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Variability in Phthalate Measures and Gestational Cardiometabolic Disease in Atlanta African American Mothers

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Bachelor of Science
Georgia Gwinnett College
2017

Thesis Committee Chair: Dana Barr

An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
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Abstract

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By Theresa Williams

PURPOSE
Phthalates are a class of chemicals that are used as plasticizers, are ubiquitous in the environment, and are known to be endocrine disrupting chemicals. This poses a serious threat to pregnant mothers, especially those mothers that may have a higher rate of exposure to phthalates. This study aims to observe any relationship between phthalate exposure and cardiometabolic disease in pregnant mothers.

METHODS
400 Mother-child pairs were selected from the sample population based on the following criteria: African American, 8-14 weeks pregnant, planned to deliver at Grady or Emory Midtown, prenatal care at one of three clinics serving Emory or at Grady, and singleton pregnancy. Each mother gave three urine samples to be tested over the course of her pregnancy. Phthalate metabolite measurements were combined to form 3 summary variables indicative of: (1) DEP exposure (MEP measurement only); (2) BzBP, DnBP, and DiBP exposure (summed MBzP, MnBP and MiBP); and (3) DEHP exposure (summed MEHP, MEHHP, and MEOHP).

RESULTS
Gestational cardiometabolic disease was more prevalent in women delivering at Grady than at Emory (OR=3.26 (CI 1.55-6.87). MEP in our population was higher than both non-Blacks and Blacks in the general US population suggesting a larger or unique exposure in our population. We observed a statistically significant interaction between lnMEP and age (P=0.05). Similarly, we observed interactions, albeit with different variables, in the models for MBPs and MEHPs. Higher concentrations of MEP and MEHP tended to result in a lower prevalence of gestational cardiometabolic disease.

CONCLUSION
In conclusion, the data collected and analyzed here suggest a significant difference between the urinary concentrations of phthalates in Atlanta-area African American pregnant mothers delivering at Emory Midtown or Grady hospitals. We observed suggestive associations between gestational cardiometabolic disease and phthalate metabolites which warrant further study.

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I want to dedicate this thesis to my grandfather, George Williams, who was the Director of CDCs Division of Accounts and Specimen Handling (DASH), and who instilled in me a love of public health, and who never stopped encouraging me and supporting me through my Masters Program. Thank you, Grandpa! I love you more than words can describe!

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INTRODUCTION

Most of us are probably accustomed to using plastic in our everyday lives without any thought given to its impact on our long-term health. We have come to expect eating food packaged in plastics or metals and using single-use plastic plates and cutlery regularly. Most of us are familiar with shampoo, deodorant, lotion, and other personal care products that come in plastic packages among so many other flexible plastics that we use daily. We live in homes constructed using vinyl flooring and furniture upholstered with all kinds of plastic fibers. Many people don't know that when using these products, they are being exposed to a class of chemicals called phthalates. (Center for Disease Control and Prevention, n.d.)

Phthalates can be found in almost every kind of plastic or vinyl where they are added as plasticizers, meaning they make these materials more flexible, rubberlike and harder to break. They can also be found in personal care products as a preservative ingredient or a solvent that act to hold color, shine or fragrance. The phthalates in these products readily leach, migrate, and off-gas because they are not molecularly bound to the polymers, especially when exposed to high temperatures. (Center for Disease Control and Prevention, n.d.) Phthalates and phthalate metabolites have also been found to be endocrine disrupting chemicals contributing to birth defects and metabolic disorders in animal studies. However, data on human phthalate exposure is limited. (Diamanti-Kandarakis, 2009)

According to the US Food and Drug Administration (FDA) most phthalates are not used in personal care products anymore. Right now, the only one left in circulation is diethyl phthalate (DEP), used as a solvent and fixative agent in fragrances (FDA, 2013). DEP is a clear, colorless liquid without significant odor. Its chemical properties include that it is insoluble in water as well as denser than water, hence it will sink. It has no difficulty penetrating soil and leaching into

ground water and contaminating waterways. It will severely irritate the eyes and skin (Agency for Toxic Substances and Disease Registry , 2015). DEP is not persistent in the environment but is known to bioaccumulate in fish living in contaminated water (CAMEO Chemicals , 2010). It is common to use monoethyl phthalate (MEP), a monoester resulting from the condensation of the carboxy groups of DEP with an ethanol and a hydrolytic metabolite of MEP, as a biomarker of DEP in the human body (HMDB, n.d.). If MEP is present in the urine it is likely that the phthalates were metabolized within the body which could result in some liver toxicity. There are little to no data for human health effects related to DEP exposure.

