Phthalate Exposure Enhances Incidence of Urinary Incontinence: US NHANES, 2003-2004 and 2005-2006

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Research Article

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Abstract

Objective: The aim of this study is to investigate the associations between phthalate exposure and UI in a nationally representative sample of US adults.

Methods: Cross-sectional data from the National Health and Nutrition Examination Survey (NHANES) database was used for analysis. In total, 2,818 participants with measurements for phthalate metabolites and complete UI questionnaire data were enrolled in our study. Further, seven phthalate metabolites were measured, which were obtained from urine samples and creatinine-standardized in the subsequent analyses. After divided these phthalate metabolites into three groups, multivariable regression models were performed to evaluate the association between phthalate metabolites and UI rates. Moreover, interaction analyses and subgroup analyses stratified by gender were performed.

Results: In these seven phthalate metabolites, high level of mono-carboxynonyl phthalate (MCNP), mono-carboxyoctyl phthalate (MCOP), mono-isobutyl phthalate (MiBP), mono-n-butyl phthalate (MBP) and mono-3-carboxypropyl phthalate (MCPP) showed increased risk of UI [odds ratio (OR) = 1.52, 1.42, 1.43, 1.50, 1.51, respectively, all p value < 0.05]. Trend test showed that incidence of UI increased significantly with concentration. A higher incidence of UI among participants was observed in the maximal tertile of phthalate when comparing with the lowest tertile. Subgroup analysis found that different phthalates have varying influence for different types of UI. Moreover, the analyses stratified for sex indicated that the high concentrations of MCNP and median concentrations of MCCP were associated with increase of the odds of UI in women and in men, respectively.

Conclusion: Overall, the exposure to phthalates was positively associated with UI among US adults. Notably, different phthalates have varying influence for different types of UI, and male and female exposure to phthalate could result in the different prevalence of UI.

Highlights

- Phthalate exposure is positively associated with the risk of UI among US adults.
- Different phthalates have varying influence for different types of UI.
- Male and female exposure to phthalate could result in the different prevalence of UI.

1. Introduction

Phthalates are a group of chemical additives commonly used in plastics and personal care products (Barr, et al. 2003; Hauser and Calafat 2005). Previous study has reported that urinary metabolites of phthalates were detectable in 75–90% of the individuals, with global annual production of phthalates approximately 8 million tons (Gao and Wen 2016; Silva, et al. 2004). In addition, people encounter widespread exposures to phthalates for the weak binding of phthalates to these products and vulnerable to release into the environment (Meeker, et al. 2009b). By hydrolysis and oxidation, phthalates are quickly metabolized to monoester metabolites in vivo and then excreted in urine within 24 h (Albro, et al. 1982).

Urinary incontinence (UI) is defined as the involuntary loss of urine, represents a common health problem worldwide (Keller 2010; Rogers, et al. 2018). The symptoms of UI adversely affect these individuals’ life and work, including poor personal hygiene, poor self-esteem and restricted social networks. Hence, it can be debilitating the life quality and satisfaction of life in this population. Additionally, the ongoing pain will cause a significant burden for individuals and the healthcare system (Abrams, et al. 2010; Farrington, et al. 2015; Pintos-Díaz, et al. 2019). Many factors were involved in the progression of UI, including chronic diseases, medicine, intrapartum-related complications and environmental factors (Sun, et al. 2016; Tähtinen, et al. 2016). The conservative and surgical interventions were used to treat UI, and both of them have achieved some therapeutic effects (Lightner, et al. 2019; Lucas, et al. 2012; Qaseem, et al. 2014). However, UI treatment remains complicated due to its multiple etiologies.

As a type of endocrine-disrupting chemicals, phthalate had been proved that it is closely related to the occurrence of many diseases, especially for the reproductive system diseases and cardiovascular diseases (Hauser and Calafat 2005; Mariana, et al. 2016). As reported previously, phthalate resulted in significant decrease in testosterone (Meeker 2010), and some phthalates, such as di-2-ethylhexyl phthalate (DEHP) and di-n-butyl phthalate (DnBP), exhibited weak estrogenic activity (Hannas, et al. 2011). Beyond endocrine disruption, phthalate can also involve in the processes of oxidative stress and inflammation (Ferguson, et al. 2011; Wang, et al. 2020). Some phthalates enhanced inflammation through the induction of macrophage-releasing chemokines and growth factors (Nishioka, et al. 2012). Similarly, it can also increase the rate of obesity, alter thyroid function, increase insulin resistance, impair the respiratory system (Hoppin, et al. 2004; Huang, et al. 2007; Meeker, et al. 2009a; Trasande, et al. 2013). The etiology and pathogenesis of UI are complicated and multifactorial, including intrinsic sphincter deficiency, pelvic floor dysfunction (PFD), inflammation, changes in circulating estrogen levels, oxidative stress and others (Hakimi, et al. 2020; Markland, et al. 2011).

Currently, the association between phthalates and UI remained unclear. Considering the previous studies identified that UI is associated with inflammation, oxidative stress, estrogen levels, androgen levels, obesity and depression, there may be a potential relationship between phthalate exposure and UI. Thus, we hypothesized that there might be some relationships between phthalate exposure and UI. The National Health and Nutrition Examination Survey (NHANES) datasets were analyzed to assess the relationship between phthalate exposure and UI.

