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Associations of Urinary Phthalates with Body Mass Index, Waist Circumference, and Serum Lipids Among Females: National Health and Nutrition Examination Survey 1999–2004

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Abstract

Background/Objectives—Exposure to environmental chemicals could be one of the contributors to the increasing obesity epidemic. Very little is known about the association of phthalates, ubiquitous chemicals widely used in consumer products, with obesity and lipid metabolism. This study investigated the association of urinary phthalate metabolites and, for the first time, the ratios of the major metabolites of the most common phthalate, di-2-ethylhexyl phthalate (DEHP), with body mass index (BMI), waist circumference, and serum lipid levels in the U.S. female population.

Methods—This cross-sectional study used the data from the National Health and Nutrition Examination Survey, 1999–2004 and was restricted to women aged ≥18 years, who were not pregnant and had no history of diabetes. Using multivariate ordered logistic regression, we examined associations of seven urinary phthalate metabolites and their metabolic ratios with the BMI, waist circumferences, total cholesterol, triglycerides, and high-density and low-density lipoprotein cholesterol.

Results—BMI was positively associated with monobutyl phthalate (MBP) and mono-2-ethylhexyl phthalate (MEHP) (OR=1.13, 95% CI, 1.03-1.23 and OR=1.12, 95% CI, 1.03-1.23, respectively). Waist circumference was positively associated with MBP (OR=1.13, 95% CI, 1.03-1.24). A higher ratio of MEHP to mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP) was positively associated with both BMI (OR=1.21, 95% CI, 1.09-1.34) and waist circumference (OR=1.20, 95% CI, 1.10-1.31). There were no other significant associations.

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Conclusions—A higher metabolic ratio of MEHP to MEHHP, reflective of slower oxidative conversion of MEHP, is associated with greater BMI and waist circumference.

Introduction

Phthalates are ubiquitous chemicals that are widely used in numerous consumer products and detectable in wild life and humans (1). Secondary phthalate metabolites are detected in 100% of the samples from the general U.S. population (2–4). Recent research suggests that the exposure to environmental chemicals could be one of the relevant contributors to the recent dramatic rise in obesity in developed countries (5–7). Several endocrine disruptors were shown to interfere with the body's adipose tissue biology, endocrine hormone systems or central hypothalamic-pituitary-adrenal axis via different mechanisms important to weight control (8). Previous studies in animals suggested that phthalates can significantly alter normal metabolism in liver and several other tissues and affect blood lipid levels (9). It was suggested that the effect of phthalates on lipid metabolism could be mediated through the peroxisome proliferator activated receptors (PPARs) leading to either hypolipidemic and anti-adipogenic effects as the result of PPARα activation or pro-adipogenic effects due to the activation of PPARγ (10, 11). While PPARα-dependent stimulation of fatty acid oxidation requires continuous mode of exposure, PPARγ effects could occur even with a single or episotic exposure and lead to permanent changes in adipocyte differentiation and increased cell number (5).

The evidence on the association of phthalates with obesity and lipid metabolism is very limited and inconsistent (12). Furthermore, the majority of the previous studies focusing on females have been limited to pregnant women, mothers of children in birth cohorts, and women undergoing evaluations in fertility clinics. It has been previously shown that a higher ratio of mono-2-ethylhexyl phthalate to mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHP/MEHHP) or MEHP to mono-(2-ethyl-5-oxohexyl) phthalate (MEHP/MEOHP), major secondary metabolites of the most common phthalate, di-2-ethylhexyl phthalate (DEHP) (Figure 1) (13, 14), is associated with a greater physiologic effect and potentially greater endocrine disrupting capacity as compared to individual metabolites (15). We investigated the association of urinary phthalate metabolites and, for the first time, the ratios of the major DEHP metabolites with body mass index (BMI), waist circumference, and serum lipid levels in a representative sample of the U.S. female population, using the data from the National Health and Nutrition Examination Survey (NHANES), 1999–2004.

Methods

Study population

National Health and Nutrition Examination Survey (NHANES) is an ongoing survey conducted by the National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention (CDC) to assess health of the U.S. population. The survey utilizes a multistage, stratified, clustered design that selects a representative sample of the civilian, non-institutionalized U.S. population with oversampling of specific subgroups including adults older than 60, Mexican Americans, non-Hispanic blacks, and low-income persons (16). The survey data are collected through household interviews and standardized

examinations at mobile examination centers throughout the United States as described in detail previously (16). Blood, serum and urine samples were collected as part of the NHANES examination. Environmental chemicals were measured in randomly selected subsamples of participants within specific age groups. All NHANES protocols were approved by the National Center for Health Statistics'(NCHS) Research Ethics Review Board and all participants signed a consent form before their participation.

This analysis was restricted to women who were 18 and older at the time of the survey who were not pregnant and did not have a history of diabetes (72.3% of the NHANES 99-04 sample). Of 6,005 eligible women, 1,702 women had data on BMI, serum lipids, and phthalate measurements, and 1,690 women had data on waist circumference and phthalate levels (Figure 2).

Two of the phthalate metabolites, MEHHP and MEOHP, were measured only in 2001–2002 and 2003–2004, reducing sample size for the analyses with these metabolites and their ratios to 1,289 women for analyses of BMI and serum lipids and 1,281 women for analysis of waist circumference. Mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP) was measured only in 2003–2004, and, thus, the associations of MECPP and the corresponding metabolite ratios were investigated only in this subset of women (634 for analyses of BMI and serum lipids and 621 for analysis of waist circumference) (Figure 2).

