-(3-carboxypropyl) phthalate; MECPP, mono-2-ethyl-5-carboxypentyl phthalate; MEHHP, mono-(2-ethyl-5-hydroxyhexyl) phthalate; MEHP, mono-(2-ethyl)-hexyl phthalate (ng/mL); MEOHP, mono-(2-ethyl-5-oxoheptyl) phthalate; MEP, mono-ethyl phthalate (ng/mL); MHNCH, cyclohexane 1,2-dicarboxylic acid monohydroxy isononyl ester (ng/mL); MiBP, mono-isobutyl phthalate; MNP, mono-isononyl phthalate (ng/mL); T1, first tertile; T2, second tertile; T3, third tertile.
### eTable 2. Cluster Analysis of Metabolites of Phthalates

| Group | Metabolites | Weight/phthalates | SRC | R2 with own Cluster | R2 with next Closest | 1–R2 | Variation explained by clusters | Proportion explained by clusters |
|-------|-------------|--------------------|-----|---------------------|---------------------|------|-------------------------------|----------------------------------|
| Group 1 | MCNP | HMW/DDP | 0.17 | 0.46 | 0.08 | 0.59 | 4.48 | 0.34 |
|       | MECPP | HMW/DEHP | 0.23 | 0.91 | 0.10 | 0.10 |               |                                |
|       | MEHHP | HMW/DEHP | 0.24 | 0.96 | 0.08 | 0.05 |               |                                |
|       | MEHP  | HMW/DEHP | 0.22 | 0.78 | 0.13 | 0.25 |               |                                |
|       | MEOHP | HMW/DEHP | 0.24 | 0.95 | 0.09 | 0.06 |               |                                |
| Group 2 | MCOP | HMW/DNP | 0.47 | 0.70 | 0.10 | 0.34 | 5.95 | 0.47 |
|       | MCPP | HMW/DiNOP | 0.43 | 0.58 | 0.08 | 0.46 |               |                                |
|       | MNP  | HMW/DNP | 0.40 | 0.50 | 0.03 | 0.52 |               |                                |
| Group 3 | MBP  | LMW/DBP | 0.47 | 0.54 | 0.02 | 0.46 | 7.39 | 0.57 |
|       | MEP  | LMW/DEP | 0.20 | 0.09 | 0.00 | 0.91 |               |                                |
|       | MiBP | LMW/DiBP | 0.45 | 0.48 | 0.03 | 0.53 |               |                                |
|       | MBzP | HMW/BzBP | 0.42 | 0.44 | 0.01 | 0.57 |               |                                |
| Group 4 | MHNCH | HMW/DINCH | 1.00 | 1.00 | 0.00 | 0.00 | 8.39 | 0.65 |

Abbreviations: SRC, standardized regression coefficient; MCNP, mono(carboxynonyl) phthalate (ng/mL); MECPP, mono (carboxyoctyl) phthalate(ng/mL); MEHHP, mono-(2-ethyl-5-carboxypentyl) phthalate; MBP, mono-n-butyl phthalate (ng/mL); MCPP, mono-(3-carboxypropyl) phthalate; MEP, mono-ethyl phthalate (ng/mL); MEHP, mono-(2-ethyl-5-hydroxyhexyl) phthalate; MEOHP, mono-isobutyl phthalate; MBzP, mono-benzyl phthalate (ng/mL); MHNCH, cyclohexane 1,2-dicarboxylic acid monohydroxy isononyl ester (ng/mL); HMW, high molecular weight; LMW, low molecular weight; DDP, Di-isodecyl phthalate; DEHP, Di(2-ethylhexyl) phthalate; DNP, Di-isononyl phthalate; DiNOP, Di-n-octyl phthalate; DBP, Di-n-butyl phthalate; DEP, Di-ethyl phthalate; DiBP, Di-isobutyl phthalate; BzBP, benzylbutyl phthalate; DINCH, 1,2-Cyclohexane dicarboxylic acid, disiononyl ester; R2, coefficient of variation.