2. Methods

2.1 Study design and participants

The NHANES is an ongoing cross-sectional study of a nationally representative sample of the noninstitutionalized civilian US population. It is conducted by the National Center for Health Statistics (NCHS), and the data were collected using a complex, multistage, stratified, clustered probability design. Participants
completed household interviews about their demographic, dietary, socioeconomic, behavioral factors and health information. After that, they were invited to undergo a further physical examination, and urine and blood sampling were conducted at mobile examination centers. Ethics approval for NHANES was granted by the National Center for Health Statistics Research Ethics Review Board.

Our analysis included four years of NHANES data, 2003–2004 and 2005–2006. Participants who had measurements for the phthalate metabolites and urine creatinine levels were enrolled. In addition, individuals with incomplete UI questionnaire data and/or missing data were excluded from this study (Fig. 1).

2.2 Assessment of UI

Two incontinence questions were studied. Participants were defined as stress UI if they had answered yes to the question “During the past 12 months, have you leaked or lost control of even a small amount of urine with an activity like coughing, lifting, or exercise?”. Participants were defined as urgency UI if they had answered yes to the question “During the past 12 months, have you leaked or lost control of even a small amount of urine with an urge or pressure to urinate and you couldn’t get to the toilet fast enough?”. If participants responded yes to both questions, they were classified as mixed UI. In the concurrent phase, both questions also asked the frequency of the situation that occurred (every day, a few times a week, a few times a month, a few times a year).

2.3 Urinary phthalate metabolites

Phthalate metabolites were measured by single spot urine samples obtained from a one-third subsample of respondents who provided spot urine specimens during physical examinations. These spot urine samples were collected and then frozen at −20°C and shipped to the National Center for Environmental Health for analysis of various phthalate metabolites. High-performance liquid chromatography-electrospray ionization-tandem mass spectrometry was used for phthalate analyzing. Further details on the laboratory procedures are provided elsewhere(Silva, et al. 2004).

The following seven phthalate metabolites were measured: mono-carboxynonyl phthalate (MCNP), mono-carboxyoctyl phthalate (MCOP), mono-isobutyl phthalate (MiBP), mono-n-butyl phthalate (MBP), mono-ethyl phthalate (MEP), mono-3-carboxypropyl phthalate (MCP), di-2-ethylhexyl phthalate (DEHP). Phthalate metabolites for which > 75% of measurements were below the limit of detection (LOD) were excluded in our further statistical analysis. Additionally, phthalate values below the LOD were assigned a value equal to the LOD divided by the square root of two(Varshavsky, et al. 2018). Phthalate levels were adjusted by urinary creatinine (presented as ng/ml creatinine) to account for dilution of the urine.

2.4 Covariates

Age, race/ethnicity (Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black, other Race), education (above high school, high school or equivalent, under high school), marital status (married or living with partner, living alone), family poverty income ratio (PIR) (≤ 1.3, 1.3–3.5, > 3.5), physical activity in recreational time (less than moderate, moderate, vigorous), smoking status (current, never, former) in participants were self-reported by questionnaire. Body mass index was categorized as normal weight of < 25, overweight of 25 to < 30 and obesity of ≥ 30.

2.5 Statistical analysis

All statistical analyses were performed using EmpowerStats (http://www.empowerstats.com), version number 2018-05-05 (X&Y Solutions, Inc., Boston, MA, UA). Because NHANES is a complex and multistage design, appropriate sample weights, primary sampling units, strata and cluster variables were applied to improve the accuracy of data. Moreover, differences with P < 0.05 were considered significant. Numbers, percentages, mean values and standard errors were calculated to describe demographics. Chi-square test ($\chi^2$) or Fisher exact test was adopted in categorical variables, and Kruskal-Wallis was used in continuous variables to determine the differences between groups. The creatinine-corrected urinary phthalate metabolite concentrations were weighted using sample weights, and we depicted the phthalate level by the geometric means (GM), 95 % confidence intervals (CIs) and percentile.

In this study, all concentrations for analysis were creatinine-standardized. We assigned tertiles of urinary phthalate metabolites as exposure variables. Log-transformed phthalate metabolite concentrations were also used as exposure variables due to skewed distributions. The association between phthalate and urinary incontinence was estimated by multivariable linear regression models with β coefficient and 95% CIs. Tertile 1 as a reference with OR = 1. In further analyses, we adjusted for the following confounders in multivariable regression models (model 1): age, race/ethnicity, BMI, education level, ratio of family income to poverty, comorbidity index. Otherwise, we also adjusted marital status, physical activity and smoking status in addition to the factors listed above in model 2. In order to evaluate the tendency between phthalates and UI, we performed trend test.

In order to explore association between phthalate exposure and different types of UI, subgroup analysis was conducted according to the different UI types. According to previous data, UI presents more commonly in the woman(Abrams, et al. 2018). Thus, we also performed stratified analyses by sex, and assigned tertiles of urinary phthalate metabolites as exposure variables. With the exception of the sex variable, the multivariable linear multiple regression models were identical as described above.

3. Results

3.1 Characteristic of participants

A total of 20,470 participants from NHANES for cycles 2003-2004 and 2005-2006 were interviewed and underwent a physical examination. However, only a small fraction of them (n=5,153) measured the levels of urinary phthalate biomarkers. Among them, participants who did not complete the incontinence questions or with incomplete UI data were excluded (n=2,335). Finally, 2,818 participants were included in the final analytic data set.