Apart from the phthalates that are present in personal care products, there are many others that may be more common and abundant in our environment. Di(2-ethylhexyl) phthalate (DEHP) is the most common member of the phthalates class and is mostly used in the production of polyvinylchloride (PVC) and softer plastics like a garden hose or pool liner, or even some food packaging. It is a colorless, odorless liquid that does not dissolve in water, but readily dissolves in oil. It also does not evaporate easily, making it more persistent in sediment and soil. DEHP is not harmful at the levels typically present in the general environment, but studies have shown that higher doses of exposure can lead to liver and kidney damage as well as reproductive harm in mice. It is common to look for metabolites of DEHP, including mono(2-ethylhexyl) phthalate (MEHP) and other oxidative metabolites, as biomarkers for humans (ATSDR, 2011).

Another type of phthalate we wish to focus on is dibutyl phthalate (DBP). DBP, like the other phthalates covered so far, is used as a plasticizer and can be found in many plastic products with a range of industries and functions. DBP is ubiquitous in the environment and poses a threat to humans. In animal studies involving acute exposure to DBP results have shown moderate

toxicity form inhalation exposure and low toxicity form oral exposure (U.S. Environmental Protection Agency , 2012).

Some phthalates are suspected to be endocrine disrupting chemicals, meaning they can block and deregulate different pathways in the endocrine system. The human body's normal endocrine function involves miniscule changes to the body's hormone levels, which can regulate entire bodily systems, such as pancreas function or reproductive organs (Diamanti-Kandarakis, 2009). This is done by the hormone molecules binding to a protein on the outside of a cell called a receptor, which once bound, will change shape and cause a chemical reaction that begins a cell process that serves some function in the body. These tiny changes can cause significant developmental and biological changes. Endocrine disrupting chemicals (EDCs) throw off the delicate balance of the endocrine system by decreasing or increasing the body's normal hormone levels through competitive inhibition where the EDC mimics the hormone or by blocking cell receptors thus inhibiting normal cell function (Zlatnik, 2016).

People can be exposed to phthalates in a variety of ways, depending on the properties of the individual phthalate and on the environment a person lives. Normal exposure happens through ingestion of food or drink that has been in contact with containers or products containing phthalates (US National Library of Medicine, 2017). To a lesser extent exposure can occur from inhalation of air or dust particles that contain phthalate vapors or particles. Young children may have a higher risk of exposure to phthalates because of their hand-to-mouth behaviors (U.S. Environmental Protection Agency , 2012).

Once phthalates enter the body either through inhalation, ingestion, or dermal contact, they will go through normal metabolic processes. If ingested these chemicals will be metabolized first in the GI tract then in the liver and will be expelled in the urine. If phthalates are inhaled or

absorbed in the skin, they will likely also make it to the liver or kidneys where phase 1 and phase 2 condensation reactions take please. The metabolites will then be excreted in the urine and used as an indicator that metabolism has taken place (Sharpiro, 2015).

In a 2007 study different levels of specific phthalates and their metabolites, such as DEHP and MEHP, were observed being excreted in a mother's breast milk or urine. Phthalates being present in the breastmilk poses a concern for the child as this will increase exposure to phthalates. The study found that breastmilk contains relatively more of the lipophilic phthalates such as DEHP, and the urine contains more of the hydrophilic phthalate metabolites such as MEHP. This may contribute to endocrine disruption for the child during development and may cause problems later in life (Frederiksen, 2007).

Different phthalate metabolites seem to effect patients differently according to race. In a study looking at racial disparities in maternal phthalate exposure and birth outcomes, it was found that there is greater risk of pre-term birth in association with MBP (monobutyl phthalate, a metabolite of DBP) among African American mothers and MEHP among white mothers. But the study admits that these differences may be a result of unknown environmental influence or on biology or lifestyle factors (James-Todd, 2017).