*Group 1 included 4 metabolites of DEHP and 1 metabolite of DDP and was represented by high molecular weight (HMW) with MCNP, MECPP, MEHHP, MEOHP, and MEHP. Group 2 was represented by 3 HMW metabolites of DNP and DiNOP. Group 3 included 3 low molecular weight (LMW) metabolites and 1 HMW metabolite and was represented by MBP, MiBP, and MBzP. Group 4 included HMW MHNCH, a metabolite of DINCH.
**eTable 3. Adjusted Association of Each Phthalate Metabolite With TT and SHBG Concentrations**

| Factor | TT Concentration (N=1999) | SHBG Concentration (N=1862) |
|--------|--------------------------|-----------------------------|
|        | RC* (95% CI)              | p-value                      | RC* (95% CI)              | p-value |
| MCNP   |                          |                             |                           |         |
| T1     |                          |                              |                           |         |
| T2     | -0.067 (-0.176,0.043)    | 0.224                        | -0.114 (-0.218,-0.011)    | 0.031   |
| T3     | -0.035 (-0.128,0.059)    | 0.452                        | -0.185 (-0.268,-0.102)    | <0.001  |
| MCOP   |                          |                              |                           |         |
| T1     |                          |                              |                           |         |
| T2     | -0.116 (-0.217,-0.016)   | 0.025                        | -0.068 (-0.142,0.006)     | 0.069   |
| T3     | -0.076 (-0.186,0.035)    | 0.173                        | -0.194 (-0.273,-0.114)    | <0.001  |
| MECPP  |                          |                              |                           |         |
| T1     |                          |                              |                           |         |
| T2     | -0.023 (-0.127,0.081)    | 0.658                        | -0.063 (-0.132,0.006)     | 0.073   |
| T3     | 0.023 (-0.07,0.115)      | 0.623                        | -0.116 (-0.176,-0.055)    | <0.001  |
| MBP    |                          |                              |                           |         |
| T1     |                          |                              |                           |         |
| T2     | -0.043 (-0.139,0.052)    | 0.365                        | -0.028 (-0.118,0.063)     | 0.539   |
| T3     | 0.025 (-0.076,0.126)     | 0.618                        | -0.052 (-0.147,0.042)     | 0.267   |
| MCPP   |                          |                              |                           |         |
| T1     |                          |                              |                           |         |
| T2     | -0.096 (-0.213,0.021)    | 0.104                        | -0.113 (-0.181,-0.044)    | 0.002   |
| T3     | -0.061 (-0.160,0.040)    | 0.206                        | -0.169 (-0.260,-0.080)    | 0.001   |
| MEP    |                          |                              |                           |         |
| T1     |                          |                              |                           |         |
| T2     | 0.080 (-0.043,0.202)     | 0.196                        | -0.128 (-0.222,-0.033)    | 0.010   |
| T3     | 0.028 (-0.082,0.139)     | 0.605                        | -0.054 (-0.167,0.058)     | 0.332   |
| MEHHHP |                          |                              |                           |         |
| T1     |                          |                              |                           |         |
| T2     | -0.045 (-0.153,0.063)    | 0.403                        | -0.047 (-0.150,0.056)     | 0.359   |
| T3     | -0.005 (-0.095,0.085)    | 0.911                        | -0.095 (-0.161,-0.029)    | 0.007   |
| MEHHP  |                          |                              |                           |         |
| T1     |                          |                              |                           |         |
| T2     | 0.010 (-0.064,0.083)     | 0.792                        | 0.041 (-0.048,0.130)      | 0.358   |
| T3     | -0.009 (-0.105,0.086)    | 0.846                        | 0.027 (-0.052,0.106)      | 0.496   |
| MiBP   |                          |                              |                           |         |
| T1     |                          |                              |                           |         |
| T2     | -0.014 (-0.137,0.110)    | 0.822                        | -0.083 (-0.155,-0.010)    | 0.026   |

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| Abbreviation | T1 | T2 | T3 |
|--------------|----|----|----|
| MNP          |    |    |    |
| T1/T2        |    |    |    |
| T3           | -0.024 (-0.105, 0.057) | 0.551 | -0.105 (-0.193, -0.018) |
| MEOHP        |    |    |    |
| T1           |    |    |    |
| T2           | -0.016 (-0.116, 0.084) | 0.746 | -0.055 (-0.152, 0.041) |
| T3           | 0.006 (-0.087, 0.099) | 0.893 | -0.054 (-0.121, 0.013) |
| MBzP         |    |    |    |
| T1           |    |    |    |
| T2           | -0.046 (-0.140, 0.048) | 0.324 | -0.061 (-0.147, 0.025) |
| T3           | -0.005 (-0.093, 0.082) | 0.904 | -0.075 (-0.174, 0.024) |
| MHNCH        |    |    |    |
| T1           |    |    |    |
| T2           | 0.09 (-0.087, 0.268) | 0.307 | -0.001 (-0.122, 0.119) |
| T3           | 0.019 (-0.056, 0.094) | 0.606 | -0.093 (-0.165, -0.021) |