The basic characteristics of 2,818 participants were presented in Table 1, of which 987 participants of those exposed to phthalates developed UI. Univariate analysis revealed that the following factors were significantly associated with UI among participants with a history of phthalates exposure: age, education,
androgens receptor to affect pelvic musculature. Likewise, urethral tissue contains estrogen receptors, and the decrease of estrogen is related to laxity of pelvic floor muscles.

2018), found that low levels of serum testosterone increase the risk of SUI and mixed UI in women, and the underlying mechanism may be through depression-like behavior in adult mice (Zuo, et al. 2014). In addition, it has been reported previously that MCPP, MCNP and MBP exposure were positively correlated with the incidence of SUI. This might be an explanation for the higher OR of UI in individuals exposed to MCPP, MCNP and MBP. Indeed, in our subgroup analysis, we found that MCNP and MBP exposure were positive associated with the incidence of SUI (Table 3).

3.3 Subgroup analysis

Tables 4-5 show the results of subgroup analysis. We found that different phthalates have varying influence for different types of UI. Higher concentrations of MIBP increases the risk of developing UII, SUI and MUI. MCOP and MCPP showed an increased risk in the incidence of UII. MCNP and MBP showed an increased risk in the incidence of SUI. Besides, MBP was also positive associated with MUI. In addition, stratified modeling revealed outcomes vary between males and females. After adjusting by age, race and BMI, we found that highest tertile of MCNP metabolite concentrations was associated with increase of the odds of UI in women (OR=1.67, 95%CI=1.16-2.41). Moreover, highest tertile of MCPP metabolite concentrations was associated with increase of the odds of UI in men (OR=1.72, 95%CI=1.06-2.80), but following the adjustments for confounding parameters, there was no significant difference. Notably, males in tertile 2 had a significantly higher risk of UI with MBP metabolite concentrations (OR=1.59, 95%CI=1.01-2.49).

4. Discussion

The present cross-sectional, population-based analysis based on a nationally representative sample of general adults from NHANES evidenced positive associations between phthalate exposure and urinary incontinence. Specifically, it was found that a one-unit increase in log-transformed phthalates MNCP, MIBP, MBP and MCPP in participants, could have a higher likelihood of UI. Moreover, a higher level of phthalate exposure displayed a higher incidence of UI in comparison with those in the lowest tertile after multivariable adjustment. Importantly, our study was the first study that considered the relationship between exposure to phthalates and UI in general adults.

The underlying mechanisms involved in increasing risk of UI by phthalate exposure had not been unraveled. As described in previous studies, phthalate exposure may have an effect on inflammation and oxidative stress. For example, Nishioka et al. (Nishioka, et al. 2012) reported that DEHP stimulated macrophages to express inflammatory cytokines and chemokines that exacerbating their inflammatory response. Mono(2-ethylhexyl) phthalate (MEHP) was found to increase the production of IL-8 in adult neutrophils and IL-1β in neonatal neutrophils (Vetrano, et al. 2010). Furthermore, within animals, DEHP could rapidly activate NADPH oxidase and nuclear factor-kB (NF-kB) in the liver, resulting in the production of cytokines and TNFα (Rusyn, et al. 2001). And di-n-butyl phthalate (DBP) exhibited cell apoptosis induction effects by infection-induced oxidative stress in testes (Kasahara, et al. 2002; Zhou, et al. 2010). Taken together, these studies provide evidences that phthalate exposure leads to UI that is potentially mediated through oxidative stress and inflammation.

Inflammation plays a key role in the process of UI (stress UI or urgency UI). Long-term inflammation could lead to bladder fibrosis, reduce bladder compliance, decrease the functional capacity of the bladder progressively and increase intravesical pressure, ultimately results in the occurrence of UI. Excessive production of reactive oxygen species (ROS) can lead to oxidative damage, leading to cell apoptosis (Jia, et al. 2015). Additionally, persistent inflammation and oxidative stress could lead to persistent urethral irritation, which might be the crucial factor for promoting bladder overactivity (Li, et al. 2011).

The association between phthalate exposure and UI might be explained by depression and obesity. Phthalate exposure was associated with depression-like behavior in adult mice (Zuo, et al. 2014). In addition, it has been reported previously that MCPP, MCNP and MBP exposure were positively correlated with the risk of depression (Kim, et al. 2016). Some studies have accounted for the association between phthalate exposure and obesity, although the results are controversial. Specifically, there is a positive association between urinary low molecular weight (LMW) phthalates metabolites and rate of obesity. While urinary high molecular weight (HMW) phthalates and DEHP phthalate exposure are associated with higher OR for obesity in male adults (more than or equal to 60 years old) (Buser, et al. 2014; Trasande, et al. 2013). Notably, depression and obesity can cause chronic damage to the pelvic floor muscles and diminish the effect on supporting pelvic viscera. This identifies them as a factor in the pathogenesis of SUI (Bart, et al. 2008; Moser, et al. 2018; Treister-Goltzman and Peleg 2018). This might be an explanation for the higher OR of UI in individuals exposed to MCPP, MCNP and MBP. Indeed, in our subgroup analysis, we found that MCNP and MBP exposure were positive associated with the incidence of SUI.