Apart from race other factors that may influence phthalate exposure levels include income, marital status, education level, and age. These may influence a person's diet and personal care product use. If one's education level or income only allows for the purchase of cheaper, more processed foods or personal care products, it is likely that lower income also contributes to higher phthalate exposure. Education level can influence income and income level often determines the geographic region a person lives. Living near a manufacturing plant that

releases phthalates into the environment will surely cause an increase in exposure to phthalates (Li-Li Huang, 2018).

Since phthalates pose such a threat to human health through endocrine disruption, it is important to limit exposure to phthalates. A person concerned with the harms associated with phthalate exposure should avoid foods that have been packaged in plastics, they should read the labels on personal care products to avoid buying anything that contains phthalates. For pregnant mothers this is especially important, as phthalates can have serious effects on fetal development. If possible, it would be best to replace plastic containers in our homes with glass or metal. Awareness about where phthalates are present in the environment and presence in which products can be the best way to decrease exposure by simply avoiding situations that might pose a risk (US National Library of Medicine, 2017).

Since phthalates are endocrine disrupting chemicals, they may play a role in some pregnancy complications related to endocrine disruption and hormone imbalance, such as gestational diabetes, preeclampsia, or eclampsia. Gestational diabetes is type 2 diabetes that onsets during pregnancy and can cause some major complications for both mother and child (Fisher, 2018). Preeclampsia is characterized by high blood pressure and signs of other organ harm, most often in the liver and kidneys. If it effects the brain preeclampsia can develop into eclampsia which can cause seizures (Werner, 2015). All of these are gestational cardiometabolic diseases (gCMD) which can be fatal if left untreated. The causes for any of these deadly complications are yet unknown. It is possible that phthalates contribute to the risk of developing gestational diabetes, eclampsia, or preeclampsia (Zhang, 2018).

This study aims to evaluate the association between urinary phthalate metabolite levels and gCMD in mother child pairs enrolled in the Center for Children’s Health, the Environment,

the Microbiome, and Metabolomics (CCHEM^2) study. We hypothesize that levels of selected phthalate metabolites are higher in our population than in the general US population and are associated with prevalence of gCMD.

METHODS

Study Population

400 Mother-child pairs were selected from the sample population based on the following criteria: African American, 8-14 weeks pregnant, planned to deliver at Grady or Emory Midtown, prenatal care at one of three clinics serving Emory or at Grady, and singleton pregnancy. Each mother gave three urine samples to be tested over the course of her pregnancy. The first sample was obtained at 8-14 weeks during a regular OB/GYN visit using residual urine. The second collection was conducted at home at 20-24 weeks. With this visit an environmental questionnaire was also conducted in order to gain an idea of what the mothers might be exposed to, and thus what the unborn child is exposed to. The final urine collection was at 24-30 weeks at another regular OB/GYN appointment. Three samples were collected to establish some temporality to the data. It is not possible to take continuous urine samples due to patient burden and cost constrains, so three samples throughout pregnancy was a compromise to reduce patient burden but provide adequate information to assess exposure throughout pregnancy.

Phthalate Measurements

For the purposes of this study, the prenatal sample taken at enrollment was used for exposure assessment because we had the most complete data on these participants. Urine aliquots (0.5 mL) were spiked with stable isotopically labeled ^{13}C analogues of the target phthalate metabolites (Table 1) then mixed. 2000 units of β-glucuronidase in 1 mM ammonium acetate (pH 5) buffer were added and the samples were incubated at 37° C overnight to liberate glucuronide-bound phthalate metabolites. Following incubation, 0.15 M sodium phosphate buffer was added to terminate enzyme activity. The hydrolysates were loaded onto preconditioned ABS Elut-NEXUS mixed mode polymeric solid phase extraction (SPE) cartridges (Agilent, Santa Clara, CA) and the hydrolysates were pulled through to waste. The SPE cartridges were washed with 0.1 M formic acid followed by purified water then dried thoroughly with vacuum. The SPE cartridges were eluted with acetonitrile followed by ethyl acetate. The eluates were collected and combined, concentrated to dryness, re-suspended in 0.1% acetic acid then transferred to vials.