Abbreviations: MCNP, mono(carboxynonyl) phthalate (ng/mL); MCOP, mono (carboxyoctyl) phthalate(ng/mL); MECPP, mono-2-ethyl-5-carboxypentyl phthalate; MBP, mono-n-butyl phthalate (ng/mL); MCPP, mono-(3-carboxypropyl) phthalate; MEP, mono-ethyl phthalate (ng/mL); MEHHP, mono-(2-ethyl-5-hydroxyhexyl) phthalate; MEHP, mono-(2-ethyl)-hexyl phthalate (ng/mL); MiBP, mono-isobutyl phthalate; MNP, mono-isononyl phthalate (ng/mL); MEOHP, mono-(2-ethyl-5-oxohexyl) phthalate; MBzP, mono-benzyl phthalate (ng/mL); MHNCH, cyclohexane 1, 2-dicarboxylic acid monohydroxy isononyl ester (ng/mL); T1, first tertile; T2, second tertile; T3, third tertile; TT, total testosterone; SHBG, sex hormone-binding globulin; RC, regression coefficient; CI, confidence interval.

*All analyses adjusted for age, race and ethnicity, income, marital status, birth country, educational level, smoking status, alcohol use status, physical activity, and creatinine level.
**eTable 4. Adjusted Association of Each Phthalate Metabolite Concentration With TT and SHBG Concentrations**

|                   | Overall                          | Premenopausal       | Postmenopausal       |
|-------------------|----------------------------------|---------------------|----------------------|
|                   | RC (95% CI)                      | p-value             | RC (95% CI)          | p-value             |
| **TT concentration** |                                  |                     |                      |
| MCNP              | 0.001 (-0.030,0.031)             | 0.969               | -0.005 (-0.034,0.025)| 0.758               | 0.006 (-0.054,0.066) | 0.845 |
| MCOP              | -0.018 (-0.049,0.013)            | 0.246               | -0.010 (-0.036,0.016)| 0.427               | -0.027 (-0.087,0.033)| 0.366 |
| MECPP             | -0.001 (-0.035,0.033)            | 0.942               | 0.001 (-0.033,0.035)| 0.940               | -0.006 (-0.066,0.055)| 0.852 |
| MBP               | -0.006 (-0.045,0.032)            | 0.734               | 0.005 (-0.019,0.029)| 0.677               | -0.023 (-0.098,0.051)| 0.524 |
| MCP              | -0.022 (-0.059,0.015)            | 0.228               | -0.008 (-0.040,0.023)| 0.594               | -0.043 (-0.118,0.032)| 0.253 |
| MEP               | -0.004 (-0.036,0.028)            | 0.807               | 0.003 (-0.026,0.031)| 0.851               | -0.008 (-0.064,0.049)| 0.785 |
| MEHHP            | -0.019 (-0.053,0.015)            | 0.266               | 0.001 (-0.031,0.033)| 0.938               | -0.049 (-0.115,0.018)| 0.144 |
| MEHP              | -0.005 (-0.045,0.036)            | 0.820               | 0.019 (-0.024,0.062)| 0.369               | -0.054 (-0.120,0.013)| 0.109 |
| MiBP              | -0.008 (-0.042,0.026)            | 0.625               | 0.012 (-0.009,0.034)| 0.241               | -0.038 (-0.097,0.021)| 0.201 |
| MNP               | -0.023 (-0.056,0.010)            | 0.171               | -0.012 (-0.047,0.023)| 0.483               | -0.043 (-0.150,0.063)| 0.431 |
| MEOHP             | -0.013 (-0.051,0.026)            | 0.501               | 0.006 (-0.026,0.038)| 0.694               | -0.043 (-0.118,0.032)| 0.255 |
| MBzP             | -0.006 (-0.029,0.016)            | 0.577               | -0.014 (-0.038,0.010)| 0.234               | -0.004 (-0.043,0.035)| 0.844 |
| MHNCH            | 0.010 (-0.024,0.045)             | 0.542               | -0.010 (-0.041,0.020)| 0.492               | 0.062 (0.009,0.114)  | 0.023 |
| **SHBG concentration** |                                  |                     |                      |
| MCNP              | -0.066 (-0.099,-0.032)           | <0.001              | -0.077 (-0.117,-0.038)| <0.001              | -0.061 (-0.114,-0.009)| 0.024 |
| MCOP              | -0.064 (-0.089,-0.038)           | <0.001              | -0.068 (-0.099,-0.037)| <0.001              | -0.058 (-0.098,-0.017)| 0.007 |
| MECPP            | -0.041 (-0.074,-0.008)           | 0.018               | -0.059 (-0.100,-0.019)| 0.006               | -0.025 (-0.072,0.022)| 0.286 |
| MBP               | -0.030 (-0.063,0.003)            | 0.075               | -0.023 (-0.066,0.020)| 0.277               | -0.037 (-0.077,0.003)| 0.071 |
| MCP              | -0.058 (-0.091,-0.026)           | 0.001               | -0.067 (-0.104,-0.031)| 0.001               | -0.046 (-0.092,0.00) | 0.048 |
| MEP                | -0.007 (-0.033,0.019)            | 0.567               | 0.000 (-0.039,0.040)| 0.991               | -0.017 (-0.050,0.016)| 0.308 |
| MEHHP             | -0.034 (-0.065,-0.002)           | 0.037               | -0.038 (-0.079,0.003)| 0.069               | -0.031 (-0.069,0.007)| 0.106 |
| MEHP              | 0.015 (-0.022,0.051)             | 0.420               | -0.006 (-0.05,0.037)| 0.765               | 0.051 (-0.014,0.116)| 0.123 |
| MiBP              | -0.047 (-0.080,-0.014)           | 0.007               | -0.048 (-0.099,0.003)| 0.064               | -0.048 (-0.089,-0.007)| 0.022 |
| MNP               | -0.048 (-0.092,-0.004)           | 0.033               | -0.045 (-0.103,0.014)| 0.130               | -0.040 (-0.117,0.036)| 0.292 |
| MEOHP            | -0.015 (-0.046,0.016)            | 0.331               | -0.018 (-0.058,0.022)| 0.375               | -0.021 (-0.058,0.015)| 0.242 |
| MBzP             | -0.034 (-0.058,-0.011)           | 0.005               | -0.037 (-0.071,-0.003)| 0.033               | -0.034 (-0.076,0.007)| 0.099 |
| MHNCH            | -0.058 (-0.088,-0.027)           | <0.001              | -0.070 (-0.114,-0.026)| 0.003               | -0.045 (-0.092,0.001)| 0.057 |

