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

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Objectives: To examine the association between phthalate 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 premenopausal women undergoing either hysterectomy or myomectomy for fibroids.
Intervention(s): None.
Main Outcome Measure(s): The 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 antiandrogenic phthalate metabolites (∑AA Phthalates) using linear regression, adjusting for age, race/ethnicity, and body mass index. Fibroid outcomes were also examined dichotomously (divided at the median) using logistic regression.
Results: Most women were of black ethnicity, 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 33.2% (95% confidence interval 6.6–66.5) and 26.8% (95% confidence interval 2.2–57.4) 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 phthalate exposures may be associated with fibroid outcomes. Additional studies are needed to confirm these relationships. (Fertil Steril® 2019;111:112–21. ©2018 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: Consumer product chemicals, endocrine-disrupting chemicals, health disparities, uterine leiomyoma, women's health

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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 and a disproportionate impact on black women (1). Although the majority of reproductive-aged women will develop fibroids, only approximately 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, because 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 diisobutyl 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 can 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 that exposure to phthalates among reproductive-aged women is ubiquitous (17, 21, 22). There is also some evidence of disparate exposures; compared with 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 nonpregnant, premenopausal, English speaking, $\geq$18 years of age, and intending to have their surgery at The George Washington University Hospital. We oversampled women with small ($\leq$3 cm in diameter) or large ($\geq$6 cm in diameter) fibroids 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 her 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 (in centimeters [cm]) was reported in up to 3 dimensions, and the largest recorded dimension was used. The default data source was magnetic resonance imaging (MRI), 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 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 taken within a 6-month period (n = 14, Spearman's $r_s = 0.82$).

The default data source for uterine size was MRI within 12 months of surgery (n = 35), followed by ultrasound (n = 20). In one case in which no imaging data were available, uterine size was abstracted from the surgical pathology

report. Uterine size was missing for 1 participant. Uterine size was reported in up to 3 dimensions. Uterine volume (in cubic centimeters [cm^3]) was calculated using the formula for a prolate ellipsoid, $\Pi \times$ (diameter 1 $\times$ diameter 2 $\times$ diameter 3)/6 (36). Uterine volume was highly correlated in participants who had both an ultrasound and MRI performed within a 6-month period (n = 12, Spearman's $r_s = 0.85$).

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 because 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., Tokyo, Japan), divided into aliquots in polypropylene cryovials and stored at −80°C. One aliquot was shipped on dry ice overnight to the CDC (Atlanta, GA) 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 4 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 nanograms per milliliter (ng/mL) (17).

To further examine the association between fibroid characteristics and the subset of phthalates with antiandrogenic properties, we calculated a potency-weighted sum of antiandrogenic 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 antiandrogenic 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 × monohydroyisobutyl 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

TABLE 1

Descriptive statistics of phthalate biomarker concentrations in urine (N = 57).

Parent compound and phthalate biomarker	LOD (ng/mL)	% 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)

GM = geometric mean; GSD = geometric standard deviation; LOD = limit of detection; SG = specific gravity.

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[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 by Varshavsky et al. (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; however, it was administered after fibroid characteristics were assessed, so their data were 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 before 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 (below the median vs. at or above the median). From these models, we estimated odds ratios (ORs) and 95% confidence intervals (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 2 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 (StataCorp LLC, College Station, TX). An α 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 1 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 227–1,013 cm^3). Fibroid size and uterine volume were correlated (Spearman's $r_s = 0.70$). 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 Fig. 1). Geometric means of 3 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 vs. white or Latina women were 183.5 ng/mL and 35.4 ng/mL, respectively ($P<.0001$) (Supplemental Fig. 2).

In multivariable linear regression models, higher urinary concentrations of several phthalate biomarkers were significantly associated with greater uterine volume. A doubling in $\sum$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 $\sum$AA phthalates (percent difference: 26.8% [95 CI 2.2%–57.4%]). Associations between most phthalate biomarkers and fibroid size were positive; however, none were statistically significant (Table 3).