The extracts were separated using high performance liquid chromatography on a Betasil Phenyl (3µ 150 x 2.1 mm, Thermo Scientific, San Jose, CA) column and analyzed by tandem mass spectrometry on an Agilent 6460 triple quadrupole mass spectrometer (Agilent, Santa Clara, CA). The ions monitored and limits of quantification (LOQs) are listed in Table 2. Concentrations were derived from a linear regression analysis of the area of the analyte ion divided by the area of the internal standard ion and the calibrant concentrations.

Quality assurance and control parameters were incorporated into the analyses. In each analytic run of 23 unknown samples, two blank samples (1 urine blank, one reagent blank), 2 quality control materials and a full calibration set (0.1 ng/mL to 400 ng/mL) were analyzed. The quality control material concentrations had to fall within two standard deviations of the mean

expected concentration to be considered a valid run. Target analytes must possess the correct retention times, coelute with their labeled analogue, and possess both the quantification and confirmation ion transitions to be considered a valid measurement.

Statistical Analysis

Phthalate metabolites that were less than the LOQ were replaced with imputed values equal to the LOQ divided by the square root of 2. To reduce the number of comparisons, phthalate metabolite measurements were combined to form 3 summary variables indicative of: (1) DEP exposure (MEP measurement only); (2) BzBP, DnBP, and DiBP exposure (summed MBzP, MnBP and MiBP); and (3) DEHP exposure (summed MEHP, MEHHP, and MEOHP) referred to henceforth as MEP, MBPs and MEHPs, respectively. In the case of MBPs and MEHPs, each individual metabolite value was converted to its molar equivalent, summed, then expressed as MBP and MEHP equivalents in ng/mL units. All analyte data were log transformed prior to statistical analysis because the metabolite data were right skewed.

The outcome variable gCMD, was dichotomous and was derived from abstracted medical data on the participants. If a participant was diagnosed with gestational diabetes, pre-eclampsia, or eclampsia, they were coded as having a gCMD event during the current pregnancy. Covariates included age, gravidity, education, income, insurance status, number of people living in the household, relationship status and their interactive terms.

SAS statistical software was used in all analyses (SAS Corporation, Cary, NC). Univariate and multivariate statistics were calculated for all summary phthalate and outcome variables. Logistic regressions were performed with gCMD as the outcome variable and one of the three summary phthalate concentrations as the exposure variable. Covariates were evaluated

using a backward elimination until a final model could be obtained. Statistical significance was set at $p<0.05$.

RESULTS

In Table 3, we present baseline study population characteristics stratified by the hospital at which each mother chose for prenatal care and delivery. The mean age for all mothers was 25.6± 5.0, with the mean gestational age at enrollment being 11.2± 2.5 weeks; these did not differ by hospital of delivery. Approximately 42% of the mothers had at least some college education, and 71% were in a relationship and living with their partner. About 66% of the mothers had an income less than 100% of the poverty level, and 83% used Medicaid for health insurance. The mean number of people living in the mother's household was 3.4±1.5, with the mean number of pregnancies (gravidity) was 2.6±1.6. Women who delivered at Emory Midtown hospital were more educated, had higher incomes and education, tended to be in stable relationships and had a lower prevalence of gCMD than our Grady participants. In addition, the prevalence of Medicaid insurance (vs private insurance) was much lower at Emory (97% Grady vs. 58% Emory). 19% of our participants experienced gestational diabetes, preeclampsia or eclampsia collectively representing our outcome variable gCMD. gCMD was more prevalent in women delivering at Grady than at Emory (OR=3.26 (CI 1.55-6.87).

The distribution of phthalates in our population are shown in Table 4 and Figures 1-3 by hospital of delivery. The GMs for MEP ($p=0.04$) and MBPs ($p=0.0027$) were significantly higher in Grady participants than in Emory participants; MEHPs concentrations were similar in the two population subgroups ($p=0.171$). The overall distribution of metabolites levels for MEP and MBPs tended to be higher in Grady vs Emory participants. MEP in our population was

higher than both non-Blacks and Blacks in the general US population suggesting a larger or unique exposure in our population (Figure 1). MBPs and MEHPs tended to be similar to US population- based levels (Figures 2-3).