Abbreviations: MCNP, mono(carboxynonyl) phthalate (ng/mL); MCOP, mono (carboxyoctyl) phthalate (ng/mL); MECPP, mono-2-ethyl-5-carboxypentyl phthalate; MBP, mono-n-butyl phthalate (ng/mL); MCPP, mono-(3-carboxypropyl) phthalate; MEP, mono-ethyl phthalate (ng/mL); MEHHP, mono-(2-ethyl-5-hydroxyhexyl) phthalate; MEHP, mono-(2-ethyl)-hexyl phthalate (ng/mL); MiBP, mono-isobutyl phthalate; MNP, mono-isononyl phthalate (ng/mL); MEOHP, mono-(2-ethyl-5-oxohexyl) phthalate; MBzP, mono-benzyl phthalate (ng/mL); MHNCH, cyclohexane 1,2-dicarboxylic acid monohydroxy isononyl ester (ng/mL); TT, total testosterone; SHBG, sex hormone-binding globulin; RC, regression coefficient; CI, confidence interval.
Phthalate metabolites, SHBG and TT were log-transformed in the analyses and all analyses adjusted for age, race and ethnicity, income, marital status, birth country, educational level, smoking status, alcohol use status, physical activity, and creatinine level.
### eTable 5. Adjusted Association of Each Phthalate Metabolite Concentration With Obesity and Metabolic Syndrome