In multivariable models in which fibroid outcomes were modeled dichotomously, MEHHP, MEOHP, MECPP, $\sum$DEHP, and $\sum$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 $\sum$DEHP; each log-unit increase in $\sum$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 (adjusted odds ratio 1.9; 95% CI

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, y			
26–33	15 (26)	8 (29)	7 (24)
34–43	27 (47)	15 (54)	12 (41)
44–54	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[b]			
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 y	14 (29)	8 (33)	6 (25)
≥1 y	34 (71)	16 (67)	18 (75)
		Median (IQR)	
No. 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)
Uterine volume[b] (cm^3)	645 (227, 1013)	235 (127, 553)	850 (662, 1272)

BMI = body mass index; FORGE = Fibroids, Observational Research on Genes and the Environment; IQR = interquartile range.
[a] One participant self-identified as Latina.
[b] Number missing = 1.
[c] One participant did not undergo surgery.
[d] Number missing = 9.

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1.0–3.5), and this association was marginally significant (P=.05) (Table 4).

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 premenopausal women seeking surgical care for their fibroids, we found that concentrations of several phthalate biomarkers, including MEHHP, MEOHP, MECPP, ∑DEHP 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 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 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 Fig. 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 in further understanding 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), whereas 2 other studies reported null (31) or protective (32) associations. Results from the current study advance the existing literature because this is the first study 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).

Although 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

TABLE 3

Percent difference in fibroid size and uterine volume associated with specific gravity-adjusted phthalate biomarker concentrations.

	% Difference (95% CI)[a]			
	Fibroid size (cm)[b]		Uterine volume (cm^3)[b]	
	Unadjusted	Adjusted[c]	Unadjusted	Adjusted[c]
	N = 57	N = 57	N = 56	N = 56
Phthalate biomarkers (ng/mL)[b]				
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)[d]	26.2 (3.1, 54.6)[d]
MEOHP	5.0 (−6.9, 18.3)	1.5 (−9.4, 13.7)	31.8 (8.0, 60.9)[d]	27.1 (4.7, 54.3)[d]
MECPP	9.9 (−3.7, 25.4)	6.3 (−6.3, 20.5)	36.6 (9.1, 71.1)[d]	31.6 (5.9, 63.5)[d]
ΣDEHP	8.6 (−5.3, 24.6)	4.8 (−8.0, 19.4)	39.3 (10.7, 75.3)[d]	33.2 (6.6, 66.4)[d]
ΣAA Phthalates	10.0 (−3.0, 24.7)	5.0 (−7.3, 18.9)	30.3 (4.9, 61.9)[d]	26.8 (2.2, 57.4)[d]

CI = confidence interval.
[a] Percent difference is for a doubling of phthalate biomarker concentration (ng/mL).
[b] Natural-log transformed.
[c] Adjusted for age (continuous), body mass index (continuous), and race/ethnicity (black vs. white or Latina).
[d] $P < .05$.

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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, as many phthalates are considered estrogenic and antiandrogenic (10, 54). Specifically, the strong associations observed between the weighted sum of antiandrogenic 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

TABLE 4

Odds ratios 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)[b]				
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]

AOR = adjusted odds ratio; CI = confidence interval; OR = odds ratio.
[a] Adjusted for age (continuous), body mass index (continuous), and race/ethnicity (black vs. white or Latina).
[b] Natural log-transformed.
[c] $P < .05$.

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and growth (42). A related finding is that early-life exposure to a mixture of antiandrogenic 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 affected 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 antiandrogenic 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, as we accounted for use of only 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 because 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 before surgery. Future studies should improve exposure assessment by collecting multiple urine samples for quantification of phthalate metabolites before 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 1 or 2 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 interoperator variability. However, this likely results in nondifferential misclassification and biases our results toward the null, as 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 individuals at risk for fibroids. Identification of environmental risk factors could also help inform secondary preventions for those recently diagnosed with fibroids, as greater fibroid burden has been associated with more severe symptoms and more invasive surgical treatments. Translational 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.