Table 5 shows the results of a logistic regression analysis with gCMD as the outcome variable and the natural log of the analyte concentrations as the exposure variable, adjusted for confounding variables. The final models obtained after backward elimination are shown in Equations 1-3. We observed a statistically significant interaction between lnMEP and age (P=0.05). Similarly, we observed interactions, albeit with different variables, in the models for MBPs and MEHPs. Higher concentrations of MEP and MEHP tended to result in a lower prevalence of gCMD.

EQUATIONS

Equation 1. Final model for gCMD vs lnMEP after backward elimination

$$gCMD=\beta_0 + \beta_1 \, lnMEP + \beta_2 \, lnMEP*age$$

Equation 2. Final model for gCMD vs lnMBPs after backward elimination

$$gCMD=\beta_0 + \beta_1 \, lnMBPs + \beta_2 \, \#household + \beta_3 \, gravidity + \beta_4 \, lnMBPs*\#household$$

Equation 3. Final model for gCMD vs lnMEHPs after backward elimination

$$gCMD=\beta_0 + \beta_1 \, lnMEHPs + \beta_2 \, \#household + \beta_3 \, lnMEHPs*age + \beta_4 \, lnMEHPs*gravidity + \beta_5 \, \#household*age$$

DISCUSSION

We found significant differences in urinary phthalate metabolite concentrations between mothers who went to Emory for prenatal care and delivery or mothers who went to Grady. Phthalate metabolite levels were higher in the mothers who chose Grady for prenatal care and delivery. Of the phthalate metabolites focused on in this study MEP had the highest GM in our population which is consistent with its use in personal care products. For MEP the concentrations found in our population were much higher than for African Americans (AA) or non-AA in the US population. In general, MEP has been shown to be higher in AA populations, however, the levels in our population were about 20% higher than that of AAs in the overall US population suggesting a unique or more concentrated exposure source. This may be reflected in specific hair products designed for African American hair types. Hair washing practices for African Americans, specifically frequency of hair washing, may explain the higher levels of exposure to certain phthalates in AA groups. However, this would not explain the higher levels of exposure in our populations as opposed to the overall US population. Our population is unique in that it is strictly located in a southern/southeastern region where specific products such as pesticides are used more. Some pesticides contain phthalates as inert ingredients which may explain the higher levels of exposure to phthalates in our population. Furthermore, foods consumed in the south may be unique to the rest of the country as well, highlighting that food wrapping, pagakegs, or containers may also contain phthalates.

Conversely, the concentrations of MEHP were on average lower than the concentrations in the general US population. MEHP is used primarily in plastics. Economic disadvantage or other use factors may be attributed to the lower levels observed in our population.

The increased phthalate metabolites may help to partially explain the presence of gCMD. In the literature there is evidence of a proportionate relationship between phthalate exposure and different metabolic effects such as diabetes, hypertension, preeclampsia and eclampsia. In a systematic review by Elizabeth Radke there is support for higher exposure to phthalates being related to increased likelihood of developing diabetes. In another study by Zhang et al. A positive association between phthalate exposure and high blood pressure or hypertension was observed. A positive association between preeclampsia or eclampsia with elevated phthalates exposure levels was found by Werner et al.

While our study has many solid advantages such as its prospective longitudinal collection of data allowing detailed phenotypic characterization, multiple biological samples for exposure assessment, and SES diversity, it still is not without limitations. First, we did not yet have complete exposure data on all participants resulting in a smaller sample size than intended which may have reduced our ability (i.e., power) to detect differences. Another limitation was that in order to increase the number of participants with the outcome of interest, we created a summary variable, gCMD, that included preeclampsia, eclampsia, and gestational diabetes for evaluation although the potential effects especially with diabetes and hypertension may differ in pathways and mechanistic etiologies. Further, this precluded our ability to evaluate each specific condition.

By summing metabolites and not evaluating them individually or applying a “mixtures analysis” approach like Weighted Quantile Sums or Bayesian Kernal Machine Regression, we were not able to evaluate individual effects or collective effects. Only looking at the three phthalate metabolite classes limited our ability to evaluate interactions including synergistic, additive or competitive interactions that may have obscured any true associate between

phthalates and gCMD. Despite these limitations, however, we were still able to glean some important findings.