|                    | Overall         | P-value | Premenopausal | P-value | Postmenopausal | P-value |
|--------------------|-----------------|---------|---------------|---------|----------------|---------|
| **Obesity**        |                 |         |               |         |                |         |
| RR* (95% CI)       |                 |         |               |         |                |         |
| MCNP               | 1.098 (1.036,1.164) | 0.003   | 1.079 (0.995,1.171) | 0.065   | 1.142 (1.051,1.240) | 0.003   |
| MCOP               | 1.102 (1.053,1.153) | <0.001  | 1.088 (1.024,1.155) | 0.007   | 1.126 (1.050,1.207) | 0.002   |
| MECPP              | 1.126 (1.053,1.205) | 0.001   | 1.128 (1.026,1.241) | 0.014   | 1.137 (1.030,1.256) | 0.013   |
| MBP                | 1.138 (1.066,1.216) | <0.001  | 1.165 (1.063,1.277) | 0.002   | 1.115 (1.022,1.217) | 0.017   |
| MCP                | 1.081 (1.028,1.136) | 0.004   | 1.056 (0.985,1.133) | 0.122   | 1.116 (1.033,1.206) | 0.007   |
| MEP                | 1.064 (1.009,1.123) | 0.023   | 1.044 (0.973,1.120) | 0.219   | 1.103 (1.022,1.189) | 0.013   |
| MEHHP              | 1.114 (1.032,1.202) | 0.007   | 1.112 (1.013,1.220) | 0.026   | 1.118 (1.006,1.242) | 0.039   |
| MEHP               | 0.972 (0.904,1.045) | 0.426   | 0.990 (0.901,1.087) | 0.823   | 0.931 (0.804,1.079) | 0.331   |
| MiBP               | 1.141 (1.062,1.226) | 0.001   | 1.158 (1.046,1.283) | 0.006   | 1.125 (1.024,1.235) | 0.016   |
| MNP                | 1.029 (0.946,1.120) | 0.494   | 0.996 (0.895,1.108) | 0.933   | 1.097 (0.960,1.255) | 0.166   |
| MEOHP              | 1.117 (1.033,1.207) | 0.007   | 1.123 (1.025,1.230) | 0.014   | 1.119 (1.002,1.250) | 0.047   |
| MBzP               | 1.128 (1.064,1.196) | <0.001  | 1.182 (1.103,1.267) | <0.001  | 1.073 (0.988,1.164) | 0.090   |
| MNCH               | 1.072 (1.010,1.136) | 0.023   | 1.087 (1.007,1.174) | 0.035   | 1.049 (0.948,1.162) | 0.343   |
| **Metabolic syndrome** |                |         |               |         |                |         |
| RR* (95% CI)       |                 |         |               |         |                |         |
| MCNP               | 1.018 (0.964,1.074) | 0.511   | 1.070 (0.999,1.146) | 0.052   | 0.993 (0.928,1.063) | 0.830   |
| MCOP               | 1.023 (0.984,1.063) | 0.239   | 1.015 (0.953,1.082) | 0.632   | 1.034 (0.986,1.083) | 0.161   |
| MECPP              | 1.054 (0.985,1.128) | 0.121   | 1.097 (1.007,1.196) | 0.035   | 1.029 (0.956,1.108) | 0.439   |
| MBP                | 1.053 (0.99,1.121) | 0.097   | 1.063 (0.957,1.180) | 0.246   | 1.052 (0.987,1.122) | 0.115   |
| MCP                | 1.00 (0.955,1.048) | 0.996   | 1.003 (0.943,1.066) | 0.918   | 1.001 (0.943,1.063) | 0.967   |
| MEP                | 1.018 (0.975,1.064) | 0.404   | 1.024 (0.973,1.077) | 0.351   | 1.025 (0.969,1.085) | 0.380   |
| MEHHP              | 1.081 (1.010,1.157) | 0.025   | 1.107 (1.017,1.205) | 0.020   | 1.061 (0.986,1.141) | 0.108   |
| MEHP               | 0.980 (0.911,1.053) | 0.566   | 1.031 (0.937,1.135) | 0.519   | 0.925 (0.842,1.017) | 0.104   |
| MiBP               | 1.054 (0.980,1.132) | 0.149   | 1.043 (0.950,1.146) | 0.361   | 1.067 (0.985,1.155) | 0.109   |
| MNP                | 0.997 (0.923,1.076) | 0.930   | 0.997 (0.901,1.102) | 0.950   | 1.003 (0.912,1.104) | 0.947   |
| MEOHP              | 1.061 (0.99,1.137) | 0.091   | 1.107 (1.011,1.211) | 0.029   | 1.031 (0.959,1.107) | 0.401   |
| MBzP               | 1.076 (1.021,1.133) | 0.008   | 1.076 (0.987,1.172) | 0.092   | 1.090 (1.035,1.147) | 0.002   |
| MNCH               | 1.027 (0.979,1.101) | 0.265   | 1.071 (1.015,1.130) | 0.014   | 0.980 (0.908,1.058) | 0.595   |

Abbreviations: MCNP, mono(carboxynonyl) phthalate (ng/mL); MCOP, mono (carboxyoctyl) phthalate(ng/mL); MECPP, mono-2-ethyl-5-carboxypentyl phthalate; MBP, mono-n-butyl phthalate (ng/mL); MCPP, mono-(3-carboxypropyl) phthalate; MEP, mono-ethyl phthalate (ng/mL); MEHHP, mono-(2-ethyl-5-hydroxyhexyl) phthalate; MEHP, mono-(2-ethyl)-hexyl phthalate (ng/mL); MiBP, mono-isobutyl phthalate; MNP, mono-isononyl phthalate (ng/mL); MEOHP, mono-(2-ethyl-5-oxohexy) phthalate; MBzP, mono-benzyl phthalate (ng/mL); MNCH, cyclohexane 1, 2-dicarboxylic acid monohydroxy isononyl ester (ng/mL); TT, total testosterone; SHBG, sex hormone-binding globulin; RR, relative risk; CI, confidence interval.