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REFERENCES

1. Cardozo ER, Clark AD, Banks NK, Henne MB, Stegmann BJ, Segars JH. The estimated annual cost of uterine leiomyomata in the United States. Am J Obstet Gynecol 2012;206:211.
2. Baird DD, Dunson DB, Hill MC, Cousins D, Schectman JM. High cumulative incidence of uterine leiomyoma in black and white women: ultrasound evidence. Am J Obstet Gynecol 2003;188:100–7.
3. Drayer SM, Catherino WH. Prevalence, morbidity, and current medical management of uterine leiomyomas. Int J Gynecol Obstet 2015;131:117–22.
4. Wegienka G, Baird DD, Hertz-Picciotto I, Harlow SD, Steege JF, Hill MC, et al. Self-reported heavy bleeding associated with uterine leiomyomata. Obstet Gynecol 2003;101:431–7.
5. Stewart EA. Uterine fibroids. Lancet 2001;357:293–8.
6. Baird DD, Saldana TM, Shore DL, Hill MC, Schectman JM. A single baseline ultrasound assessment of fibroid presence and size is strongly predictive of future uterine procedure: 8-year follow-up of randomly sampled premenopausal women aged 35-49 years. Hum Reprod 2015;30:2936–44.
7. Bulun SE. Uterine fibroids. N Engl J Med 2013;369:1344–55.
8. Messerlian C, Souter I, Gaskins AJ, Williams PL, Ford JB, Chiu YH, et al. Urinary phthalate metabolites and ovarian reserve among women seeking infertility care. Hum Reprod 2016;31:75–83.
9. Lovekamp-Swan T, Davis BJ. Mechanisms of phthalate ester toxicity in the female reproductive system. Environ Health Perspect 2003;111:139–45.
10. Howdeshell KL, Rider CV, Wilson VS, Gray LE Jr. Mechanisms of action of phthalate esters, individually and in combination, to induce abnormal reproductive development in male laboratory rats. Environ Res 2008;108:168–76.
11. Craig ZR, Singh J, Gupta RK, Flaws JA. Co-treatment of mouse antral follicles with 17beta-estradiol interferes with mono-2-ethylhexyl phthalate (MEHP)-induced atresia and altered apoptosis gene expression. Reprod Toxicol 2014;45:45–51.
12. Bility MT, Thompson JT, McKee RH, David RM, Butala JH, Vanden Heuvel JP, et al. Activation of mouse and human peroxisome proliferator-activated receptors (PPARs) by phthalate monoesters. Toxicol Sci 2004;82:170–82.
13. Dodson RE, Nishioka M, Standley LJ, Perovich LJ, Brody JG, Rudel RA. Endocrine disruptors and asthma-associated chemicals in consumer products. Environ Health Perspect 2012;120:935–43.
14. Koniecki D, Wang R, Moody RP, Zhu J. Phthalates in cosmetic and personal care products: concentrations and possible dermal exposure. Environ Res 2011;111:329–36.
15. Kelley KE, Hernández-Díaz S, Chaplin EL, Hauser R, Mitchell AA. Identification of phthalates in medications and dietary supplement formulations in the United States and Canada. Environ Health Perspect 2012;120:379–84.
16. Hauser R, Calafat AM. Phthalates and human health. Occup Environ Med 2005;62:806–18.
17. Zota AR, Calafat AM, Woodruff TJ. Temporal trends in phthalate exposures: findings from the National Health and Nutrition Examination Survey, 2001-2010. Environ Health Perspect 2014;122:235–41.
18. Tickner JA, Schettler T, Guidotti T, McCally M, Rossi M. Health risks posed by use of Di-2-ethylhexyl phthalate (DEHP) in PVC medical devices: a critical review. Am J Indust Med 2001;39:100–11.
19. Weschler CJ, Bekö G, Koch HM, Salthammer T, Schripp T, Toftum J, et al. Transdermal uptake of diethyl phthalate and di (n-butyl) phthalate directly from air: experimental verification. Environ Health Perspect 2015;123:928–34.
20. Wittassek M, Angerer J. Phthalates: metabolism and exposure. Int J Androl 2008;31:131–8.
21. Centers for Disease Control and Prevention (CDC). Fourth National Report on Human Exposure to Environmental Chemicals: Updated Tables. Atlanta, GA: Centers for Disease Control and Prevention. US Department of Health and Human Services; 2018.
22. Woodruff TJ, Zota AR, Schwartz JM. Environmental chemicals in pregnant women in the United States: NHANES 2003-2004. Environ Health Perspect 2011;119:878–85.
23. Zota AR, Shamasunder B. The environmental injustice of beauty: framing chemical exposures from beauty products as a health disparities concern. Am J Obstet Gynecol 2017;217:418.e1–6.