Body mass index and waist circumference

Participant's height, weight, and waist circumference were measured as a part of the physical examination. BMI was calculated as weight in kilograms divided by height in meters squared and was categorized as <18.5 kg/m^2 (underweight), 18.5-<25 kg/m^2 (normal weight), 25-<30 kg/m^2 (overweight), and ≥30 kg/m^2 (obese or morbidly obese) (17). Waist circumference was measured in centimeters (cm). In the analysis, we defined waist circumference as quartiles based on the distribution in the study sample (<81.3, 81.3-<91.6, 91.6-<102.8, and ≥102.8 cm) rather than defined cutoffs as some previous studies suggest that these cutoffs as criteria of abdominal obesity might not apply to all populations and ethnic groups (18).

Serum lipids

Sample collection and processing has been described in details in the NHANES Laboratory/ Medical Technologists Procedures Manual. Briefly, fasting levels of total cholesterol and triglycerides were measured enzymatically. High-density lipoprotein (HDL) cholesterol was measured in adults using the heparin-manganese (Mn) method where apolipoprotein B containing lipoproteins were first removed by precipitation with heparin sulfate and $MnCl_2$. Low-density lipoptotein (LDL) cholesterol levels were calculated using the Friedewald formula (19). For each lipid, the quartiles were defined based on the distribution of corresponding lipid's levels in the study sample (total cholesterol: <172, 172-<197, 197-<226, ≥226 mg/dL; HDL: <45, 45-<55, 55-<65, ≥65 mg/dL; triglycerides: <76, 76-<108, 108-<157, ≥157 mg/dL; LDL: <94, 94-<114, 114-<139, ≥139 mg/dL).

Urinary phthalates

Urine samples were collected according to the standard protocol from participants at age 6 years and older at the time of the medical examination. Urine specimens were processed, stored at −20°C, and then shipped to the Division of Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention for analysis (20–22). Urinary phthalates were quantified with high performance liquid chromatography–tandem mass spectrometry as previously described (23–25). To standardize for the renal function and urine dilution, we adjusted absolute concentrations of phthalates by urinary creatinine. Creatinine-adjusted concentrations of phthalate metabolites (μg/g creatinine) were calculated by dividing the absolute phthalate concentration (ng/mL) by creatinine concentration (mg/dL) and multiplying it by 100 (26). In addition to creatinine-corrected phthalate concentrations, we examined the associations of obesity-related outcomes with ratios of different DEHP metabolites as follows: MEHP to MEHHP (MEHP:MEHHP), MEHHP to MECPP (MEHHP:MECPP), MEHHP to MEOHP (MEHHP:MEOHP), and MEOHP to MECPP (MEOHP:MECPP). Finally, we created a composite measure of DEHP metabolites defined as the sum of MEHP and two downstream metabolites, MEHHP and MEOHP.

Seven metabolites were measured between 1999 and 2004: monobutyl phthalate (MBP), mono-benzyl phthalate (MBzP), MEHP, mono-ethyl phthalate (MEP), MEHHP, MEOHP, and MECPP. Among these, MEHHP and MEOHP were measured as part of NHANES 2001–2004 only, and MECPP measurements were limited to NHANES 2003–2004. All phthalates with exception of MEHP were detectable in at least 99% of the samples; MEHP was detectable in 63% of the samples. The values below limit of detection (LOD) were substituted with LOD for the given analyte (specific to the NHANES cycle) divided by the square root of 2 (27).

Covariates

Information on the following variables was extracted from the NHANES questionnaires: age, race/ethnicity, poverty level, education, dietary fat and total calorie intake, menopausal status and postmenopausal hormone use, physical activity, alcohol consumption, and smoking.

Statistical Analysis

All analyses were performed using SAS version 9.3 (SAS Institute, Inc, Cary, NC, USA). We accounted for the complex survey structure (multistage probability sample design) throughout the analyses. After weighting, our analyses included 76,075,598 women for BMI and for serum lipids and 75,799,724 women for waist circumference.

We used χ^2 test to compare distributions of the following socio-demographic characteristics and other covariates across BMI categories (the primary outcome of interest): age (quintiles as 18-<25, 25-<38, 38-<50, 50-<66, and ≥66 years), race/ethnicity (Hispanic, African American, White, and other), poverty level (below, above poverty), education (≤high school, >high school), menopausal status and postmenopausal hormone use (premenopausal, postmenopausal with no history of hormone use, postmenopausal with past hormone use, postmenopausal with current hormone use, and postmenopausal with unknown hormone

use), current alcohol use (none, any), smoking status (never smoker, past smoker, current smoker), physical activity (inactive, moderately active, active), total calorie intake (quartiles as <1280, 1280-<1698, 1698-<2228, and ≥2228 Kcal), and total fat intake (quartiles as <42.16, 42.16-<62.57, 62.57-<86.89 and ≥86.89 g/day). Distribution of phthalate levels, their ratios and composite metabolite concentration measure in the study sample were presented as their medians and geometric means (standard error), adjusted for age and race. Tests for the difference in geometric means across BMI categories were performed (28).