*Phthalate metabolites were log-transformed in the analyses and all analyses adjusted for age, race and ethnicity, income, marital status, birth country, educational level, smoking status, alcohol use status, physical activity, and creatinine level. .

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### eTable 6. Adjusted Associations of Composite Scores of Phthalate Metabolites With TT and SHBG Concentrations

|                | Overall | Premenopausal | Postmenopausal |
|----------------|---------|---------------|----------------|
|                | RC* (95% CI) | p-value | RC* (95% CI) | p-value | RC* (95% CI) | p-value |
| **TT concentration** |         |               |               |         |               |         |
| **Data-driven groups** |         |               |               |         |               |         |
| Composite score 1<sup>a</sup> | 0.010 (-0.044,0.064) | 0.707 | 0.019 (-0.035,0.072) | 0.481 | -0.010 (-0.118,0.098) | 0.849 |
| Composite score 2<sup>b</sup> | -0.022 (-0.061,0.016) | 0.243 | -0.017 (-0.049,0.015) | 0.286 | -0.029 (-0.112,0.053) | 0.473 |
| Composite score 3<sup>c</sup> | -0.007 (-0.053,0.039) | 0.759 | 0.004 (-0.041,0.050) | 0.844 | -0.015 (-0.089,0.059) | 0.675 |
| Composite score 4<sup>d</sup> | 0.013 (-0.019,0.045) | 0.418 | -0.014 (-0.046,0.018) | 0.383 | 0.072 (0.028,0.117) | 0.002 |
| **Molecular weight-based groups** |         |               |               |         |               |         |
| HMW score<sup>e</sup> | -0.018 (-0.057,0.022) | 0.368 | -0.015 (-0.055,0.026) | 0.456 | -0.026 (-0.108,0.056) | 0.523 |
| LMW score<sup>f</sup> | -0.0003 (-0.038,0.037) | 0.987 | 0.011 (-0.026,0.048) | 0.553 | -0.008 (-0.069,0.052) | 0.779 |
| **Compounds based groups** |         |               |               |         |               |         |
| DEHP-HMW score<sup>g</sup> | 0.009 (-0.043,0.062) | 0.720 | 0.031 (-0.023,0.086) | 0.251 | -0.024 (-0.128,0.081) | 0.648 |
| DNP-HMW score<sup>h</sup> | -0.022 (-0.059,0.015) | 0.232 | -0.008 (-0.041,0.024) | 0.61 | -0.036 (-0.116,0.044) | 0.361 |
| LMW score<sup>i</sup> | -0.003 (-0.044,0.039) | 0.888 | 0.012 (-0.029,0.054) | 0.552 | -0.009 (-0.076,0.058) | 0.777 |
| Other-HMW score<sup>j</sup> | -0.001 (-0.031,0.030) | 0.973 | -0.040 (-0.079,0.000) | 0.049 | 0.036 (-0.020,0.092) | 0.201 |
| **SHBG concentration** |         |               |               |         |               |         |
| Composite score 1<sup>a</sup> | 0.024 (-0.029,0.078) | 0.361 | 0.007 (-0.060,0.074) | 0.831 | 0.036 (-0.024,0.095) | 0.228 |
| Composite score 2<sup>b</sup> | -0.076 (-0.115,-0.038) | <0.001 | -0.079 (-0.122,-0.036) | 0.001 | -0.071 (-0.13,-0.012) | 0.021 |
| Composite score 3<sup>c</sup> | 0.009 (-0.031,0.049) | 0.654 | 0.033 (-0.028,0.093) | 0.279 | -0.016 (-0.067,0.035) | 0.531 |
| Composite score 4<sup>d</sup> | -0.054 (-0.083,-0.026) | <0.001 | -0.069 (-0.112,-0.027) | 0.002 | -0.038 (-0.084,0.007) | 0.095 |
| **Molecular weight-based groups** |         |               |               |         |               |         |
| HMW score<sup>e</sup> | -0.085 (-0.126,-0.045) | <0.001 | -0.103 (-0.155,-0.052) | <0.001 | -0.067 (-0.125,-0.011) | 0.022 |
| LMW score<sup>f</sup> | 0.017 (-0.018,0.052) | 0.318 | 0.034 (-0.017,0.085) | 0.186 | -0.001 (-0.044,0.042) | 0.964 |
| **Compounds based groups** |         |               |               |         |               |         |
| DEHP-HMW score<sup>g</sup> | 0.042 (-0.009,0.093) | 0.102 | 0.027 (-0.038,0.091) | 0.406 | 0.061 (-0.004,0.126) | 0.066 |
| DNP-HMW score<sup>h</sup> | -0.064 (-0.104,-0.025) | 0.002 | -0.062 (-0.109,-0.015) | 0.012 | -0.063 (-0.125,0.000) | 0.049 |
| LMW score<sup>i</sup> | 0.013 (-0.024,0.049) | 0.482 | 0.035 (-0.021,0.091) | 0.214 | -0.009 (-0.054,0.035) | 0.670 |
| Other-HMW score<sup>j</sup> | -0.058 (-0.095,-0.020) | 0.004 | -0.074 (-0.13,-0.017) | 0.012 | -0.054 (-0.117,0.010) | 0.096 |