Previous studies confirmed that phthalate exposure has an antiandrogenic effect (Radke, et al. 2018; Swan 2006; Swan, et al. 2015) and was associated with lower testosterone in male animals and humans (Botelho, et al. 2009; Meeker and Ferguson 2014). Data from NHANES, 2013–2016 demonstrated HMW phthalates could reduce the level of total, free and bioavailable testosterone among men aged ≥ 60 (Woodward, et al. 2020). For menopausal women, DEHP exposure was associated with lower bioavailable testosterone and estradiol concentrations (Long, et al. 2021). A study done by Kim et al. (Kim and Kreydin 2018), found that low levels of serum testosterone increase of the risk of SUI and mixed UI in women, and the underlying mechanism may be through androgens receptor to affect pelvic musculature. Likewise, urethral tissue contains estrogen receptors, and the decrease of estrogen is related to laxity of urethral sphincter and ligament, which results in a high incidence of SUI (Adamiak-Godlewska, et al. 2018; Aoki, et al. 2017). Thus, exposure to phthalates may	

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lead to UI by affecting testosterone and estradiol concentrations. In brief, phthalate exposure has been found to participate in UI development by affecting multifaceted etiology.

The following are the key strengths of the present study. This is the first report on the association between phthalate exposure and UI. A nationally representative sample was used for analyses. Therefore, the present results might be generalizable to the entire population of US adults. Strict quality control procedures were performed to analyze 7 urinary phthalate metabolites. Moreover, to get more accurate results, regressions were adjusted for the main potential confounders, including age, race/ethnicity, BMI, education level, comorbidity index, etc. Uniquely, our study took into account the difference between the sexes in terms of UI occurrence, and the analyses stratified for sex indicate that male and female exposure to phthalate can result in the different prevalence of UI. We also considered the association between phthalate exposure and different types of UI.

There are some limitations in our study. Firstly, since the overall study design is a cross-sectional study, no causal relationships could be deduced. We have adjusted possible confounders. Nevertheless, residual confounding remains a possibility. Second, with four years (2003–2004 and 2005–2006) of NHANES data involved phthalate exposure and UI at the same time, the sample size analyzed in this study was sufficient. Third, concentrations of phthalate metabolites were detected from spot urine samples instead of 24-hour urine samples, which may not take into account potential changes of phthalate within-person over time. Nevertheless, a single measurement of urine may be representative in the long term, although phthalate metabolites have a short half-life. Last but not least, the questionnaire interview on UI is not a diagnostic tool, but it is a valid and reliable tool for identifying UI.

5. Conclusion

In this study, we found that several phthalates were positively associated with the risk of UI among the general US population. These findings may motivate people to reduce exposure to phthalate to achieve the purpose of decreasing the incidence of UI. However, further studies are warranted to verify our findings and explore the potential mechanisms.

Abbreviations

urinary incontinence, UI
mono-carboxynonyl phthalate, MCNP
mono-carboxyoctyl phthalate, MCOP
mono-isobutyl phthalate, MiBP
mono-n-butyl phthalate, MBP
mono-ethyl phthalate, MEP
mono-3-carboxypropyl phthalate, MCPP
di-2-ethylhexyl phthalate, DEHP
odds ratio, OR
National Health and Nutrition Examination Survey, NHANES
Body mass index, BMI
family poverty income ratio, PIR
geometric means, GM
confidence intervals, CIs

Declarations

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Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.
Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

J. Ai, Q. Wei and X. Yi conceived the project and drafted the manuscript, K. Jin, X. Xiong, T. Zhang and G. Peng searched the databases, S. Qiu, X. Zheng, D. Liao and H. Xu analyzed data, H. Li and L. Yang revised the manuscript.

All authors read and approved the final version of the manuscript.

Competing interests

The authors declare that they have no competing interests

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Tables

Table 1. Basic characteristics of participants in US adults, NHANES 2003-2004 and 2005-2006.
| Population characteristics | Normal | Urinary Incontinence | P value |
|----------------------------|--------|---------------------|---------|
| N                          | 1831   | 987                 |         |
| Age (years, mean(SD))      | 45.86 (18.82) | 54.79 (18.11) | <0.001 |
| Race/ethnicity, n (%)      |        |                     | 0.457   |
| Mexican American           | 362 (19.77%) | 200 (20.26%) |         |
| Other Hispanic             | 52 (2.84%)  | 28 (2.84%)   |         |
| Non-Hispanic White         | 940 (51.34%) | 533 (54.00%) |         |
| Non-Hispanic Black         | 400 (21.85%) | 187 (18.95%) |         |
| Other Race                 | 77 (4.21%)  | 39 (3.95%)   |         |
| Education, n (%)           |        |                     | 0.011   |
| Under high school          | 471 (25.72%) | 297 (30.09%) |         |
| High school or equivalent  | 442 (24.14%) | 250 (25.33%) |         |
| Above high school          | 918 (50.14%) | 440 (44.58%) |         |
| PIR\(^a\), n (%)           |        |                     | 0.11    |
| ≤1.3                      | 457 (24.96%) | 269 (27.25%) |         |
| 1.3-3.5                   | 762 (41.62%) | 425 (43.06%) |         |
| >3.5                      | 612 (33.42%) | 293 (29.69%) |         |
| Marital status, n (%)      |        |                     | 0.118   |
| Married or living with partner | 1155 (63.08%) | 593 (60.08%) |         |
| Living alone               | 676 (36.92%) | 394 (39.92%) |         |
| BMI\(^b\), n (%)           |        |                     | <0.001  |
| ≤25                        | 630 (34.41%) | 267 (27.05%) |         |
| 25-30                      | 637 (34.79%) | 324 (32.83%) |         |
| ≥30                        | 564 (30.80%) | 396 (40.12%) |         |
| Physical activity in recreational time, n (%) |         |         | <0.001 |
| Less than moderate         | 608 (33.21%) | 389 (39.41%) |         |
| Moderate                   | 521 (28.45%) | 338 (34.25%) |         |
| Vigorous                   | 702 (38.34%) | 260 (26.34%) |         |
| Smoking status, n (%)      |        |                     | <0.001  |
| Never                      | 940 (51.34%) | 804 (81.46%) |         |
| Former                     | 535 (29.22%) | 63 (6.38%)   |         |
| Current                    | 356 (19.44%) | 120 (12.16%) |         |

