# Phthalates exposure and uterine fibroid burden among women undergoing surgical treatment for fibroids: a preliminary study

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## Abstract

**Objectives.—**To examine the association between phthalates exposure and two measures of uterine fibroid burden: diameter of largest fibroid and uterine volume.

**Design:** Pilot, cross-sectional study

**Setting:** Academic medical center

**Patient(s):** Fifty-seven pre-menopausal women undergoing either hysterectomy or myomectomy for fibroids.

**Intervention:** None

**Main Outcome Measures:** Diameter of the largest fibroid and uterine dimensions were abstracted from medical records. Spot urine samples were analyzed for 14 phthalate biomarkers using mass spectrometry. We estimated associations between fibroid outcomes and individual phthalate metabolites, sum of di(2-ethylhexyl) phthalate metabolites ( DEHP), and a weighted sum of anti-androgenic phthalate metabolites ( AA Phthalates) using linear regression, adjusting for age, race/ethnicity, and BMI. Fibroid outcomes were also examined dichotomously (divided at the median) using logistic regression.

**Results.**—Most women were Black, overweight or obese, and college-educated. In multivariable models, higher levels of mono-hydroxyisobutyl phthalate, monocarboxyoctyl phthalate,monocarboxynonyl phthalate, mono(2-ethylhexyl) phthalate, mono(2-ethyl-5-hydroxyhexyl phthalate) (MEHHP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), and mono(2-ethyl-5-carboxypentyl) phthalate (MECPP), ∑DEHP and ∑AA Phthalates were positively associated with uterine volume. Associations were most pronounced for individual DEHP metabolites(MEHHP, MEOHP, MECPP), ∑DEHP and ∑AA Phthalates. For example, a doubling in ∑DEHP and ∑AA Phthalates was associated with 33.19% (95% CI 6.59, 66.43) and 26.81% (95% CI 2.19, 57.37) increase in uterine volume, respectively. There were few associations between phthalate biomarkers and fibroid size.

**Conclusions.**—Exposure to some phthalate biomarkers was positively associated with uterine volume, which further supports the hypothesis that phthalates exposures may be associated with fibroid outcomes. Additional studies are needed to confirm these relationships.

## Keywords

consumer product chemicals; endocrine-disrupting chemicals; health disparities; uterine leiomyoma; women's health

## Introduction

The social and economic costs of uterine leiomyomas (fibroids) in the United States is immense, with an annual estimated cost of up to $34 billion, with a disproportionate impact on Black women (1). While the majority of reproductive-aged women will develop fibroids, only ~25% will experience symptoms (2). Most fibroids are asymptomatic, but larger fibroid size is associated with greater morbidity including abdominal pain (3), heavy menstrual bleeding (4), preterm labor (5), and risk of hysterectomy (6). Yet, the dynamics of fibroid growth and the causes of racial/ethnic disparities remain poorly understood.

Endocrine disrupting chemicals (EDCs), or chemicals that interfere with hormone action, may represent a modifiable risk factor since estrogen and progesterone play a critical role in fibroid growth (7). Phthalates, a family of multifunctional chemicals, specifically warrant concern because several phthalates, such as di-n-butyl phthalate (DnBP) and di(2-ethylhexyl) phthalate (DEHP), can disrupt signaling pathways mediated via estrogen, androgen, and/or peroxisome proliferator-activated receptors, and are reproductive toxicants in female and male animals (8–12). Low-molecular phthalates, such as diethyl phthalate (DEP), DnBP, and di-isobutyl phthalate (DiBP), are commonly used as solvents in personal care products, including perfumes, lotions, and cosmetics (13, 14), and as excipients in medications and supplements (15). High-molecular phthalates, such as butylbenzyl phthalate, DEHP, di-isononyl phthalate , and diisodecyl phthalate, are primarily used as plasticizers in polyvinyl chloride applications found in building materials such as vinyl flooring, food packaging, and medical devices (DEHP only) (16–18). Phthalates can leach, migrate, or off-gas from products over time and enter the human body through ingestion, inhalation, direct dermal application, or even transdermal exposure from air (17, 19). Once ingested, inhaled, or absorbed, phthalates are rapidly metabolized and excreted in urine and feces. Urinary concentrations of phthalate metabolites are commonly used as exposure

biomarkers (20). Biomonitoring studies suggest exposure to phthalates among reproductive-aged women is ubiquitous (17, 21, 22). There is also some evidence of disparate exposures; compared to White women, Black women have higher levels of certain phthalate metabolites, independent of socioeconomic status (23–25).