Abbreviations: TT, total testosterone; SHBG, sex hormone-binding globulin; RC, regression coefficient; CI, confidence interval.

<sup>a</sup>Composite score 1 includes mono(carboxy)nonyl phthalate (ng/mL), mono-2-ethyl-5-carboxypentyl phthalate, mono-(2-ethyl-5-hydroxyhexyl) phthalate, mono-(2-ethyl)-hexyl phthalate (ng/mL) and mono-(2-ethyl-5-oxohexyl) phthalate.

<sup>b</sup>Composite score 2 includes mono (carboxyoctyl) phthalate(ng/mL), mono-(3-carboxypropyl) phthalate and mono-isononyl phthalate (ng/mL).
Composite score 3 includes mono-n-butyl phthalate (ng/mL), mono-ethyl phthalate (ng/mL), mono-isobutyl phthalate and mono-benzyl phthalate (ng/mL).

Composite score 4 includes only cyclohexane 1, 2-dicarboxylic acid monohydroxy isononyl ester (ng/mL).

High molecular weight (HMW) score is the sum of all HMW phthalate metabolite concentrations including MCNP, MECPP, MEHHP, MEHP, MEOHP, MCOP, MCPP, MNP, MBzP, and MHNCH.

Low molecular weight (LMW) score is the sum of all LMW phthalate metabolite concentrations including MBP, MEP, and MiBP.

DEHP-HMW score is the total concentration of di(2-ethylhexyl) phthalate metabolites (DEHP) including MECPP, MEHHP, MEHP, and MEOHP.

DNP-HMW score is the total concentration of di-isononyl phthalate metabolites (DNP) including MCOP and MNP and MCPP metabolite of di-n-octyl phthalate (DiNOP).

LMW score is the total concentration of LMW phthalate metabolites MBP, MEP, and MiBP.

Other-HMW score is the total concentration of MCNP, MBzP, and MHNCH.

*Composite scores, SHBG and TT were log-transformed in the analyses and all analyses adjusted for age, race and ethnicity, income, marital status, birth country, educational level, smoking status, alcohol use status, physical activity, and creatinine level.
## eTable 7. Adjusted Associations of Composite Scores of Phthalate Metabolites With Obesity and Metabolic Syndrome

| Overall | Premenopausal | Postmenopausal |
|---------|---------------|---------------|
| Obesity | RR* (95% CI)  | p-value       | RR* (95% CI)  | p-value |
| **Data-driven groups** |          |               |               |         |
| Composite score 1\(^a\) | 1.001 (0.917,1.092) | 0.984 | 1.015 (0.912,1.128) | 0.783 |
| Composite score 2\(^b\) | 1.075 (1.017,1.136) | 0.012 | 1.052 (0.978,1.131) | 0.163 |
| Composite score 3\(^c\) | 1.087 (1.009,1.171) | 0.030 | 1.078 (0.987,1.178) | 0.091 |
| Composite score 4\(^d\) | 1.043 (0.976,1.115) | 0.203 | 1.060 (0.979,1.147) | 0.146 |

| **Molecular weight-based groups** |          |               |               |         |
| HMW score\(^e\) | 1.122 (1.041,1.210) | 0.004 | 1.122 (1.028,1.225) | 0.012 |
| LMW score\(^f\) | 1.052 (0.983,1.127) | 0.138 | 1.036 (0.957,1.122) | 0.366 |