\(^a\) PIR: family poverty income ratio

\(^b\) BMI: body mass index

Table 2. Concentrations of sample-weighted, creatinine-corrected urinary phthalates metabolites (μg/g creatinine), NHANES 2003-2004 and 2005-2006
| Phthalate (ng/ml creatinine) | LOD\(^{a}\) | GM\(^{b}\) (95%CI\(^{c}\)) | Percentile |
|-----------------------------|--------------|-----------------------------|------------|
|                             |              | 5  | 10 | 25 | 50 | 75 | 90 | 95 | 100 |
| MCNP                        | 0.12         | 2.60 (2.50, 2.70)           | 0.62       | 0.90 | 1.45 | 2.43 | 4.25 | 8.30 | 13.40 | 702.00 |
| MCOP                        | 0.19         | 5.14 (4.93, 5.35)           | 1.14       | 1.54 | 2.56 | 4.54 | 8.88 | 20.62 | 38.05 | 3875.55 |
| MIBP                        | 0.12         | 5.71 (5.50, 5.92)           | 1.25       | 1.88 | 3.33 | 5.75 | 9.79 | 16.79 | 24.29 | 8451.74 |
| MNBP                        | 0.09         | 21.50 (20.74, 22.29)        | 5.46       | 7.56 | 12.18 | 20.99 | 36.70 | 65.26 | 95.88 | 3596.00 |
| MEP                         | 1.27         | 128.2 (121.97, 134.79)      | 19.40      | 26.69 | 50.06 | 114.40 | 295.65 | 717.14 | 1349.06 | 20316.25 |
| MCPP                        | 0.03         | 2.84 (2.75, 2.94)           | 0.75       | 1.02 | 1.67 | 2.70 | 4.64 | 8.14 | 12.29 | 426.22 |
| DEHP                        | 0.44         | 72.09 (69.26, 75.03)        | 16.98      | 22.77 | 35.91 | 63.13 | 123.95 | 277.15 | 528.94 | 4681.07 |

\(^{a}\) LOD: limit of detection

\(^{b}\) GM: geometric Means

\(^{c}\) CI: confidence intervals

Table 3 Association between exposure to phthalate and UI among US adults, NHANES 2003-2004 and 2005-2006.
|          | Unadjusted | Model 1\(^c\) | Model 2\(^d\) |
|----------|------------|---------------|---------------|
|          | OR\(^a\) of Urinary Incontinence (95% CI\(^b\)) | P | OR\(^a\) of Urinary Incontinence (95% CI\(^b\)) | P | OR\(^a\) of Urinary Incontinence (95% CI\(^b\)) | P |
| MCNP     |            |               |               |
| Tertile 1| Reference  | Reference      | Reference      |
| Tertile 2| 1.28 (0.97, 1.68) | 0.081 | 1.26 (0.95, 1.69) | 0.110 | 1.29 (0.96, 1.73) | 0.088 |
| Tertile 3| 1.52 (1.15, 2.00) | 0.003 | 1.41 (1.05, 1.89) | 0.021 | 1.43 (1.06, 1.93) | 0.018 |
| Trend test| 1.23 (1.07, 1.41) | 0.003 | 1.19 (1.03, 1.38) | 0.021 | 1.20 (1.03, 1.39) | 0.018 |
| MCOP     |            |               |               |
| Tertile 2| 1.41 (1.08, 1.84) | 0.013 | 1.45 (1.09, 1.92) | 0.011 | 1.41 (1.06, 1.89) | 0.020 |
| Tertile 3| 1.42 (1.07, 1.86) | 0.013 | 1.43 (1.07, 1.92) | 0.017 | 1.46 (1.08, 1.97) | 0.013 |
| Trend test| 1.19 (1.04, 1.37) | 0.010 | 1.20 (1.04, 1.39) | 0.014 | 1.21 (1.05, 1.41) | 0.011 |
| MiBP     |            |               |               |
| Tertile 2| 1.07 (0.82, 1.40) | 0.597 | 1.11 (0.84, 1.47) | 0.455 | 1.14 (0.86, 1.52) | 0.365 |
| Tertile 3| 1.43 (1.08, 1.89) | 0.011 | 1.44 (1.07, 1.93) | 0.015 | 1.42 (1.05, 1.91) | 0.022 |
| Trend test| 1.19 (1.03, 1.36) | 0.015 | 1.19 (1.03, 1.38) | 0.017 | 1.19 (1.02, 1.38) | 0.023 |
| MBP      |            |               |               |
| Tertile 2| 1.51 (1.17, 1.95) | 0.002 | 1.63 (1.25, 2.14) | <0.001 | 1.66 (1.26, 2.18) | <0.001 |
| Tertile 3| 1.50 (1.15, 1.97) | 0.003 | 1.47 (1.11, 1.97) | 0.008 | 1.46 (1.09, 1.95) | 0.011 |
| Trend test| 1.24 (1.08, 1.41) | 0.002 | 1.23 (1.07, 1.42) | 0.004 | 1.22 (1.06, 1.41) | 0.005 |
| MEP      |            |               |               |
| Tertile 2| 1.19 (0.91, 1.56) | 0.211 | 1.29 (0.97, 1.73) | 0.081 | 1.29 (0.97, 1.73) | 0.084 |
| Tertile 3| 1.13 (0.87, 1.46) | 0.367 | 1.21 (0.91, 1.59) | 0.186 | 1.21 (0.91, 1.60) | 0.188 |
| Trend test| 1.06 (0.93, 1.21) | 0.387 | 1.09 (0.95, 1.26) | 0.203 | 1.09 (0.95, 1.26) | 0.206 |
| MCPP     |            |               |               |
| Tertile 2| 1.20 (0.94, 1.54) | 0.146 | 1.14 (0.87, 1.49) | 0.333 | 1.13 (0.86, 1.48) | 0.372 |
| Tertile 3| 1.51 (1.14, 1.99) | 0.004 | 1.44 (1.07, 1.94) | 0.015 | 1.44 (1.07, 1.94) | 0.017 |
| Trend test| 1.23 (1.07, 1.41) | 0.004 | 1.20 (1.03, 1.39) | 0.017 | 1.19 (1.03, 1.38) | 0.019 |
| DEHP     |            |               |               |
| Tertile 2| 1.24 (0.96, 1.59) | 0.097 | 1.19 (0.91, 1.55) | 0.211 | 1.20 (0.92, 1.57) | 0.184 |
| Tertile 3| 1.10 (0.84, 1.45) | 0.472 | 1.10 (0.82, 1.47) | 0.516 | 1.13 (0.84, 1.51) | 0.418 |
| Trend test| 1.06 (0.93, 1.21) | 0.393 | 1.06 (0.91, 1.22) | 0.457 | 1.07 (0.92, 1.24) | 0.366 |