In vitro studies suggest that phthalates such as DEHP can influence biological processes in fibroid and myometrial cells, such as cellular proliferation and apoptosis, which are critical to fibroid pathogenesis (26). Epidemiologic studies of phthalates exposure and incidence or prevalence of fibroids have found mixed results (26–32). A recent meta-analysis of 5 case-control studies reported a statistically significant positive association between urinary concentrations of DEHP metabolites and risk of fibroids (33). Other epidemiologic studies have identified increased risk of fibroids associated with exposure to consumer products likely to contain phthalates, such as hair relaxers (34), plastic products, and cosmetics (35).

However, to our knowledge, no prior epidemiologic study has examined associations between phthalate exposures and clinical measures of fibroid burden. Accordingly, the objective of this study is to examine associations between urinary phthalate biomarkers and two measures of fibroid burden (uterine volume and fibroid size), among a racially diverse population of women seeking surgical care for their fibroids in an urban academic hospital.

## Materials and Methods

### Study Population.

In 2014–2017, we recruited and consented women into the Fibroids, Observational Research on Genes and the Environment (FORGE) study who were presenting to the Medical Faculty Affiliates gynecology clinic at The George Washington University for evaluation of symptomatic fibroid tumors and subsequently undergoing surgical management. The George Washington University Medical Center is a medium-sized, urban academic hospital that serves the Washington DC metropolitan area, which has a large Black/African American population and a broad socioeconomic base. Eligible women were non-pregnant, pre-menopausal, English-speaking, 18 years of age, and intending to have their surgery at the George Washington University Hospital. We oversampled women with small ( 3 cm in diameter) or large ( 6 cm in diameter) fibroids in order to capture variability in fibroid size. We initially limited recruitment to women who were non-Hispanic Black or non-Hispanic White, and then expanded recruitment to all racial/ethnic groups in 2017. Of the 68 women approached, 90% consented to participate (n=61). The sample for our current study is limited to the 57 women with urinary phthalate metabolite data. One participant did not undergo surgery during the study period but their data were retained in the current analysis. The study was approved by the Institutional Review Board at The George Washington University. The involvement of the Centers for Disease Control and Prevention (CDC) laboratory did not constitute engagement in human subjects research.

### Outcome Assessment:

Data from radiographic studies, electronic medical records, and pathology reports were used to confirm fibroid diagnosis and to obtain information on fibroid characteristics including

number, location, and size. Fibroid size (cm) was reported in up to 3 dimensions, and the largest recorded dimension was used. The default data source was MRI imaging, as this modality is considered the gold standard for fibroid detection and measurement (36). MRI data were available for 69% of patients who underwent myomectomy and 46% of patients who underwent hysterectomy. If MRI imaging was unavailable within 12 months prior to surgery, the next preferred source for fibroid size was an ultrasound (n=19), followed by the operative report (n=3) or surgical pathology report (n=1) based on availability. Fibroid size was highly correlated in a subset of participants who had both ultrasound and MRI imaging taken within a 6-month period (n = 14, Spearman $r_s$ = 0.82).

The default data source for uterine size was MRI imaging within 12 months of surgery (n=35), followed by ultrasound (n=20). In one case where no imaging data were available, uterine size was abstracted from the surgical pathology report. Uterine size was missing for one participant. Uterine size was reported in up to 3 dimensions. Uterine volume (cm$^3$) was calculated using the formula for a prolate ellipsoid, $\pi$ * (diameter 1 * diameter 2 * diameter 3) / 6 (36). Uterine volume was highly correlated in participants who had both an ultrasound and MRI taken within a 6-month period (n = 12, Spearman $r_s$ = 0.85).

### Exposure Assessment.

We collected spot urine samples from participants in sterile polypropylene cups. For 91% of participants, urine was collected during a clinical visit prior to surgery. For 5 participants (9%), urine was collected up to 2 months after surgery. Urine was not collected on the day of surgery since we wanted to capture typical phthalate exposures and patients may change their dietary patterns or personal care product use in preparation for surgery. Also, phthalate exposures may occur from the use of medical devices while at the hospital. Each urine sample was analyzed for specific gravity (SG) using a handheld refractometer (Atago Company, Inc.), divided into aliquots in polypropylene cryovials and stored at −80°C. One aliquot was shipped on dry ice overnight to the CDC (Atlanta, GA, USA) for the quantification of 14 phthalate metabolites by online-solid phase extraction-high performance liquid chromatography-isotope dilution tandem mass spectrometry (37). The names of the phthalate biomarkers, their parent compounds, and limits of detection (LODs) are presented in Table 1. Biomarker concentrations were adjusted for urine dilution using the following formula: (phthalate biomarker concentration) * [(1.017 – 1) / (SG - 1)], where 1.017 is the median specific gravity in this study sample and SG is the specific gravity of the individual's urine sample (38). Biomarker concentrations below the LOD were replaced with the LOD divided by the square root of 2 prior to SG adjustment or calculation of phthalate biomarker summary measures (39).