CONCLUSIONS

In conclusion, the data collected and analyzed here suggest a significant difference between the urinary concentrations of phthalates in Atlanta-area African American pregnant mothers delivering at Emory Midtown or Grady hospitals. We observed suggestive associations between gCMD and phthalate metabolites which warrant further study.

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TABLES AND FIGURES

Table 1. Common environmental sources of target phthalates and their metabolites

Parent Phthalate [Abbreviation]	**Phthalate Metabolite(s) [Abbreviation]**	**Environmental Source**
Diethyl phthalate [DEP]	Monoethyl phthalate [MEP]	Personal care products, cosmetics, industrial solvent, medications
Di-*n*-butyl phthalate [DnBP]	Mono-*n*-butyl phthalate [MnBP]	Adhesives, caulk, industrial solvents, cosmetics, medications
Diisobutyl phthalate [DiBP]	Monoisobutyl phthalate [MiBP]	Adhesives, caulk, industrial solvents, cosmetics
Butyl benzyl phthalate [BBP]	Monobenzyl phthalate [MBzP]; Mono-*n*-butyl phthalate [MnBP]	Vinyl flooring, adhesives, sealants, industrial solvents
Di(2-ethylhexyl) phthalate [DEHP]	Mono(2-ethyl-5-oxohexyl) phthalate [MEOHP]; Mono(2-ethyl-5-hydroxyhexyl phthalate [MEHHP]; Mono(2-ethlyhexyl) phthalate [MEHP]	Toys, food containers and packaging, tubing

Table 2. Analyte MS/MS transitions and limits of quantification.

Analyte	**Quantification transition (*m/z*)**	**Labeled Standard Transition (*m/z*)**	**Limit of Quantification (ng/mL)**
MEP	193→77.1	197.2→79.1	0.2
MEHHP	293→121	297.3→124.0	0.2
MBP	221→77.1	225.2→79.1	0.2
MiBP	221→77.1	225.2→79.1	0.1
MEOHP	291→121	295.3→124.0	0.2
MBzP	255→183.1/77.1	259.0→77.1	0.1
MEHP	277→134	281.3→137.0	0.1

Table 3. Study Population Demographics

Variable		Emory Midtown	Grady	All
N		100	183	283
Age (years, mean±SD)		27.5±5.1	24.6±4.6	25.6±5.0
Gestational Age at Enrollment (weeks)		11.6±2.8	11.0±2.3	11.2±2.5
Education **	<High school	0 (0%)	1 (<1%)	1 (<1%)
	High school or graduate/equivalency	32 (32%)	132 (72%)	164 (58%)
	College or more	68 (68%)	50 (27%)	118 (42%)
Relationship **	Single	14 (14%)	55 (30%)	69 (24%)
	In a relationship	35 (35%)	49 (27%)	84 (30%)
	Married or cohabitating	51 (51%)	79 (43%)	130 (71%)
Income as a % poverty level **	<100%	28 (28%)	92 (50%)	120 (66%)
	100-149%	20 (20%)	49 (27%)	69 (38%)
	150-199%	15 (15%)	21 (11%)	36 (20%)
	≥300%	30 (30%)	4 (2%)	34 (19%)
	Missing	7 (7%)	17 (9%)	24 (8%)
Insurance **	Medicaid	58 (58%)	177 (97%)	235 (83%)
	Private	42 (42%)	6 (3%)	48 (16%)
# living in household		3.3±1.4	3.5±1.6	3.4±1.5
Gravidity		2.7±1.6	2.6±1.6	2.6±1.6
gCMD **	No	79 (79%)	109 (60%)	199 (70%)
	Yes	10 (10%)	45 (25%)	55 (19%)
	Missing	11 (11%)	29 (16%)	40 (14%)
GM MEP (ng/mL) **		83.9±3.6	113.6±3.1	102.1±3.2
GM MBPs (ng/mL) **		20.6±2.9	31.2±3.0	26.9±3.0
GM MEHPs (ng/mL)		9.2±2.9	11.0±2.8	10.4±2.8

gCMD=gestational cardiometabolic disease; SD=standard deviation; GM=geometric mean; MEP=monoethylphthalate; MBPs=monobutylphthalate equivalents; MEHP=monoethylphthalate equivalents; **=statistically significant difference between Grady and Emory hospitals at $p<0.05$.