\(^a\) OR: odds ratio  
\(^b\) CI: confidence intervals

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Table 4. Association between phthalate exposure and different types of UI among US adults.
|        | **UUI** |          |          | **SU** |          |          | **MUI** |          |          |
|--------|---------|----------|----------|--------|----------|----------|---------|----------|----------|
|        | Unadjusted result | Adjusted result | Unadjusted result | Adjusted result | Unadjusted result | Adjusted result |
|        | OR of Urinary Incontinence (95% CI) | P | OR of Urinary Incontinence (95% CI) | P | OR of Urinary Incontinence (95% CI) | P | OR of Urinary Incontinence (95% CI) | P |
| **MCNP** |         |          |          |        |          |          |         |          |          |
| Tertile 1 | Reference | Reference | Reference | Reference | Reference | Reference | Reference | Reference |
| Tertile 2 | 1.21 (0.88, 1.66) | 0.239 | 1.25 (0.89, 1.74) | 0.196 | 1.39 (1.02, 1.90) | 0.036 | 1.39 (1.01, 1.93) | 0.046 |
| Tertile 3 | 1.25 (0.90, 1.72) | 0.179 | 1.22 (0.86, 1.72) | 0.263 | 1.53 (1.12, 2.09) | 0.008 | 1.46 (1.05, 2.03) | 0.026 |
| Trend test | 1.04 (0.97, 1.12) | 0.240 | 1.03 (0.96, 1.11) | 0.377 | 1.08 (1.01, 1.16) | 0.017 | 1.07 (1.00, 1.15) | 0.057 |
| **MCOP** |         |          |          |        |          |          |         |          |          |
| Tertile 1 | Reference | Reference | Reference | Reference | Reference | Reference | Reference | Reference |
| Tertile 2 | 1.33 (0.97, 1.82) | 0.080 | 1.43 (1.02, 2.00) | 0.036 | 1.52 (1.12, 2.05) | 0.007 | 1.53 (1.12, 2.11) | 0.008 |
| Tertile 3 | 1.41 (1.02, 1.94) | 0.036 | 1.56 (1.11, 2.20) | 0.011 | 1.29 (0.94, 1.77) | 0.109 | 1.30 (0.93, 1.81) | 0.128 |
| Trend test | 1.03 (1.00, 1.05) | 0.069 | 1.03 (1.00, 1.06) | 0.028 | 1.01 (0.99, 1.04) | 0.314 | 1.01 (0.98, 1.04) | 0.365 |
| **MBP** |         |          |          |        |          |          |         |          |          |
| Tertile 1 | Reference | Reference | Reference | Reference | Reference | Reference | Reference | Reference |
| Tertile 2 | 1.01 (0.73, 1.38) | 0.967 | 1.07 (0.77, 1.49) | 0.686 | 1.18 (0.87, 1.59) | 0.292 | 1.20 (0.87, 1.64) | 0.261 |
| Tertile 3 | 1.47 (1.07, 2.01) | 0.017 | 1.41 (1.01, 1.98) | 0.044 | 1.53 (1.12, 2.09) | 0.007 | 1.49 (1.08, 2.07) | 0.017 |
| Trend test | 1.04 (1.01, 1.08) | 0.013 | 1.04 (1.00, 1.07) | 0.039 | 1.04 (1.01, 1.08) | 0.007 | 1.04 (1.01, 1.07) | 0.017 |
| **MEP** |         |          |          |        |          |          |         |          |          |
| Tertile 1 | Reference | Reference | Reference | Reference | Reference | Reference | Reference | Reference |
| Tertile 2 | 1.38 (1.03, 1.84) | 0.031 | 1.46 (1.08, 1.99) | 0.015 | 1.62 (1.21, 2.16) | 0.001 | 1.72 (1.28, 2.32) | <0.001 |
| Tertile 3 | 1.37 (1.01, 1.86) | 0.046 | 1.31 (0.94, 1.81) | 0.107 | 1.72 (1.28, 2.33) | <0.001 | 1.77 (1.29, 2.41) | <0.001 |
| Trend test | 1.01 (1.00, 1.01) | 0.081 | 1.01 (1.00, 1.01) | 0.202 | 1.01 (1.00, 1.02) | 0.001 | 1.01 (1.00, 1.02) | 0.002 |
| **MCPP** |         |          |          |        |          |          |         |          |          |
| Tertile 1 | Reference | Reference | Reference | Reference | Reference | Reference | Reference | Reference |
| Tertile 2 | 1.17 (0.87, 1.56) | 0.288 | 1.13 (0.83, 1.54) | 0.423 | 1.30 (0.98, 1.71) | 0.067 | 1.21 (0.90, 1.61) | 0.202 |
| Tertile 3 | 1.27 (0.94, 1.71) | 0.114 | 1.38 (1.01, 1.90) | 0.044 | 1.06 (0.79, 1.42) | 0.702 | 1.14 (0.84, 1.55) | 0.396 |
| Trend test | 1.00 (1.00, 1.00) | 0.137 | 1.00 (1.00, 1.00) | 0.061 | 1.00 (1.00, 1.00) | 0.669 | 1.00 (1.00, 1.00) | 0.928 |