24. James-Todd TM, Chiu YH, Zota AR. Racial/ethnic disparities in environmental endocrine disrupting chemicals and women's reproductive health outcomes: epidemiological examples across the life course. Curr Epidemiol Rep 2016;3:161–80.
25. Varshavsky JR, Zota AR, Woodruff TJ. A novel method for calculating potency-weighted cumulative phthalates exposure with implications for identifying racial/ethnic disparities among U.S. reproductive-aged women in NHANES 2001-2012. Environ Sci Technol 2016;50:10616–24.
26. Kim JH, Kim SH, Oh YS, Ihm HJ, Chae HD, Kim CH, et al. In vitro effects of phthalate esters in human myometrial and leiomyoma cells and increased urinary level of phthalate metabolite in women with uterine leiomyoma. Fertil Steril 2017;107:1061–9.
27. Sun J, Zhang MR, Zhang LQ, Zhao D, Li SG, Chen B. Phthalate monoesters in association with uterine leiomyomata in Shanghai. Int J Environ Health Res 2016;26:306–16.
28. Kim YA, Kho Y, Chun KC, Koh JW, Park JW, Bunderson-Schelvan M, et al. Increased urinary phthalate levels in women with uterine leiomyoma: a case-control study. Int J Environ Res Public Health 2016;13:1247.
29. Huang PC, Li WF, Liao PC, Sun CW, Tsai EM, Wang SL. Risk for estrogen-dependent diseases in relation to phthalate exposure and polymorphisms of CYP17A1 and estrogen receptor genes. Environ Sci Pollut Res Int 2014;21:13964–73.
30. Huang PC, Tsai EM, Li WF, Liao PC, Chung MC, Wang YH, et al. Association between phthalate exposure and glutathione S-transferase M1 polymorphism in adenomyosis, leiomyoma and endometriosis. Hum Reprod 2010;25:986–94.
31. Pollack AZ, Buck Louis GM, Chen Z, Sun L, Trabert B, Guo Y, et al. Bisphenol A, benzophenone-type ultraviolet filters, and phthalates in relation to uterine leiomyoma. Environ Res 2015;137:101–7.
32. Weuve J, Hauser R, Calafat AM, Missmer SA, Wise LA. Association of exposure to phthalates with endometriosis and uterine leiomyomata: findings from NHANES, 1999-2004. Environ Health Perspect 2010;118:825–32.
33. Fu Z, Zhao F, Chen K, Xu J, Li P, Xia D, et al. Association between urinary phthalate metabolites and risk of breast cancer and uterine leiomyoma. Reprod Toxicol 2017;74:134–42.
34. Wise LA, Palmer JR, Reich D, Cozier YC, Rosenberg L. Hair relaxer use and risk of uterine leiomyomata in African-American women. Am J Epidemiol 2012;175:432–40.
35. Shen Y, Xu Q, Xu J, Ren ML, Cai YL. Environmental exposure and risk of uterine leiomyoma: an epidemiologic survey. Eur Rev Med Pharmacol Sci 2013;17:3249–56.
36. Levens ED, Wesley R, Premkumar A, Blocker W, Nieman LK. Magnetic resonance imaging and transvaginal ultrasound for determining fibroid burden: implications for research and clinical care. Am J Obstet Gynecol 2009;200:537.e1–7.
37. Silva MJ, Samandar E, Preau JL Jr, Reidy JA, Needham LL, Calafat AM. Quantification of 22 phthalate metabolites in human urine. J Chromatogr B Analyt Technol Biomed Life Sci 2007;860:106–12.
38. Boeniger MF, Lowry LK, Rosenberg J. Interpretation of urine results used to assess chemical exposure with emphasis on creatinine adjustments: a review. Am Ind Hyg Assoc J 1993;54:615–27.
39. Hornung RW, Reed LD. Estimation of average concentration in the presence of nondetectable values. Appl Occup Environ Hyg 1990;5:46–51.
40. National Research Council. Phthalates and cumulative risk assessment: the task ahead. Washington, DC: National Academies Press; 2008.
41. Zota AR, Needham BL, Blackburn EH, Lin J, Park SK, Rehkopf DH, et al. Associations of cadmium and lead exposure with leukocyte telomere length: findings from National Health and Nutrition Examination Survey, 1999-2002. Am J Epidemiol 2015;181:127–36.
42. Wong JYY, Gold EB, Johnson WO, Lee JS. Circulating sex hormones and risk of uterine fibroids: Study of Women's Health Across the Nation (SWAN). J Clin Endocrinol Metab 2016;101:123–30.
43. Branch F, Woodruff TJ, Mitro SD, Zota AR. Vaginal douching and racial/ethnic disparities in phthalates exposures among reproductive-aged women: National Health and Nutrition Examination Survey 2001-2004. Environ Health 2015;14:57.
44. Serrano SE, Karr CJ, Seixas NS, Nguyen RHN, Barrett ES, Janssen S, et al. Dietary phthalate exposure in pregnant women and the impact of consumer practices. Int J Environ Res Public Health 2014;11:6193–215.