We calculated the molar sum of DEHP metabolites (ΣDEHP) by dividing each of the following four metabolites by their molecular weight and then summing the molar concentrations: mono(2-ethylhexyl) phthalate (MEHP), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), and mono(2-ethyl-5-carboxypentyl) phthalate (MECPP). We multiplied the molar sum by the average molecular weight (293.34) of the DEHP metabolites to convert ΣDEHP to ng/mL (17).

To further examine the association between fibroid characteristics and the subset of phthalates with anti-androgenic properties, we calculated a potency-weighted sum of anti-androgenic metabolites, using an approach modified from Varshavsky et al. (25). The summary biomarker (ΣAA Phthalates) was calculated by multiplying the SG-adjusted concentration of each of these 11 individual metabolites by the relative anti-androgenic potency of the parent compound and summing the weighted concentrations: ΣAAPhthalates = mono-n-butyl (MnBP) + mono-hydroxybutyl phthalate (MHBP) + (0.24 ∗ monoisobutyl phthalate (MiBP)) + (0.24 * mono-hydroyisobutyl phthalate (MHiBP)) + (0.26 ∗ monobenzyl phthalate (MBzP)) + (0.61 ∗ MEHP)+ (0.61 ∗ MEHHP) +(0.61 ∗ MEOHP) +(0.61 ∗ MECPP) + (0.26 * monocarboxyoctyl phthalate [MCOP]) + (0.024 * monoethyl phthalate (MEP)). Relative potencies for most metabolites were based on benchmark doses associated with a 5% reduction in rat fetal testis testosterone concentrations as described by the National Academy of Sciences (40) except for MCOP and MEP, which were estimated in (25).

### Covariate Assessment.

We abstracted data from patients' medical records on race/ethnicity, age, parity, body mass index (BMI), last menstrual period, insurance type, use of oral contraceptives or Lupron, and medical history. One participant was prescribed Lupron, a GnRH agonist that can reduce the size of fibroids, but it was administered after fibroid characteristics were assessed so their data was retained in the current analysis. We collected information on smoking behavior and educational attainment through interviewer-administered surveys. Time since diagnosis was obtained from the medical record and cross-referenced with information collected via interview.

### Statistical Analysis.

We calculated descriptive statistics for demographic, clinical, and environmental variables. Median and interquartile ranges (IQRs) were calculated for fibroid characteristics. Phthalate metabolites that were detected in at least 50% of participants were included in the analysis. SG-adjusted phthalate biomarkers were natural log-transformed prior to statistical analysis. Comparisons of phthalate biomarkers by race/ethnicity were performed using t-tests. Correlations between phthalate metabolites were assessed with Spearman correlations.

We evaluated associations between phthalate biomarker concentrations and fibroid characteristics with multivariable linear regression models in which we modeled both the outcomes and exposures as log-transformed continuous variables. From these models, percent difference in fibroid size and uterine volume for a doubling of phthalate biomarker concentrations was calculated as $(\exp(\ln 2 \times \beta) - 1) \times 100\%$, with the 95% confidence intervals (CIs) estimated as $(\exp[\ln 2 \times (\beta \pm 1.96 \times SE)] - 1) \times 100\%$ (41). We then fit multivariable logistic regression models to evaluate the associations between phthalate biomarker concentrations (modeled continuously) and fibroid size and uterine volume (< median vs.    median). From these models, we estimated odds ratios (ORs) and 95% CIs. Confounding was assessed using prior knowledge on biological relevance and through the use of directed acyclic graphs. The variables considered as potential confounders included factors previously related to fibroid outcomes in this and other studies, and factors

associated with phthalate exposures in this study. The final models were adjusted for age (years, continuous), BMI ($kg/m^2$, continuous), and race/ethnicity (Black vs. White or Latina). We collapsed White and Latina women into one racial/ethnic category because there was only one Latina woman in our study sample.

We conducted two sensitivity analyses to assess the robustness of our main results from the multivariable linear regression models. We excluded 6 women who had previously undergone surgery for fibroids because surgical interventions may alter fibroid biology (42). We excluded 5 women who provided a urine sample after surgery to assess potential for exposure misclassification bias. All analyses were performed using Stata software version 13.1 (College Station, TX). An alpha level of 0.05 was used for statistical significance.

## Results

Most women were Black (63%), overweight or obese (75%), had private insurance (65%), and had completed college (70%) (Table 2). Myomectomies were more common than hysterectomies and 11% of participants had prior surgery for fibroids. The median number of fibroids per participant was 3, and approximately half of the participants had at least one submucosal fibroid. The median size of the largest fibroid was 7.5 cm (IQR 5.5, 11 cm), and the median uterine volume was 645 $cm^3$ (IQR 227, 1013 $cm^3$). Fibroid size and uterine volume were correlated (Spearman $r_s = 0.70$). Presence of submucosal fibroids was inversely associated with fibroid size, and BMI was positively associated with fibroid size. Age, BMI, parity, and hysterectomy were positively associated with uterine volume (data not shown).