Table 4. Phthalate percentile distributions in our study population (CCHEM2, 2016-present)

Metabolite Name	Hospital	N	Geometric mean (SD)	Minimum	5th	25th	Median	75th	95th	Maximum
MEP (ng/mL)	ALL	283	83.9±3.6	5.02	15.4	44.8	92.9	223.8	788.8	3231
	Emory	100	113.6±3.1	5.02	9.80	34.4	71.5	216.0	739.7	3231
	Grady	183	102.1±3.2	9.88	22.6	49.2	97.1	234.4	794.7	2157
MBPs (ng/mL)	ALL	283	20.6±2.9	0.40	4.37	14.0	27.9	58.7	135.4	301
	Emory	100	31.2±3.0	0.81	3.84	10.1	20.3	43.3	118.4	301
	Grady	183	26.9±3.0	0.40	5.12	17.0	31.3	68.8	168.1	292
MEHPs (ng/mL)	ALL	283	9.2±2.9	0.42	2.03	5.56	10.3	18.7	63.5	352
	Emory	100	11.0±2.8	0.42	2.03	4.25	8.93	16.75	70.78	116
	Grady	183	10.4±2.8	0.76	2.03	6.20	10.7	19.3	58.4	352

CCHEM2=Center for Children's Health, the Environment, Microbiome and Metabolomics; SD=standard deviation

Table 5. Table of effects for logistic regression of cardiometabolic disease final model

Variable	β	Standard Error	p-Value
MEP†* **	-1.2855	0.6473	0.0470
Age*	-0.2353	0.1201	0.0501
Lnmep*age**	0.0482	0.0241	0.0456
Intercept	5.0222	3.1861	0.1150
MEHPs†*	-1.1210	0.5890	0.0570
#household*	0.8418	0.4444	0.0582
lnmehp*age**	0.0512	0.0230	0.0258
lnmehp*gravidity**	-0.1114	0.0549	0.0423
#household*age**	-0.0358	0.0181	0.0481
Intercept*	-0.9071	0.5053	0.0726
MBPs†	0.6239	0.3822	0.1026
#household*	0.6755	0.3714	0.0689
Gravidity*	-0.2245	0.1280	0.0794
lnmbp*#household**	-0.2144	0.1072	0.0455
Intercept**	-2.6675	1.3415	0.0468

†exposure variables were ln transformed before analysis; ** statistically significant at p<0.05; *statistically significant at p<0.1

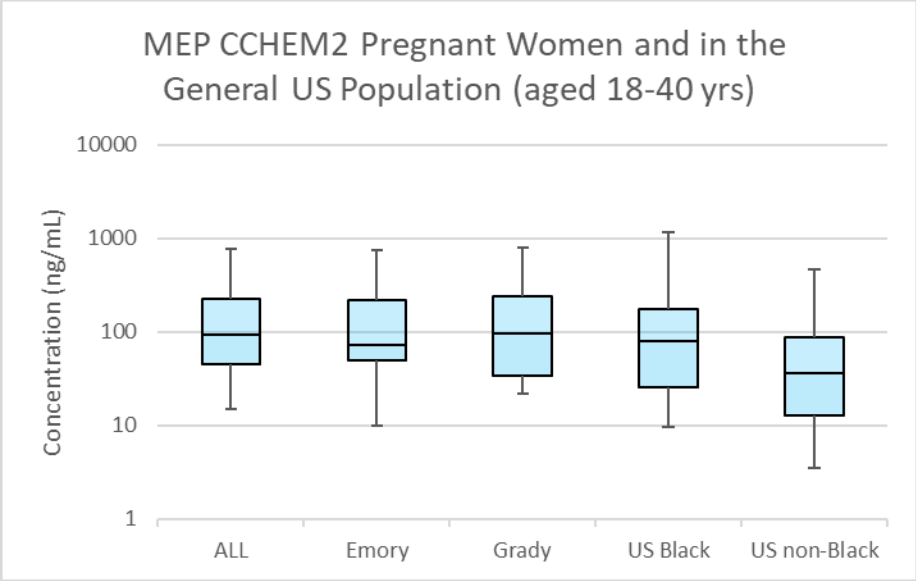

Figure 1. Concentrations of urinary MEP, the metabolite of Diethylphthalate, in our population and the general US population (NHANES 2015-2016, Females aged 8-40)