We used ordered multivariate logistic regression to analyze the association of phthalate measures with BMI, waist circumference, and serum lipids. Each of the phthalate measures was modeled as quartiles based on its distribution in the study sample. The quartile cutoffs for individual metabolites are presented in supplemental material, table S1. The risk estimates were adjusted for age, race, education, poverty level, total calorie intake, total fat intake, physical activity, menopausal status/postmenopausal hormone use, alcohol consumption, and smoking. Additionally, the models for serum lipids were adjusted for BMI.

In a secondary analysis, we used polychotomous logistic regression to examine the associations of phthalate measures with obesity-related outcomes. In the analysis for BMI, underweight, overweight and obese women were compared to women with normal weight. In the analysis for waist circumference and serum lipids, women in the lowest quartile were used as the comparison group. However, the risk estimates were unstable in the polychotomous logistic regression analyses due to the small number of women in some of the strata, and we report the results of the ordered logistic regression analysis instead. Statistical significance was assessed at the level of 0.05 in all analyses.

Results

Characteristics of the study population (weighted N=76,075,598) stratified by BMI category are presented in Table 1. Women with BMI ≥25kg/m^2 were more likely to be older ($p=0.0005$), to be African American or Hispanic ($p<0.0001$), to be postmenopausal ($p<0.0001$), and to be non-drinkers ($p<0.0001$). Greater proportion of women with BMI≥25kg/m^2 had higher levels of total cholesterol, triglycerides, LDL, and lower levels of HDL, as compared to women with BMI<25. Distributions of other characteristics across BMI groups were similar. Age and race adjusted phthalate levels in the study sample by BMI category are presented in Table 2.

In multivariate logistic regression, BMI was positively associated with creatinine-adjusted concentrations of MBP (OR=1.13, 95% CI 1.03-1.23) and MEHP (OR=1.12; 95% CI 1.03-1.23) (Table 3). A positive association was also found for BMI and the ratio of MEHP to MEHHP (OR=1.21; 95% CI 1.09-1.34). Similarly, positive associations of MBP and MEHP to MEHHP ratio were found for waist circumference (OR=1.13, 95% CI 1.03-1.24 for MBP; OR=1.20, 95% CI 1.10-1.31 for MEHP:MEHHP). We did not find any significant associations of other metabolites or their ratios with either BMI or waist circumference. Serum total cholesterol, triglycerides, HDL and LDL were not associated with any of the metabolites or their ratios (Table 3).

Discussion

In this study of 76,075,598 women representative of the U.S. female population, we found significant association of BMI and waist circumference with MBP, MEHP, and the ratio of MEHP to MEHHP. None of the other phthalate measures were associated with BMI, waist circumference, or serum lipids.

This is the first study to examine the association of urinary phthalate metabolite ratios, rather than only individual metabolite concentrations, with BMI, waist circumference, and serum lipids. The differences in the ratios of phthalate metabolites are reflective of inter-individual differences in oxidative metabolism of DEHP, the most common phthalate (29). Previous studies suggest that a higher ratio of MEHP to MEHHP or MEHP to MEOHP is associated with a greater physiologic effect and potentially greater endocrine disrupting capacity as compared to individual metabolites (15, 30). Our findings show a positive association of BMI with the ratio of MEHP to MEHHP, suggesting that women with greater BMI may have slower rate of oxidative metabolism of MEHP. A similar association was observed for waist circumference, a measure of abdominal obesity that has shown stronger associations with several health outcomes as compared to BMI (31). MEHHP is formed as the result of MEHP oxidation by cytochrome P450 enzymes and differences in the ratio of MEHP to MEHHP could reflect underlying genetic variation in metabolizing capacity and, as the result, higher susceptibility to the endocrine disrupting effects of MEHP (32, 33). On the other hand, these differences in the phthalate metabolism rate might occur due to the overall slower metabolic rate in obese individuals (34, 35). Further, some previous reports suggest possible decrease in activity of selected P450 enzymes among obese, which might in turn affect metabolism of xenobiotics, including phthalates (36). However, due to the cross-sectional nature of the study, the temporal sequence of the exposure and outcome cannot be determined and prospective studies are needed to explore the association of the phthalate exposure to the subsequent risk of obesity and to provide an evidence of possible causal relationship.

Our findings on the association of MBP with obesity and waist circumference are consistent with some of the previous reports (37, 38). However, unlike previous studies, we found a positive rather than an inverse association of MEHP with BMI (39). Hatch et al. found an inverse association of both MBP and MEHP with BMI and waist circumference. Our analysis included a larger sample of women by combining NHANES 1999–2004, while Hatch et al. only included data from NHANES 1999–2002 (1,702 women at age 18 or older in our study versus 1,129 women at age 20 and older in Hatch et al.). In addition, the findings from the study by Hatch et al. were limited to the subset of women aged 60–80, while our results apply to women at age 18 and older. To compare our results with the findings in Hatch et al., we conducted an additional stratified analysis for the associations of MBP and MEHP with BMI and waist circumference in women at age 20–59 years and at age 60 years and older in our study sample. We found that the associations of MBP and MEHP were similar in these two age subgroups. Further, the statistical analyses in Hatch et al. differed from those in our study. Specifically, Hatch et al. used multiple linear regression, while our study utilized ordered logistic regression because distributions of BMI and waist circumference were not normal. Finally, the risk estimates for phthalates in Hatch et al. were

adjusted for age, race/ethnicity, creatinine, height, social economic status, dietary factors, hours of sedentary behavior, mets/month, smoking, and reproductive factors, while the risk estimates for creatinine-corrected phthalates in our study were adjusted for age, race, education, poverty level, total calorie intake, total fat intake, physical activity, menopausal status/postmenopausal hormone use, alcohol consumption, and smoking.