Phthalate exposures were ubiquitous in the study population. Nine of the 14 urinary phthalate metabolites were detected in > 90% of participants (Table 1). Most phthalate biomarkers were modestly correlated except for metabolites from the same parent compound (e.g., MEHHP, MEOHP, MECPP), which were highly correlated (Supplemental Figure 1). Geometric means of three metabolites (MiBP, MBzP, and MEP) were > 30% higher in Black women compared to White or Latina women. Differences in MEP across race/ethnicity were most pronounced, geometric mean concentrations of MEP in Black versus White or Latina women were 183.5 ng/mL and 35.4 ng/mL, respectively (p < 0.0001) (Supplemental Figure 2).

In multivariable linear regression models, higher urinary concentrations of several phthalate biomarkers were significantly associated with greater uterine volume. A doubling in ∑DEHP was associated with 33.2% (95% CI 6.6, 66.4) increase in uterine volume. We observed similar trends among the individual DEHP metabolites. A doubling in MEHHP, MEOHP, and MECPP was associated with 26.2% (95% CI 3.1, 54.6), 27.1% (95% CI 4.7, 54.3), and 31.6% (95% CI 5.9, 63.5) increase in uterine volume, respectively. We also observed a significant association between uterine volume and ∑AA phthalates (Percent difference (95% CI): 26.8% (2.2, 57.4)). Associations between most phthalate biomarkers and fibroid size were positive, however, none were statistically significant (Table 3).

In multivariable models where fibroid outcomes were modeled dichotomously, MEHHP, MEOHP, MECPP, ∑DEHP, and ∑AA phthalates remained positively associated with uterine

volume. In addition, MHiBP, MCOP, MCNP, and MEHP were also significantly associated with odds of greater uterine volume. The association of highest magnitude was for DEHP; each log-unit increase in DEHP was associated with 6.6 (95% CI 1.9, 22.8) times increased odds of greater uterine volume. MCNP was the only phthalate biomarker associated with fibroid size (AOR= 1.9 (95% CI 1.0, 3.5), and this association was marginally significant (p=0.05).

There were no meaningful changes in associations between phthalate biomarkers and fibroid outcomes when we excluded women with prior fibroid surgery or women with urine samples collected after surgery. The associations in the sensitivity analyses were generally more imprecise than the main results, likely due to smaller sample sizes (Supplemental Table S1).

## Discussion

In this cross-sectional study of pre-menopausal women seeking surgical care for their fibroids, we found that concentrations of several phthalate biomarkers, including MEHHP, MEOHP, MECPP, DEHP metabolites, and AA Phthalates were positively associated with uterine volume. These associations were large in magnitude and were generally robust to sensitivity analyses. In contrast, there were no consistent associations between urinary phthalate biomarkers and size of the largest fibroid.

Similar to the U.S. general population, exposures to phthalates in this study population were widespread (17) as every participant had multiple phthalate metabolites detected in their urine. Geometric mean concentrations of phthalate metabolites in our study population were generally similar to those calculated for women aged 25–54 years old who participated in the National Health and Nutrition Examination Survey (NHANES) in 2013–2014 (data not shown). Consistent with other studies of pregnant or reproductive-aged women, we found significantly higher concentrations of MEP, whose parent compound DEP is commonly used in fragranced products, in Black women compared to White women (43–45). However, the DEHP metabolites, which were most consistently associated with uterine volume, did not vary by race/ethnicity (see Supplemental Figure 2). Diet, particularly consumption of packaged and processed foods, is considered one of the most important pathways of exposure for DEHP and other high-molecular weight phthalates (46, 47). Additional research will assist to further understand how racial/ethnic disparities in environmental chemical exposures may contribute to racial/ethnic disparities in fibroid prevalence and severity.

Our results are consistent with the growing body of literature suggesting that phthalates may be associated with adverse female reproductive outcomes (41–45). Accumulating experimental evidence suggests that phthalates and other EDCs can alter the developing ovary and female reproductive tract, inducing structural and functional changes that may manifest as reproductive disorders across the life course (48). Furthermore, urinary phthalate biomarkers are associated with decreased fecundity (49) and increased risk of implantation failure (50), pregnancy loss (51), and preterm birth (52) in prospective epidemiologic studies. Research on phthalates and fibroids is still evolving. Five prior human studies have reported higher urinary concentrations of DEHP metabolites in fibroid cases compared to

controls (26–30), while two other studies reported null (31) or protective associations (32). Results from the current study advance the existing literature since it is the first to identify an association between phthalates exposure and uterine volume, which may be considered a proxy for total fibroid burden as it integrates the number and size of fibroids, and increases in women with fast-growing fibroids (53).