| **Compounds based groups** |          |               |               |         |
| DEHP-HMW score\(^g\) | 0.986 (0.881,1.103) | 0.797 | 0.982 (0.862,1.119) | 0.784 |
| DNP-HMW score\(^h\) | 1.054 (0.987,1.124) | 0.112 | 1.018 (0.938,1.105) | 0.658 |
| LMW score\(^i\) | 1.045 (0.974,1.121) | 0.208 | 1.011 (0.936,1.092) | 0.766 |
| Other-HMW score\(^j\) | 1.105 (0.985,1.239) | 0.087 | 1.182 (1.052,1.327) | 0.006 |

| Metabolic syndrome |          |               |               |         |
| **Data-driven groups** |          |               |               |         |
| Composite score 1\(^a\) | 1.055 (0.955,1.165) | 0.282 | 1.122 (0.980,1.284) | 0.094 |
| Composite score 2\(^b\) | 0.990 (0.941,1.041) | 0.678 | 0.967 (0.873,1.072) | 0.512 |
| Composite score 3\(^c\) | 1.024 (0.956,1.096) | 0.485 | 0.994 (0.908,1.087) | 0.890 |
| Composite score 4\(^d\) | 1.011 (0.957,1.067) | 0.697 | 1.049 (0.989,1.113) | 0.105 |

| **Molecular weight-based groups** |          |               |               |         |
| HMW score\(^e\) | 1.041 (0.965,1.122) | 0.289 | 1.067 (0.973,1.171) | 0.163 |
| LMW score\(^f\) | 1.019 (0.962,1.080) | 0.507 | 1.012 (0.943,1.087) | 0.725 |

| **Compounds based groups** |          |               |               |         |
| DEHP-HMW score\(^g\) | 1.043 (0.965,1.128) | 0.273 | 1.083 (0.961,1.22) | 0.184 |
| DNP-HMW score\(^h\) | 0.983 (0.934,1.035) | 0.511 | 0.952 (0.857,1.057) | 0.341 |
| LMW score\(^i\) | 1.009 (0.951,1.069) | 0.767 | 0.987 (0.915,1.063) | 0.717 |
| Other-HMW score\(^j\) | 1.042 (0.977,1.110) | 0.202 | 1.092 (0.983,1.214) | 0.098 |

Abbreviations: RR, relative risk; CI, confidence interval.
a Composite score 1 includes mono(carboxyonyl) phthalate (ng/mL)-MCNP, mono-2-ethyl-5-carboxypentyl phthalate-MECPP, mono-(2-ethyl-5-hydroxyhexyl) phthalate-MEHHP, mono-(2-ethyl)-hexyl phthalate (ng/mL)-MEHP and mono-(2-ethyl-5-oxohexyl) phthalate-MEOHP.

b Composite score 2 includes mono (carboxyoctyl) phthalate(ng/mL)-MCOP, mono-(3-carboxypropyl) phthalate(ng/mL)-MCPP and mono-isonylonyl phthalate (ng/mL)-MNP.

c Composite score 3 includes mono-n-butyl phthalate (ng/mL)-MBP, mono-ethyl phthalate (ng/mL)-MEP, mono-isobutyyl phthalate(ng/mL)-MiBP and mono-benzyl phthalate (ng/mL)-MBzP.

d Composite score 4 includes only cyclohexane 1, 2-dicarboxylic acid monohydroxy isononyl ester (ng/mL)-MHNCH.

e High molecular weight (HMW) score is the sum of all HMW phthalate metabolite concentrations including MCNP, MECPP, MEHHP, MEHP, MEOHP, MCOP, MCPP, MNP, MBzP, and MHNCH.

f Low molecular weight (LMW) score is the sum of all LMW phthalate metabolite concentrations including MBP, MEP, and MiBP.

g DEHP-HMW score is the total concentration of di(2-ethylhexyl) phthalate metabolites (DEHP) including MECPP, MEHHP, MEHP, and MEOHP.

h DNP-HMW score is the total concentration of di-isononyl phthalate metabolites (DNP) including MCOP and MNP and MCPP metabolite of di-n-octyl phthalate (DiNOP).

i LMW score is the total concentration of LMW phthalate metabolites MBP, MEP, and MiBP.

j Other-HMW score is the total concentration of MCNP, MBzP, and MHNCH.

*All scores were log-transformed in the analyses and all analyses adjusted for age, race and ethnicity, income, marital status, birth country, educational level, smoking status, alcohol use status, physical activity, and creatinine level.