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| Tertile 3 | 1.60 (1.17, 2.18) | 0.003 | 1.52 (1.09, 2.12) | 0.013 | 1.37 (1.01, 1.87) | 0.043 | 1.25 (0.90, 1.72) | 0.179 | 1.59 (1.06, 2.39) | 0.025 | 1.37 (0.89, 2.12) | 0.0 |
| Trend test | 1.10 (1.03, 1.18) | 0.003 | 1.09 (1.02, 1.17) | 0.012 | 1.06 (1.00, 1.13) | 0.063 | 1.04 (0.97, 1.11) | 0.227 | 1.09 (1.01, 1.19) | 0.034 | 1.06 (0.97, 1.16) | 0.0 |

**DEPH**

| Tertile | Reference | Reference | Reference | Reference | Reference | Reference | Reference | Reference | Reference |
| Tertile 1 | 1.13 (0.85, 1.51) | 0.401 | 1.00 (0.74, 1.36) | 0.983 | 1.08 (0.81, 1.43) | 0.600 | 1.04 (0.78, 1.39) | 0.805 | 0.87 (0.60, 1.27) | 0.478 | 0.74 (0.50, 1.10) | 0.0 |
| Tertile 2 | 1.06 (0.78, 1.44) | 0.703 | 1.01 (0.73, 1.41) | 0.949 | 1.04 (0.77, 1.41) | 0.774 | 1.01 (0.74, 1.38) | 0.971 | 0.97 (0.65, 1.43) | 0.858 | 0.87 (0.57, 1.32) | 0.0 |
| Tertile 3 | 1.00 (1.00, 1.00) | 0.842 | 1.00 (1.00, 1.00) | 0.949 | 1.00 (1.00, 1.00) | 0.858 | 1.00 (1.00, 1.00) | 0.979 | 1.00 (1.00, 1.00) | 0.984 | 1.00 (1.00, 1.00) | 0.0 |

| Trend test | 1.00 (1.00, 1.00) | 0.842 | 1.00 (1.00, 1.00) | 0.949 | 1.00 (1.00, 1.00) | 0.858 | 1.00 (1.00, 1.00) | 0.979 | 1.00 (1.00, 1.00) | 0.984 | 1.00 (1.00, 1.00) | 0.0 |

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*a* UUI, urge incontinence  
*b* SUI, stress incontinence  
*c* MUI, mix incontinence  
*d* adjusted for age, race, BMI, ratio of family income to poverty, education level, marital, physical activity  
*e* OR: odds ratio  
*f* CI: confidence intervals