While the specific mechanisms linking phthalates to fibroid pathogenesis are not fully delineated, our results are biologically plausible. A recent *in vitro* study of human leiomyoma cells demonstrated that DEHP can increase expression of type 1 collagen, a major component of extracellular matrix, which is the primary distinguishing feature between fibroids and their adjacent normal myometrial tissue (26). Thus DEHP could increase total fibroid burden and uterine volume by stimulating excessive production of extracellular matrix. Hormone regulation may also play a role since many phthalates are considered estrogenic and anti-androgenic (10,54). Specifically, the strong associations observed between the weighted sum of anti-androgenic phthalates and uterine volume support a potential role for pathways mediated via antagonism of the androgen receptor, which is expressed in fibroid tissue and may play a role in fibroid development and growth (42). Relatedly, early life exposure to a mixture of anti-androgenic phthalates was associated with uterine malformations in adult female rats, and inhibition of steroidogenesis was implicated as one mechanism of action (55). Future studies should consider additional approaches to analyze the effect of phthalate mixtures on fibroid outcomes.

To our knowledge, this is the first epidemiologic study to examine associations between urinary phthalate biomarkers and fibroid characteristics. Most prior epidemiologic studies of environmental chemicals and fibroids have been case-control studies assessing risk of fibroids (26–30). Another important strength of our study is that the study sample included variability in race/ethnicity, socioeconomic status, fibroid characteristics, and choice of surgical intervention, which may help capture the biologic heterogeneity of this complex disorder. Although African American women are disproportionately impacted by uterine fibroids, they have been underrepresented in previous studies of EDCs and fibroids (27–30, 35, 56). We used clinical measures of fibroid characteristics from medical records, rather than self-reported data (32). The CDC quantified the concentrations of phthalate metabolites in urine, enhancing the comparability with NHANES and other epidemiologic studies. We also examined a wide range of phthalate metabolites including a weighted sum of anti-androgenic phthalates.

As this is a preliminary study, there are some important limitations. Because all the women in our study were seeking surgical interventions for their fibroids, these results may not be generalizable in women with asymptomatic fibroids or those not seeking medical intervention. Our findings may be limited by residual confounding from hormonal contraception and/or treatment since we only accounted for use of oral contraceptives and GnRH agonists. There could also be confounding by other estrogen-dependent, gynecologic conditions, such as endometriosis and adenomyosis. We relied on a spot urine sample to estimate phthalate exposures, which may result in measurement error since phthalates have a short half-life in the body (57). Due to the cross-sectional study design, we cannot exclude the potential for reverse causality for some of our results because women who undergo more

medical treatment may have higher urinary concentrations of DEHP metabolites due to parenteral exposure from medical devices containing phthalates (e.g., blood storage bags, medical tubing) (58, 59). We attempted to evaluate this possibility by examining whether urinary concentration of ΣDEHP metabolites was associated with time since diagnosis, prior surgery for fibroids, or timing of urine collection (before or after surgery), and there were no associations (data not shown). Furthermore, the association between DEHP biomarkers and uterine volume persisted after restricting the study sample to women with a urine sample collected prior to surgery. Future studies should improve exposure assessment by collecting multiple urine samples for quantification of phthalate metabolites prior to outcome assessment.

There may also be measurement error in our outcome. Because of heterogeneity across participants' medical records, we used a variety of sources to characterize the dimensions of individual fibroids and the uterus. MRI is more accurate than ultrasound in measuring individual fibroids (36), although measurements of fibroid size and uterine volume were highly correlated in the subset of our participants with both measurements. In this study, MRI was more likely to be used among patients undergoing myomectomy. Thus, it is possible that fibroid size was measured less accurately in women undergoing hysterectomies, which may have obscured associations with fibroid size. As only one or two dimensions of fibroid size were available for many participants, we were unable to model fibroid volume. This may have further contributed to the disparate findings between fibroid size and uterine volume. Moreover, ultrasound and MRI readings were not all performed by the same technicians, increasing the potential for inter-operator variability. However, this likely results in non-differential misclassification and biases our results towards the null since prior work suggests that neither demographic nor clinical characteristics predict measurement error of individual fibroids using MRI or ultrasound (36). Despite the several limitations in outcome ascertainment, it is unlikely that the observed associations of urinary phthalate biomarkers with uterine volume are solely due to measurement error. Future studies should prospectively assess the contribution of environmental exposures to changes in fibroid and uterine size using standardized methods.