This analysis used the data from a large representative sample of the U.S. population. Nonetheless, our study has a few limitations. As mentioned previously, the cross-sectional nature of the data does not allow us to determine if phthalate exposure predicts the outcomes of interest. In addition, phthalates were measured in a single urine sample. Even though phthalates are rapidly metabolized within hours (half-life 6–12 hours) (1, 40), previous studies suggest that a single urine sample can accurately classify phthalate exposure over the previous 3 months (41, 42).

Findings of our analysis suggest an association of the metabolic conversion rate of MEHP to MEHHP with BMI and waist circumference. Nonetheless, it remains unclear whether this slower rate of MEHP metabolism could cause increase in BMI and abdominal obesity or whether it is merely a reflection of the overall slower metabolic rate in obese individuals or perhaps the influence of BMI on the activity of selected P450 enzymes responsible for oxidation of phthalates (43). Future prospective studies are needed to examine temporal relationship between phthalate exposure and obesity-related outcomes and to elucidate the causal links, if any, between phthalates and obesity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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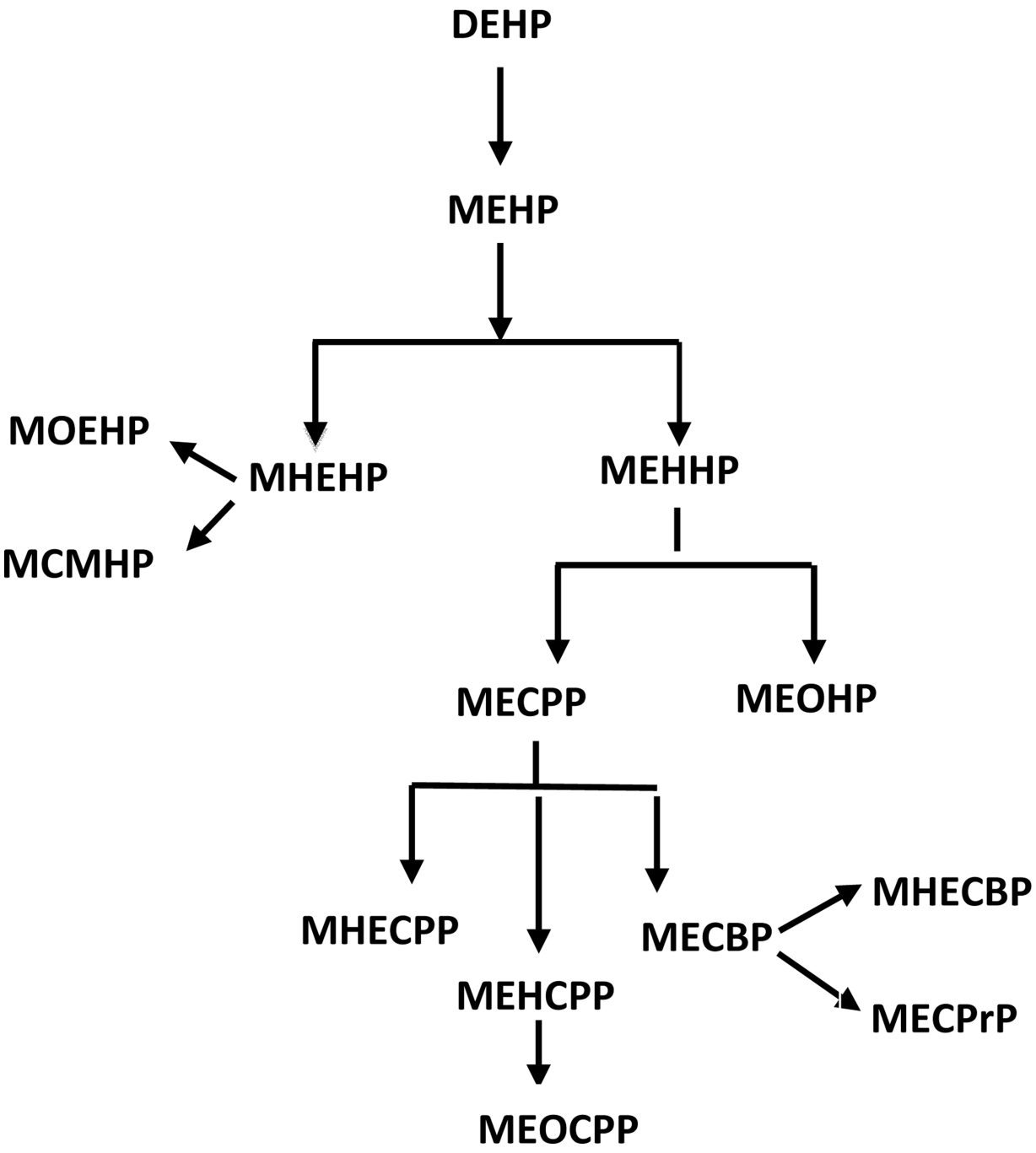