45. James-Todd TM, Meeker JD, Huang T, Hauser R, Seely EW, Ferguson KK, et al. Racial and ethnic variations in phthalate metabolite concentration changes across full-term pregnancies. J Exp Sci Environ Epidemiol 2017; 27:160–6.
46. Zota AR, Phillips CA, Mitro SD. Recent fast food consumption and bisphenol a and phthalates exposures among the U.S. population in NHANES, 2003-2010. Environ Health Perspect 2016;124:1521–8.
47. Chronic Hazard Advisory Panel on Phthalates and Phthalate Alternatives (CHAP). Chronic Hazard Advisory Panel on Phthalates and Phthalate Alternatives Final Report. Bethesda, MD: U.S. Consumer Product Safety Commission, Directorate for Health Sciences; 2014.
48. Fowler PA, Bellingham M, Sinclair KD, Evans NP, Pocar P, Fischer B, et al. Impact of endocrine-disrupting compounds (EDCs) on female reproductive health. Mol Cell Endocrinol 2012;355:231–9.
49. Thomsen AM, Riis AH, Olsen J, Jonsson BA, Lindh CH, Hjollund NH, et al. Female exposure to phthalates and time to pregnancy: a first pregnancy planner study. Hum Reprod 2017;32:232–8.
50. Hauser R, Gaskins AJ, Souter I, Smith KW, Dodge LE, Ehrlich S, et al. Urinary phthalate metabolite concentrations and reproductive outcomes among women undergoing in vitro fertilization: results from the EARTH Study. Environ Health Perspect 2016;124:831–9.
51. Toft G, Jonsson BA, Lindh CH, Jensen TK, Hjollund NH, Vested A, et al. Association between pregnancy loss and urinary phthalate levels around the time of conception. Environ Health Perspect 2012;120: 458–63.
52. Ferguson KK, McElrath TF, Meeker JD. Environmental phthalate exposure and preterm birth. JAMA Pediatr 2014;168:61–7.
53. Peddada SD, Laughlin SK, Miner K, Guyon JP, Haneke K, Vahdat HL, et al. Growth of uterine leiomyomata among premenopausal black and white women. Proc Natl Acad Sci 2008;105:19887–92.
54. Harris CA, Henttu P, Parker MG, Sumpter JP. The estrogenic activity of phthalate esters in vitro. Environ Health Perspect 1997;105:802–11.
55. Hannas BR, Howdeshell KL, Furr J, Gray LE Jr. In utero phthalate effects in the female rat: a model for MRKH syndrome. Toxicol Lett 2013;223: 315–21.
56. Shen Y, Xu Q, Ren M, Feng X, Cai Y, Gao Y. Measurement of phenolic environmental estrogens in women with uterine leiomyoma. PLoS One 2013;8: e79838.
57. Perrier F, Giorgis-Allemand L, Slama R, Philippat C. Within-subject pooling of biological samples to reduce exposure misclassification in biomarker-based studies. Epidemiology 2016;27:378–88.
58. Schettler T. Human exposure to phthalates via consumer products. Int J Androl 2006;29:134–9, discussion 81–5.
59. Marie C, Hamlaoui S, Bernard L, Bourdeaux D, Sautou V, Lemery D, et al. Exposure of hospitalised pregnant women to plasticizers contained in medical devices. BMC Womens Health 2017;17:45.