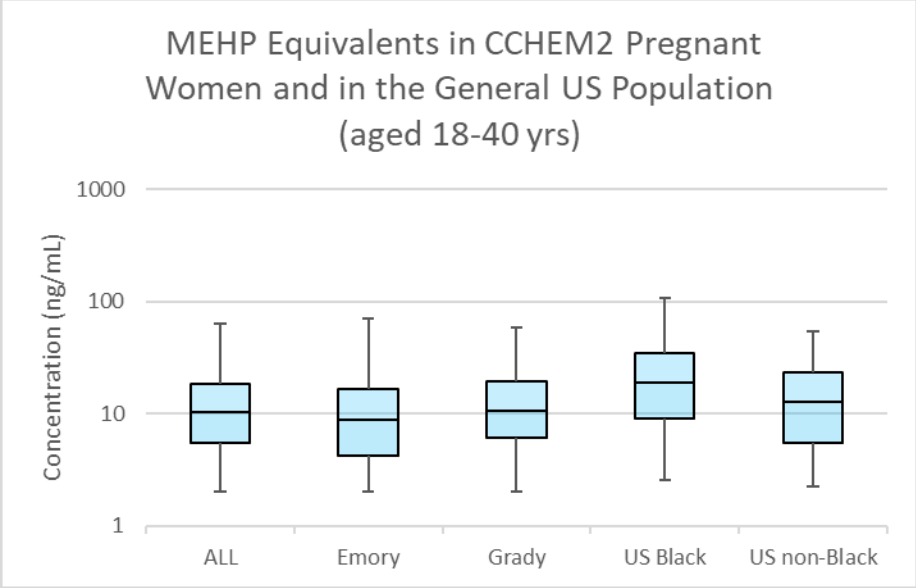

Figure 2. Concentrations of urinary MEHPs, the metabolites of Diethyhexyllphthalate, in our population and the general US population (NHANES 2015-2016, Females aged 8-40)

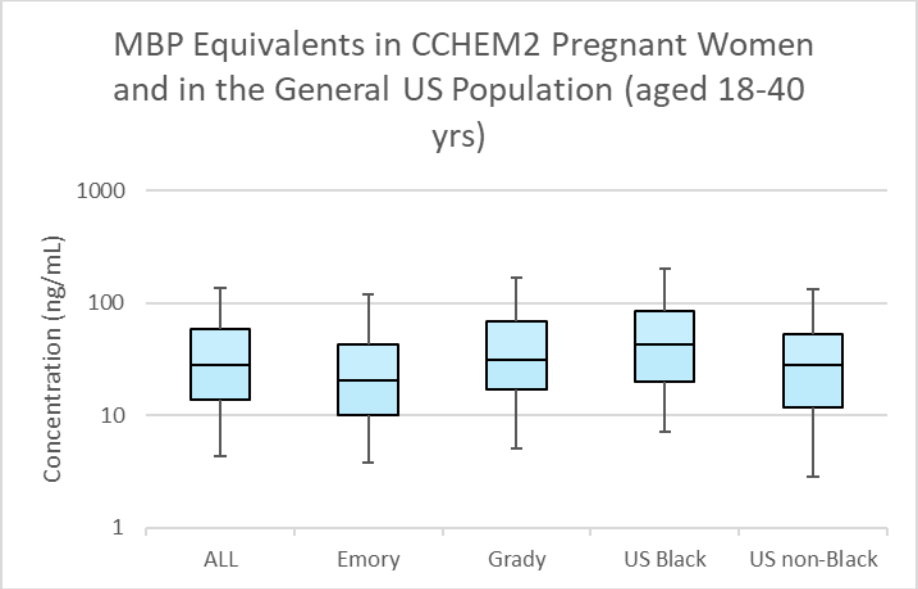

Figure 3. Concentrations of urinary MBPs, the metabolites of Dibuylphthalate and benzylbutylphthalate, in our population and the general US population (NHANES 2015-2016, Females aged 8-40)