Figure 1. Di-2-ethylhexyl phthalate (DEHP) metabolism

Abbreviations: MBP - monobutyl phthalate; MBzP - Mono-benzyl phthalate; MEHP - Mono-2-ethylhexyl phthalate; MEP - Mono-ethyl phthalate; MEHHP - Mono-(2-ethyl-5-hydroxyhexyl) phthalate; MEOHP - Mono-(2-ethyl-5-oxohexyl) phthalate; MECPP - Mono-(2-ethyl-5-carboxypentyl) phthalate; MOEHP - Mono-2-(1-oxoethyl)hexyl-d4 phthalate; MCMHP - mono(2-carboxymethylhexyl) phthalate; MHEHP - mono-2-(hydrohyethyl)hexyl phthalate, MHECPP - mono-e-(1-hydroxyethyl)-5-carboxypentyl phthalate, MEHCPP - mono-(2-ethyl-4-hydroxy-5-carboxypentyl) phthalate, MEOCPP - mono-(2-ethyl-4-oxo-5-

carboxypentyl) phthalate; MECBP - mono-(2-ehtyl-4-carboxybutyl) phthalate, MHECBP - mono-2-(1-hydroxyethyl)-4-carboxybutyl phthalate, MECPrP - Mono(2-ethyl-3-carboxypropyl) phthalate

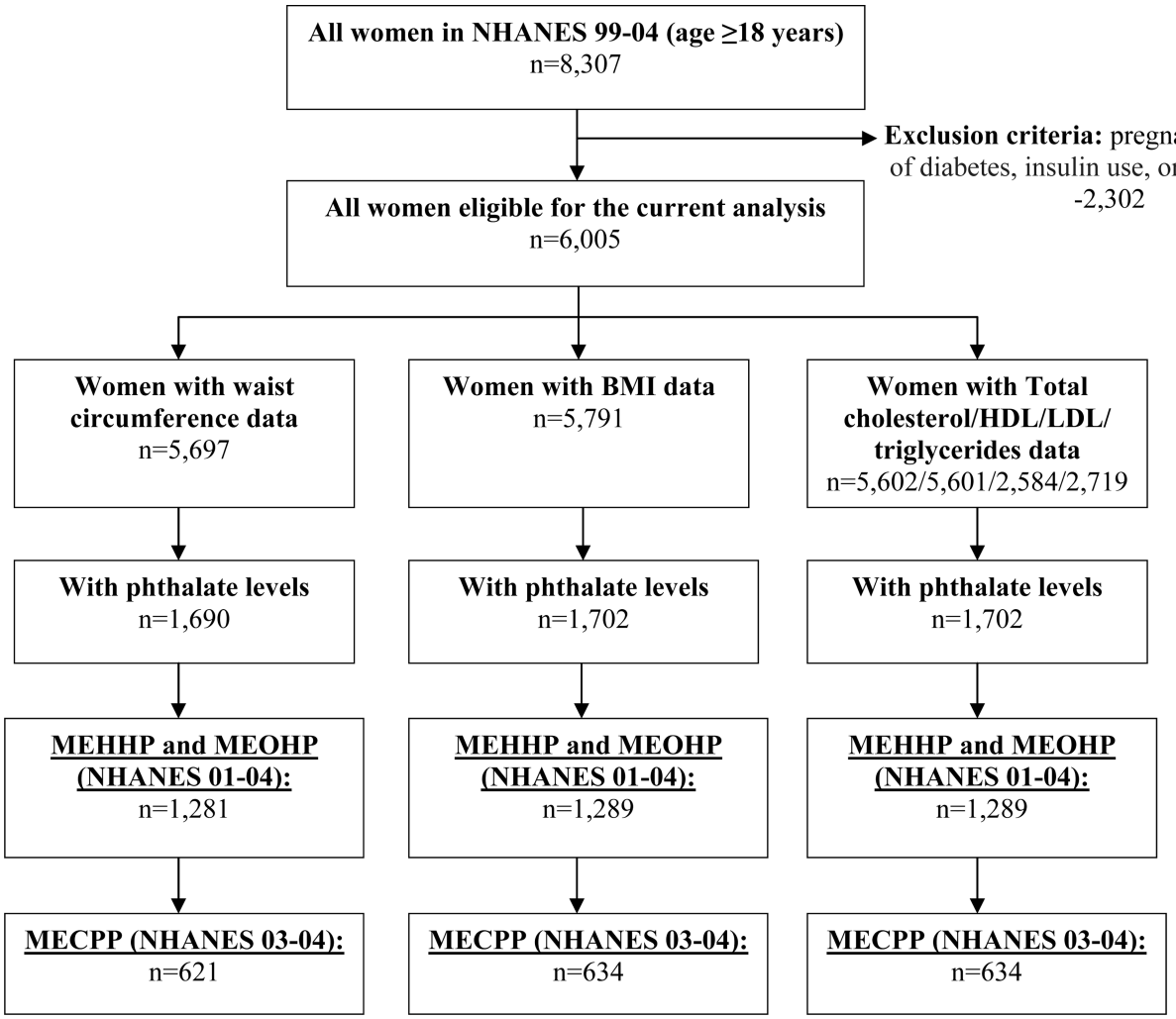

Figure 2.
Participant selection flowchart

Table 1

Weighted characteristics of the study population (percent and standard error of percent)