La exposición a ftalatos y los miomas uterinos en las mujeres sometidas a tratamiento quirúrgico por fibromas: un estudio preliminar

Objetivos: Examinar la asociación entre la exposición al ftalato y dos medidas de los fibromas uterinos: diámetro del mayor fibroma y el volumen uterino.

Diseño: Estudio piloto transversal.

Ajuste: Centro médico académico

Pacientes: 57 mujeres premenopáusicas sometidas a histerectomía o a miomectomía por fibromas.

Intervenciones: Ninguna.

Variable principal: El diámetro del mayor fibroma y las dimensiones uterinas fueron recogidas de los expedientes médicos. Se analizaron muestras de orina para 14 biomarcadores del ftalato utilizando la espectrometría de masas. Se estimaron asociaciones entre los resultados del fibroma y los metabolitos individuales de ftalato, suma de metabolitos de ftalato de di (2-etilhexilo) (∑DEHP), y una suma ponderada de metabolitos del ftalato antiandrogénicos (ftalatos de ∑AA) usando la regresión linear, ajustando para la edad, la raza/etnia, y el índice de masa corporal. Los resultados de los fribromas también fueron examinados de manera dicotómica (divididos en la mediana) usando la regresión logística.

Result: ados: La mayoría de las mujeres eran de etnia negra, sobrepeso u obesidad, y educación universitaria. En los modelos multivariables, niveles más altos de mono-hidroxisobutil ftalato, monocarboxioctil ftalato, monocarboxinonil ftalato, mono (2-ethilexil) ftalato, mono (2-Etil-5-hidroxihexil ftalato) (MEHHP), mono (2-Etill-5-oxohexil) ftalato (MEOHP), y mono (2-Etil-5-carboxipentil) ftalato (MECPP), ∑DEHP, y ∑AA ftalatos fueron positivamente asociados al volumen uterino. Las asociaciones fueron más pronunciadas para los metabolitos individuales de DEHP (MEHHP, MEOHP, MECPP), ∑DEHP y ∑AA ftalatos. Por ejemplo, un valor doble de ∑DEHP y ∑AA ftalatos se asoció con un 33,2% (intervalo de confianza del 95%: 6,6 – 1690) y 26,8% (95% intervalo de confianza 2.2 – 1458) de aumento en el volumen uterino, respectivamente. Había pocas asociaciones entre los biomarcadores del ftalato y el tamaño del fibroma.

Conclusion: es: La exposición a algunos biomarcadores de ftalato se asoció positivamente con el volumen uterino, que apoya aún más la hipótesis que las exposiciones a ftalatos podrían estar asociadas con la aparición de fibromas. Se necesitan estudios adicionales para confirmar estas relaciones.