In conclusion, results from this preliminary study support the hypothesis that exposure to certain phthalates such as DEHP may contribute to increased fibroid burden. This study suggests evidence in need of further investigation on the impact of phthalates on fibroid pathogenesis. If these results are confirmed, prevention of environmental chemical exposures could be integrated into primary prevention strategies for those at risk of fibroids. It could also help inform secondary preventions for those recently diagnosed with fibroids since greater fibroid burden has been associated with more severe symptoms and more invasive surgical treatments. Transnational research that helps to increase the range of tools for medical management of fibroids could help to reduce the significant burden of this reproductive disorder on women's lives.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgements

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**Capsule:** Some phthalate biomarkers, including di(2-ethylhexyl) phthalate metabolites, are positively associated with uterine volume among women undergoing surgery for fibroids. Results support the hypothesis that phthalates exposures are associated with fibroid outcomes.

**Table 1.**

Descriptive Statistics of Phthalate Biomarker Concentrations in Urine (N = 57)

| Parent compound: *Phthalate biomarker* | LOD (ng/mL) | Percent detected | GM (GSD) (ng/mL) SG-unadjusted | GM (GSD) (ng/mL) SG-adjusted |
|---|---|---|---|---|
| **Diethyl phthalate (DEP)** | | | | |
| *Monoethyl phthalate (MEP)* | 1.2 | 100 | 84.88 (8.54) | 100.09 (6.57) |
| **Di-*n*-butyl phthalate (DnBP)** | | | | |
| *Mono-n-butyl phthalate (MnBP)* | 0.4 | 96 | 7.22 (3.54) | 8.52 (2.45) |
| *Mono-hydroxybutyl phthalate (MHBP)* | 0.4 | 75 | 0.86 (2.4) | 1.01 (1.9) |
| **Diisobutyl phthalate (DiBP)** | | | | |
| *Monoisobutyl phthalate (MiBP)* | 0.8 | 95 | 6.12 (3.27) | 7.22 (2.19) |
| *Mono-hydroxyisobutyl phthalate (MHiBP)* | 0.4 | 89 | 2.06 (2.96) | 2.43 (2.08) |
| **Butylbenzyl phthalate (BBzP)** | | | | |
| *Monobenzyl phthalate (MBzP)* | 0.3 | 93 | 2.33 (4.08) | 2.74 (2.91) |
| **Di-*n*-octyl phthalate (DnOP)** | | | | |
| *Mono(3-carboxypropyl) phthalate (MCPP)* | 0.4 | 79 | 1.39 (4.05) | 1.64 (3.52) |
| **Diisononyl phthalate (DiNP)** | | | | |
| *Monoisononyl phthalate (MiNP)* | 0.9 | 42 | -- | -- |
| *Monocarboxyoctyl phthalate (MCOP)* | 0.3 | 98 | 12.68 (5.45) | 14.95 (4.66) |
| **Diisodecyl phthalates (DiDP)** | | | | |
| *Monocarboxynonyl phthalate (MCNP)* | 0.2 | 100 | 1.75 (3.09) | 2.07 (2.78) |
| **Di(2-ethylhexyl) phthalate (DEHP)** | | | | |
| *Mono(2-ethylhexyl) phthalate (MEHP)* | 0.8 | 63 | 1.48 (2.62) | 1.74 (2.23) |
| *Mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP)* | 0.4 | 98 | 5.02 (3.14) | 5.91 (2.35) |
| *Mono(2-ethyl-5-oxohexyl) phthalate (MEOHP)* | 0.2 | 98 | 3.29 (3.36) | 3.88 (2.42) |
| *Mono(2-ethyl-5-carboxypentyl) phthalate (MECPP)* | 0.4 | 100 | 8.47 (2.91) | 9.99 (2.21) |
| *ΣDEHP* | -- | -- | 18.79 (2.88) | 22.15 (2.16) |
| **ΣAnti-androgenic (AA) phthalates** | -- | -- | -- | 44.47 (2.29) |

Abbreviations: LOD, limit of detection, GM, geometric mean, GSD, geometric standard deviation, SG, specific gravity.

**Table 2.**

Demographic and Clinical Characteristics of Women in the FORGE Study (N=57).