Characteristic	All N=76,075,598	Underweight (BMI < 18.5) N=2,323,028	Normal weight (BMI 18.5– < 25) N=27,472,193	Overweight (BMI 25– < 30) N=20,979,698	Obese (BMI ≥ 30) N=25,300,679
Age (years)*					
18–<25	13.91 (1.01)	23.67 (9.08)	19.30 (1.90)	8.82 (1.70)	11.38 (1.55)
25–<38	23.20 (1.33)	30.41 (8.68)	24.97 (2.17)	21.08 (2.54)	22.37 (2.63)
38–<50	28.68 (1.55)	23.41 (8.53)	24.11 (2.35)	33.71 (2.50)	29.93 (2.88)
50–<66	20.31 (0.99)	14.02 (6.52)	17.38 (1.71)	19.72 (1.97)	24.57 (1.94)
≥66	13.90 (1.05)	8.49 (3.66)	14.23 (1.58)	16.67 (1.81)	11.74 (1.50)
Race*					
Hispanic	12.49 (1.90)	8.23 (4.76)	9.20 (1.54)	16.08 (2.95)	13.46 (2.49)
Black	10.38 (1.16)	3.11 (1.77)	6.46 (0.93)	10.15 (1.33)	15.51 (2.14)
White	72.92 (2.07)	82.34 (6.08)	79.07 (2.11)	68.37 (3.25)	69.17 (2.91)
Other	4.20 (0.61)	6.32 (4.40)	5.26 (1.04)	5.40 (1.39)	1.85 (0.62)
Menopausal status/hormone use**					
Pre-menopausal	52.01 (1.55)	56.93(8.07)	58.75 (2.10)	49.24 (2.71)	46.55 (2.55)
Postmenopausal, no hormone history	24.98 (1.11)	29.01(8.75)	20.70 (1.57)	26.61 (1.78)	27.90 (2.40)
Postmenopausal, past hormone use	9.35 (0.77)	0	7.51 (0.98)	9.79 (1.41)	11.82 (1.55)
Postmenopausal, current hormone use	10.85 (1.08)	12.35(6.23)	9.42 (1.62)	11.86 (1.69)	11.41 (1.70)
Postmenopausal, unknown hormone use history	2.82 (0.38)	1.71 (1.29)	3.62 (0.79)	2.50 (0.67)	2.31 (0.57)
Poverty level					
Above	83.32 (1.50)	80.09 (7.40)	85.53 (1.84)	84.63 (2.20)	80.13 (2.35)
Below	16.68 (1.50)	19.91 (7.40)	14.47 (1.84)	15.37 (2.20)	19.87 (2.35)
Total calories (Kcal)					
<1280	22.71 (1.16)	24.03 (7.50)	19.23 (1.91)	26.73 (2.13)	23.01 (2.41)
1280–<1698	24.88 (1.47)	20.38 (8.79)	24.96 (2.91)	26.88 (2.49)	23.55 (2.13)
1698–<2228	26.91 (1.26)	29.12 (8.88)	28.14 (2.31)	23.43 (2.60)	28.26 (2.50)
≥2228	25.51 (1.41)	26.47 (6.96)	27.68 (2.47)	22.96 (2.65)	25.18 (1.97)
Total fat (g/day)					
<42.16	22.31 (1.35)	32.61 (8.24)	21.25 (1.87)	25.53 (2.41)	19.84 (1.80)

Characteristic	All N=76,075,598	Underweight (BMI < 18.5) N=2,323,028	Normal weight (BMI 18.5– < 25) N=27,472,193	Overweight (BMI 25– < 30) N=20,979,698	Obese (BMI ≥ 30) N=25,300,679
42.16–<62.57	25.16 (1.27)	23.11 (8.82)	26.72 (2.31)	27.46 (2.72)	21.73 (1.73)
62.57–<86.89	25.76 (1.47)	16.37 (6.44)	26.61 (2.29)	21.92 (2.39)	28.91 (2.75)
≥86.89	26.77 (1.38)	27.92 (7.86)	25.43 (2.22)	25.08 (2.70)	29.53 (2.12)
Alcohol use (g/day) *					
0	78.37 (1.78)	61.66 (9.07)	71.29 (2.96)	79.50 (2.40)	86.66 (1.64)
>0	21.63 (1.78)	38.34 (9.07)	28.71 (2.96)	20.50 (2.40)	13.34 (1.64)
Physical activity **					
None	35.92 (1.78)	40.15 (10.35)	29.56 (2.46)	35.26 (2.97)	43.00 (3.14)
Moderate	53.93 (1.93)	53.39 (10.99)	57.78 (2.49)	57.89 (2.70)	46.50 (3.24)
Active	10.15 (0.79)	6.46 (4.59)	12.66 (1.64)	6.85 (1.38)	10.51 (1.33)
Education					
≤ High school	41.56 (1.63)	33.95 (8.17)	37.23 (2.70)	45.13 (2.82)	44.00 (2.46)
>High school	58.44 (1.63)	66.05 (8.17)	62.77 (2.70)	54.87 (2.82)	56.00 (2.46)
Waist circumference (inches) *					
≤81.3	26.86 (1.51)	100.00 (0.00)	61.64 (3.18)	5.80 (1.32)	0
81.4–91.6	25.36 (1.48)	0	34.91 (2.88)	43.12 (2.98)	2.28 (0.63)
91.7–102.8	22.90 (1.15)	0	3.46 (0.82)	44.41 (3.10)	28.03 (2.19)
≥102.9	24.89 (1.54)	0	0	6.66 (1.32)	69.69 (2.44)
Smoking status					
Never	55.02 (1.80)	51.69 (10.22)	53.49 (3.13)	54.87 (2.87)	57.12 (3.05)
Past	5.00 (0.50)	8.81 (3.41)	7.22 (1.18)	2.87 (0.71)	4.02 (0.67)
Current	39.93 (1.89)	39.50 (9.57)	39.29 (3.05)	42.26 (2.93)	38.86 (3.02)
Total cholesterol (mg/dL) **					
≤172	23.21 (1.62)	44.93 (9.23)	26.26 (2.81)	18.70 (2.35)	21.84 (2.48)
172–<197	25.72 (1.68)	31.89 (8.84)	26.13 (2.45)	25.81 (3.06)	24.66 (2.77)
197–<226	26.19 (1.47)	6.72 (4.75)	26.37 (2.10)	26.94 (2.66)	27.07 (2.19)
≥ 226	24.88 (1.56)	16.46 (6.95)	21.24 (2.36)	28.55 (3.04)	26.43 (2.54)
Triglycerides (mg/dL) *					
<76	25.05 (1.88)	27.14 (14.05)	37.18 (4.23)	21.60 (3.22)	16.28 (2.38)