Table 5. Association between phthalate exposure and UI among US adults stratified by gender.
|                  | Male Unadjusted result OR\(^a\) of Urinary Incontinence (95% CI\(^b\)) | Male Adjusted\(^c\) result OR\(^a\) of Urinary Incontinence (95% CI\(^b\)) | Female Unadjusted result OR\(^a\) of Urinary Incontinence (95% CI\(^b\)) | Female Adjusted\(^c\) result OR\(^a\) of Urinary Incontinence (95% CI\(^b\)) | P  |
|----------------|-----------------------------------------------------------------------|--------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|----|
| **MCNP**       |                                                                       |                                                                          |                                                                                               |                                                                                               |    |
| Tertile 1      | Reference                                                             | Reference                                                                | Reference                                                                                        | Reference                                                                                        |    |
| Tertile 2      | 0.87 (0.53, 1.45)                                                     | 0.600                                                                   | 1.34 (0.94, 1.91)                                                                               | 1.23 (0.83, 1.81)                                                                               | 0.301|
| Tertile 3      | 1.07 (0.65, 1.76)                                                     | 0.799                                                                   | 1.67 (1.16, 2.41)                                                                               | 1.53 (1.02, 2.29)                                                                               | 0.038|
| Trend test     | 1.02 (0.92, 1.14)                                                     | 0.709                                                                   | 1.11 (1.03, 1.20)                                                                               | 1.09 (1.00, 1.19)                                                                               | 0.043|
| **MCOP**       |                                                                       |                                                                          |                                                                                               |                                                                                               |    |
| Tertile 1      | Reference                                                             | Reference                                                                | Reference                                                                                        | Reference                                                                                        |    |
| Tertile 2      | 1.17 (0.72, 1.91)                                                     | 0.526                                                                   | 1.31 (0.92, 1.88)                                                                               | 1.16 (0.78, 1.71)                                                                               | 0.459|
| Tertile 3      | 1.12 (0.67, 1.88)                                                     | 0.673                                                                   | 1.25 (0.87, 1.80)                                                                               | 1.14 (0.77, 1.68)                                                                               | 0.528|
| Trend test     | 1.01 (0.96, 1.05)                                                     | 0.742                                                                   | 1.01 (0.98, 1.05)                                                                               | 1.01 (0.98, 1.04)                                                                               | 0.650|
| **MiBP**       |                                                                       |                                                                          |                                                                                               |                                                                                               |    |
| Tertile 1      | Reference                                                             | Reference                                                                | Reference                                                                                        | Reference                                                                                        |    |
| Tertile 2      | 0.91 (0.55, 1.50)                                                     | 0.711                                                                   | 0.95 (0.67, 1.35)                                                                               | 1.03 (0.70, 1.51)                                                                               | 0.900|
| Tertile 3      | 1.55 (0.93, 2.57)                                                     | 0.090                                                                   | 1.03 (0.72, 1.48)                                                                               | 1.07 (0.72, 1.60)                                                                               | 0.742|
| Trend test     | 1.05 (0.99, 1.10)                                                     | 0.081                                                                   | 1.01 (0.97, 1.04)                                                                               | 1.01 (0.97, 1.05)                                                                               | 0.740|
| **MBP**        |                                                                       |                                                                          |                                                                                               |                                                                                               |    |
| Tertile 1      | Reference                                                             | Reference                                                                | Reference                                                                                        | Reference                                                                                        |    |
| Tertile 2      | 1.43 (0.95, 2.16)                                                     | 0.090                                                                   | 1.06 (0.74, 1.51)                                                                               | 1.17 (0.80, 1.71)                                                                               | 0.429|
| Tertile 3      | 1.37 (0.84, 2.26)                                                     | 0.210                                                                   | 0.86 (0.60, 1.24)                                                                               | 0.91 (0.62, 1.34)                                                                               | 0.642|
| Trend test     | 1.01 (1.00, 1.02)                                                     | 0.203                                                                   | 1.00 (0.99, 1.00)                                                                               | 1.00 (0.99, 1.01)                                                                               | 0.412|
| **MEP**        |                                                                       |                                                                          |                                                                                               |                                                                                               |    |
| Tertile 1      | Reference                                                             | Reference                                                                | Reference                                                                                        | Reference                                                                                        |    |
| Tertile 2      | 0.92 (0.58, 1.47)                                                     | 0.730                                                                   | 0.97 (0.67, 1.40)                                                                               | 1.09 (0.74, 1.62)                                                                               | 0.659|
| Tertile 3      | 1.15 (0.75, 1.76)                                                     | 0.517                                                                   | 0.84 (0.59, 1.21)                                                                               | 0.88 (0.60, 1.30)                                                                               | 0.533|
| Trend test     | 1.12 (1.01, 1.24)                                                     | 0.031                                                                   | 1.00 (1.00, 1.00)                                                                               | 1.00 (1.00, 1.00)                                                                               | 0.315|
| **MCPP**       |                                                                       |                                                                          |                                                                                               |                                                                                               |    |
| Tertile 1      | Reference                                                             | Reference                                                                | Reference                                                                                        | Reference                                                                                        |    |
| Tertile 2      | 1.36 (0.90, 2.07)                                                     | 0.150                                                                   | 0.93 (0.66, 1.30)                                                                               | 0.86 (0.60, 1.24)                                                                               | 0.413|
| Tertile 3      | 1.72 (1.06, 2.80)                                                     | 0.028                                                                   | 1.02 (0.71, 1.47)                                                                               | 0.96 (0.65, 1.41)                                                                               | 0.827|
| Trend test | Reference | Reference | Reference | Reference |
|------------|-----------|-----------|-----------|-----------|
| 1.12 (1.01, 1.24) | 0.031 | 1.10 (0.98, 1.23) | 0.114 | 1.01 (0.94, 1.09) | 0.831 | 1.00 (0.92, 1.08) | 0.973 |
| DEPH |
| Tertile 1 | Reference | Reference | Reference | Reference |
| Tertile 2 | 1.45 (0.95, 2.21) | 0.086 | 1.25 (0.80, 1.98) | 0.329 | 0.84 (0.60, 1.18) | 0.317 | 0.83 (0.58, 1.20) | 0.327 |
| Tertile 3 | 1.00 (0.62, 1.60) | 0.993 | 0.83 (0.49, 1.40) | 0.486 | 0.87 (0.60, 1.25) | 0.444 | 0.88 (0.60, 1.30) | 0.522 |
| Trend test | 1.00 (1.00, 1.00) | 0.769 | 1.00 (1.00, 1.00) | 0.368 | 1.00 (1.00, 1.00) | 0.607 | 1.00 (1.00, 1.00) | 0.705 |

a OR: odds ratio  
b CI: confidence intervals  
c adjusted for age, race, BMI

Figures

Figure 1
Flow chart of participants selection.

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