| Characteristic | Total (N=57) | Fibroid size < median (n=28) | Fibroid size median (n=29) |
|---|---|---|---|
| | N (column %) | | |
| **Age** | | | |
| 26 – 33 years | 15 (26) | 8 (29) | 7 (24) |
| 34 – 43 years | 27 (47) | 15 (54) | 12 (41) |
| 44 – 54 years | 15 (26) | 5 (18) | 10 (34) |
| **Race** | | | |
| Black | 36 (63) | 20 (71) | 16 (55) |
| White or Latina[a] | 21 (37) | 8 (29) | 13 (45) |
| **BMI (kg/m$^2$)** | | | |
| <25 | 14 (25) | 9 (32) | 5 (17) |
| 25–30 | 18 (32) | 9 (32) | 9 (31) |
| 30 | 25 (44) | 10 (36) | 15 (52) |
| **Educational attainment[a]** | | | |
| Did not complete college | 17 (30) | 9 (32) | 8 (29) |
| College graduate or more | 39 (70) | 19 (68) | 20 (71) |
| **Insurance** | | | |
| Private | 37 (65) | 16 (57) | 21 (72) |
| Other | 20 (35) | 12 (43) | 8 (28) |
| **Smoking status[b]** | | | |
| Never | 38 (68) | 19 (68) | 19 (68) |
| Ever | 18 (32) | 9 (32) | 9 (32) |
| **Parity 1** | 21 (37) | 10 (36) | 11 (38) |
| **Current oral contraceptive use** | 14 (25) | 6 (21) | 8 (28) |
| **Submucosal fibroids 1** | 28 (49) | 16 (57) | 12 (41) |
| **Prior surgery for fibroids** | 6 (11) | 2 (7) | 4 (14) |
| **Surgery type[c]** | | | |
| Myomectomy | 32 (57) | 16 (57) | 16 (57) |
| Hysterectomy | 24 (43) | 12 (43) | 12 (43) |
| **Time since diagnosis[d]** | | | |
| < 1 year | 14 (29) | 8 (33) | 6 (25) |
| 1 year | 34 (71) | 16 (67) | 18 (75) |
| | Median (IQR) | | |
| **Number of fibroids[b]** | 3 (2, 6) | 2 (1, 5) | 4 (2, 8) |
| **Size of largest fibroid (cm)** | 7.5 (5.5, 11) | 5.5 (3.4, 6.8) | 11 (8.5, 11.9) |

| Characteristic | Total (N=57) | Fibroid size < median (n=28) | Fibroid size median (n=29) |
|---|---|---|---|
| | N (column %) | | |
| Uterine volume[d] (cm³) | 645 (227, 1013) | 235 (127, 553) | 850 (662, 1272) |

Abbreviations: LMP, last menstrual period, BMI, body mass index, IQR, interquartile range.

[a]One participant self-identified as Latina

[b]N missing = 1.

[c]One participant did not undergo surgery.

[d]N missing = 9

**Table 3.**

Percent Difference in Fibroid Size and Uterine Volume Associated with Specific Gravity-Adjusted Phthalate Biomarker Concentrations.

| | Percent difference (95% CI)[a] | | | |
| --- | --- | --- | --- | --- |
| | Fibroid size (cm) | | Uterine volume (cm³) | |
| | Unadjusted | Adjusted[b] | Unadjusted | Adjusted[b] |
| | N = 57 | N = 57 | N = 56 | N = 56 |
| **Phthalate biomarkers (ng/mL)** | | | | |
| MEP | 3.5 (−2.1, 9.4) | 0.4 (−5.8, 7.0) | 8.0 (−2.0, 19.1) | 6.7 (−5.0, 19.7) |
| MnBP | −0.8 (−11.9, 11.7) | −2.6 (−13.2, 9.4) | 7.6 (−12.9, 32.8) | 10.4 (−10.3, 35.9) |
| MHBP | −3.7 (−18.4, 13.6) | 1.1 (−14.0, 18.9) | 7.7 (−19.7, 44.4) | 25.7 (−5.7, 67.5) |
| MiBP | 2.8 (−10.2, 17.7) | 2.7 (−10.7, 18.0) | 3.0 (−19.0, 30.9) | 8.3 (−15.7, 39.0) |
| MHiBP | 6.0 (−8.2, 22.5) | 9.5 (−5.2, 26.6) | 7.9 (−16.5, 39.4) | 22.7 (−5.2, 58.9) |
| MBzP | 1.1 (−8.5, 11.7) | 0.7 (−8.5, 10.9) | 10.4 (−7.4, 31.5) | 11.8 (−5.8, 32.7) |
| MCPP | 4.2 (−4.2, 13.4) | 3.5 (−4.5, 12.0) | 9.1 (−5.9, 26.5) | 9.8 (−4.8, 26.5) |
| MCOP | 4.3 (−2.6, 11.6) | 4.2 (−2.3, 11.1) | 6.3 (−5.8, 20.0) | 8.2 (−3.6, 21.6) |
| MCNP | 4.1 (−6.2, 15.5) | 4.3 (−5.4, 15.0) | 13.9 (−5.0, 36.5) | 15.5 (−2.8, 37.2) |
| MEHP | 3.4 (−9.5, 18.0) | 4.7 (−7.4, 18.5) | 14.9 (−9.3, 45.7) | 18.1 (−5.6, 47.7) |
| MEHHP | 6.5 (−5.9, 20.5) | 2.8 (−8.7, 15.6) | 31.5 (6.8, 61.9)[c] | 26.2 (3.1, 54.6)[c] |
| MEOHP | 5.0 (−6.9, 18.3) | 1.5 (−9.4, 13.7) | 31.8 (8.0, 60.9)[c] | 27.1 (4.7, 54.3)[c] |
| MECPP | 9.9 (−3.7, 25.4) | 6.3 (−6.3, 20.5) | 36.6 (9.1, 71.1)[c] | 31.6 (5.9, 63.5)[c] |
| ΣDEHP | 8.6 (−5.3, 24.6) | 4.8 (−8.0, 19.4) | 39.3 (10.7, 75.3)[c] | 33.2 (6.6, 66.4)[c] |
| ΣAA Phthalates | 10.0 (−3.0, 24.7) | 5.0 (−7.3, 18.9) | 30.3 (4.9, 61.9)[c] | 26.8 (2.2, 57.4)[c] |