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Characteristic	All N=76,075,598	Underweight (BMI < 18.5) N=2,323,028	Normal weight (BMI 18.5– < 25) N=27,472,193	Overweight (BMI 25– < 30) N=20,979,698	Obese (BMI ≥ 30) N=25,300,679
76–<108	26.95 (2.12)	44.70 (13.70)	33.10 (4.07)	23.23 (3.07)	23.06 (2.90)
108–<157	24.07 (1.86)	24.18 (11.66)	20.04 (3.38)	23.77 (4.28)	28.07 (2.77)
≥157	23.92 (1.77)	3.97 (4.06)	9.68 (1.91)	31.39 (3.39)	32.59 (3.24)
LDL (mg/dL)					
<94	23.87 (2.07)	49.56 (13.54)	28.15 (3.20)	17.77 (3.12)	23.09 (3.27)
94–<114	23.20 (1.96)	24.65 (12.65)	26.58 (3.52)	24.79 (3.72)	18.62 (2.74)
114–<139	26.90 (2.06)	13.65 (11.11)	25.31 (3.12)	27.27 (3.02)	28.93 (3.97)
≥139	26.04 (2.11)	12.14 (11.40)	19.96 (3.31)	30.17 (2.99)	29.36 (4.25)
HDL (mg/dL) *					
< 45	22.91 (1.48)	16.51 (7.81)	9.20 (1.35)	25.75 (2.63)	35.71 (2.98)
45–<55	25.28 (1.52)	14.94 (6.74)	22.73 (2.16)	23.72 (2.25)	30.23 (2.98)
55–<65	23.92 (1.39)	26.11 (10.40)	27.12 (2.55)	23.44 (1.92)	20.71 (2.24)
<65	27.90 (1.24)	42.45 (8.45)	40.95 (2.11)	27.09 (2.19)	13.34 (2.17)

Abbreviations: BMI – body mass index, LDL – low density lipoprotein; HDL – high-density lipoprotein

* p<0.001 - Difference across BMI categories is significant at 0.001 level

** p<0.05 - Difference across BMI categories is significant at 0.05 level

Table 2

Distribution of phthalates in the study sample, age and race adjusted median and geometric means (standard error)

Phthalate measure	All Median GM (SE)	BMI <18.5 Median GM (SE)	BMI 18.5–< 25 Median GM (SE)	BMI 25–< 30 Median GM (SE)	BMI ≥ 30 Median GM (SE)
MBP	22.14 22.48 (1.06)	25.30 26.68 (1.21)	23.52 23.34 (1.08)	21.82 22.60 (1.11)	21.40 21.33 (1.07)
MBzP	8.89 9.00 (1.11)	10.24 10.12 (1.38)	8.77 8.70 (1.08)	8.89 9.11 (1.16)	9.19 9.17 (1.22)
MEHP[*]	3.07 3.21 (1.14)	3.83 3.26 (1.36)	3.21 3.60 (1.20)	3.10 3.09 (1.10)	3.13 2.97 (1.23)
MEP[*]	138.03 149.84 (1.24)	90.01 99.67 (1.30)	134.36 141.08 (1.24)	140.02 152.42 (1.32)	153.26 160.81 (1.27)
MEHHP[a]	16.84 18.71 (1.13)	16.10 14.46 (1.23)	17.09 19.00 (1.15)	16.40 17.35 (1.14)	18.41 20.06 (1.17)
MEOHP[a]	11.52 12.66 (1.12)	11.07 9.87 (1.24)	11.69 12.93 (1.15)	11.14 11.79 (1.11)	12.22 13.44 (1.15)
MECPP[b*]	28.49 32.51 (1.10)	20.94 18.39 (1.55)	29.43 34.27 (1.09)	27.83 28.77 (1.18)	32.14 35.31 (1.25)
MEHP:MEHHP[a*]	0.17 0.17 (1.09)	0.18 0.21 (1.74)	0.18 0.18 (1.15)	0.18 0.18 (1.17)	0.15 0.15 (1.11)
MEHHP:MECPP[b*]	0.63 0.61 (1.11)	0.64 0.68 (1.19)	0.64 0.62 (1.10)	0.60 0.56 (1.16)	0.66 0.63 (1.10)
MEHHP:MEOHP[a]	1.47 1.48 (1.03)	1.51 1.46 (1.07)	1.46 1.47 (1.05)	1.45 1.47 (1.04)	1.49 1.49 (1.02)
MEOHP: MECPP[b*]	0.42 0.40 (1.12)	0.47 0.48 (1.19)	0.43 0.41 (1.13)	0.40 0.37 (1.14)	0.42 0.42 (1.09)
ΣDEHP[a, c]	32.30 36.84 (1.12)	32.78 30.92 (1.26)	32.76 37.64 (1.16)	31.42 34.71 (1.11)	34.25 38.49 (1.18)