Abbreviations: CI, confidence interval

[a] Percent difference is for a doubling of phthalate biomarker concentration (ng/mL).

[b] Adjusted for age (continuous), BMI (continuous), and race/ethnicity (Black vs. White or Latina).

[c] P < 0.05

**Table 4.**

Odds Ratio of Greater Fibroid Size and Uterine Volume Associated with Specific Gravity-Adjusted Phthalate Biomarker Concentrations.

| | Fibroid Size | Median | Uterine Volume | Median |
|---|---|---|---|---|
| | OR (95% CI) | AOR$^a$ (95% CI) | OR (95% CI) | AOR$^a$ (95% CI) |
| | N = 57 | N = 57 | N = 56 | N = 56 |
| **Phthalate biomarkers (ng/mL)** | | | | |
| MEP | 1.1 (0.8, 1.5) | 1.2 (0.8, 1.7) | 1.3 (1.0, 1.8) | 1.3 (0.9, 2.0) |
| MnBP | 0.9 (0.5, 1.7) | 0.9 (0.5, 1.7) | 1.5 (0.8, 2.7) | 1.7 (0.8, 3.6) |
| MHBP | 0.8 (0.4, 1.8) | 0.9 (0.3, 2.2) | 1.3 (0.6, 2.9) | 2.4 (0.8, 7.1) |
| MiBP | 1.0 (0.5, 1.9) | 1.2 (0.5, 2.8) | 1.6 (0.8, 3.3) | 2.4 (1.0, 5.9) |
| MHiBP | 1.3 (0.6, 2.6) | 1.6 (0.7, 3.7) | 1.5 (0.7, 3.2) | 2.6 (1.0, 6.4)$^c$ |
| MBzP | 0.9 (0.6, 1.5) | 1.0 (0.5, 1.7) | 1.4 (0.8, 2.3) | 1.7 (0.9, 3.1) |
| MCPP | 1.4 (0.9, 2.3) | 1.3 (0.8, 2.2) | 1.6 (1.0, 2.6) | 1.7 (1.0, 2.9) |
| MCOP | 1.4 (1.0, 2.1) | 1.5 (1.0, 2.2) | 1.7 (1.1, 2.5)$^c$ | 2.1 (1.2, 3.5)$^c$ |
| MCNP | 1.6 (0.9, 2.8) | 1.9 (1.0, 3.5) | 2.1 (1.2, 3.9)$^c$ | 2.8 (1.3, 5.9)$^c$ |
| MEHP | 1.4 (0.7, 2.7) | 1.6 (0.7, 3.7) | 2.1 (1.0, 4.3) | 3.4 (1.2, 9.5)$^c$ |
| MEHHP | 1.4 (0.8, 2.7) | 1.3 (0.6, 2.7) | 4.2 (1.7, 10.7)$^c$ | 4.3 (1.5, 12.3)$^c$ |
| MEOHP | 1.4 (0.8, 2.6) | 1.3 (0.7, 2.7) | 4.1 (1.6, 10.9)$^c$ | 4.5 (1.5, 13.4)$^c$ |
| MECPP | 2.0 (1.0, 4.2) | 1.9 (0.8, 4.3) | 5.0 (1.8, 13.5)$^c$ | 5.3 (1.8, 15.9)$^c$ |
| DEHP | 1.8 (0.9, 3.8) | 1.7 (0.7, 4.0) | 6.1 (2.0, 18.5)$^c$ | 6.6 (1.9, 22.8)$^c$ |
| ΣAA Phthalates | 1.6 (0.8, 3.2) | 1.5 (0.7. 3.3) | 4.9 (1.9, 12.7)$^c$ | 4.9 (1.8, 13.6)$^c$ |

Abbreviations: OR, odds ratio, AOR, adjusted odds ratio, CI, confidence interval.

$^a$Adjusted for age (continuous), BMI (continuous), and race/ethnicity (Black vs. White or Latina).

$^b$Natural log-transformed.

$^c$P < 0.05