Abbreviations: GM – geometric mean; SE – standard error; MBP - monobutyl phthalate; MBzP - Mono-benzyl phthalate; MEHP - Mono-2-ethylhexyl phthalate; MEP - Mono-ethyl phthalate; MEHHP - Mono-(2-ethyl-5-hydroxyhexyl) phthalate; MEOHP - Mono-(2-ethyl-5-oxohexyl) phthalate; MECPP - Mono-(2-ethyl-5-carboxypentyl) phthalate; DEHP - Di-2-ethylhexyl phthalate

[a] Limited to 2001–2004 only

[b] Limited to 2003–2004

[c] ΣDEHP – sum of MEHP, MEHHP, and MEOHP

[*] p<0.001 - Difference across BMI categories is significant at 0.001 level

Table 3

Association of phthalate metabolites with Body Mass Index, waist circumference, and serum lipids in NHANES 1999–2004 (ordered logistic regression, Odds Ratios and 95% Confidence Intervals)[a]

Phthalate measure	Body Mass Index	Waist circumference	Total cholesterol	Triglycerides	HDL	LDL
MBP	1.13 (1.03, 1.23)	1.13 (1.03, 1.24)	1.04 (0.94, 1.15)	0.91 (0.78, 1.07)	0.94 (0.85, 1.03)	1.04 (0.90, 1.19)
MBzP	0.95 (0.84, 1.08)	0.93 (0.83, 1.05)	0.97 (0.88, 1.07)	0.95 (0.80, 1.12)	1.01 (0.91, 1.13)	1.00 (0.85, 1.18)
MEHP	1.12 (1.03, 1.23)	1.05 (0.96, 1.15)	1.00 (0.90, 1.11)	0.91 (0.78, 1.05)	1.02 (0.91, 1.13)	0.98 (0.85, 1.14)
MEP	1.02 (0.92, 1.14)	1.02 (0.92, 1.14)	0.97 (0.87, 1.09)	0.99 (0.87, 1.12)	0.91 (0.81, 1.02)	1.08 (0.94, 1.24)
MEHHP[b]	0.90 (0.80, 1.00)	0.88 (0.79, 1.00)	1.01 (0.90, 1.14)	0.94 (0.81, 1.09)	1.05 (0.96, 1.15)	1.10 (0.94, 1.29)
MEOHP[b]	0.90 (0.80, 1.01)	0.89 (0.78, 1.01)	0.98 (0.88, 1.10)	0.99 (0.84, 1.16)	1.03 (0.94, 1.12)	1.12 (0.96, 1.31)
MECPP[c]	0.81 (0.66, 1.00)	0.80 (0.64, 0.99)	0.95 (0.80, 1.13)	1.15 (0.88, 1.50)	1.06 (0.93, 1.21)	1.14 (0.95, 1.36)
MEHP:MEHHP[b]	1.21 (1.09, 1.34)	1.20 (1.10, 1.31)	0.95 (0.84, 1.06)	1.04 (0.87, 1.24)	0.96 (0.84, 1.09)	0.97 (0.84, 1.13)
MEHHP:MECPP[c]	1.02 (0.83, 1.26)	1.02 (0.86, 1.21)	0.98 (0.83, 1.17)	0.91 (0.68, 1.22)	0.96 (0.79, 1.16)	1.00 (0.72, 1.38)
MEOHP:MECPP[c]	1.11 (0.91, 1.36)	1.07 (0.87, 1.31)	1.00 (0.85, 1.19)	0.98 (0.78, 1.22)	0.95 (0.76, 1.19)	1.14 (0.87, 1.49)
MEHHP:MEOHP[b]	0.97 (0.83, 1.12)	0.95 (0.84, 1.08)	1.02 (0.92, 1.12)	1.00 (0.85, 1.17)	1.06 (0.92, 1.22)	1.09 (0.94, 1.26)
ΣDEHP[b, d]	0.93 (0.84, 1.03)	0.90 (0.81, 1.00)	1.00 (0.90, 1.11)	0.94 (0.81, 1.09)	1.05 (0.95, 1.15)	1.08 (0.92, 1.26)

Abbreviations: HDL –high-density lipoprotein cholesterol; LDL – low-density lipoprotein cholesterol; MBP - monobutyl phthalate; MBzP - Mono-benzyl phthalate; MEHP - Mono-2-ethylhexyl phthalate; MEP - Mono-ethyl phthalate; MEHHP - Mono-(2-ethyl-5-hydroxyhexyl) phthalate; MEOHP - Mono-(2-ethyl-5-oxohexyl) phthalate; MECPP - Mono-(2-ethyl-5-carboxypentyl) phthalate; DEHP - Di-2-ethylhexyl phthalate

[a] Adjusted for age, race, education, poverty, total calories, total fat, physical activity, menopausal status/hormone use, alcohol consumption and smoking

[b] Limited to 2001–2004 only

[c] Limited to 2003–2004

[d] ΣDEHP – sum of MEHP, MEHHP, and MEOHP