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Association between Urinary Phthalate Biomarker Concentrations and Adiposity among Postmenopausal Women

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Declaration of Competing Financial Interests

The authors declare they have no actual or potential competing financial interests.

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Abstract

Background: Obesity is a leading risk factor for chronic diseases, potentially related to excess abdominal adiposity. Phthalates are environmental chemicals that have been suggested to act as obesogens, driving obesity risk. For the associations between phthalates and adiposity, prior studies have focused primarily on body mass index. We hypothesize that more refined measures of adiposity and fat distribution may provide greater insights into these associations given the role of central adiposity in chronic disease risk.

Objectives: To evaluate associations between urinary phthalate biomarkers and both visceral and subcutaneous adipose tissue (VAT and SAT) among postmenopausal women enrolled in the Women's Health Initiative (WHI).

Methods: We included 1,125 WHI participants with available, coincident measurements of urinary phthalate biomarkers (baseline, year 3) and VAT and SAT (baseline, year 3, year 6). VAT and SAT measurements were estimated from DXA scans. Multilevel mixed-effects models estimated the prospective associations between urinary phthalate biomarkers at baseline and VAT and SAT three years later.

Results: In multivariable adjusted models, we observed positive associations between some phthalate biomarkers, including the sum of di-isobutyl phthalate (ΣDiBP) biomarkers, MCNP, and DEHP, with VAT three years later. For example, we observed positive associations between concentrations of ΣDiBP and VAT (Q4 vs Q1 β=7.15, 95% CI −1.76-16.06; Q3 vs Q1 β=10.94, 95% CI 3.55-18.33). Associations were generally attenuated but remained significant after additional adjustment for SAT. MBzP was positively associated with SAT. Other phthalate biomarkers investigated (MEP, MCOP, MCPP, ΣDBP) were not significantly associated with VAT or SAT.

Discussion: Based on robust measures of adiposity, this study provides supportive evidence that higher urinary concentrations of select phthalate compounds were associated with higher VAT levels over time in postmenopausal women. Efforts to replicate these findings are needed.

Keywords

phthalates; biomarkers; visceral adiposity; subcutaneous adiposity; postmenopausal

Introduction

Obesity is a global epidemic, and its prevalence has nearly tripled in recent decades (1). The risk of many chronic diseases is positively associated with obesity, including cardiovascular disease, diabetes, and many forms of cancer. While diet and physical activity are known to strongly influence obesity, environmental endocrine-disrupting chemicals, such as phthalates, are increasingly suspected to contribute as well (2). Phthalates are synthetic industrial compounds used to increase the flexibility of plastics and stability of other consumer products (e.g., medical devices, cosmetics, paints, shampoos, and cleaning materials). Following internal exposure, phthalates undergo a two-phase metabolism process (3), with the initial detoxification step yielding bioactive metabolites that can disrupt normal

lipid accumulation, adipogenesis, and metabolic processes (3). Phthalate metabolites may also activate peroxisome proliferator-activated receptors (PPARs), which are transcriptional factors that play an important role in energy metabolism (4).

Several prior cross-sectional studies have reported positive associations between urinary phthalate biomarkers and both BMI and waist circumference (WC) (5–10). Similarly, prospective studies reported consistent, albeit weak, positive associations between urinary phthalate biomarkers and weight gain (9,10). Notably, these studies utilized body weight and BMI, which do not accurately measure adiposity (11,12). Importantly, in older adults, adiposity accumulation can increase while body weight remains stable, resulting from increased adipose tissue mass offset by decreased lean mass, making BMI a particularly imprecise measure of adiposity in this population (13,14). As a result, the true associations between phthalate exposure and adiposity remain unclear.

Measures of adipose tissue depots, namely visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT), provide a more sensitive and robust measurement of adiposity (12). Both VAT and SAT are positively associated with risk of cardiovascular and metabolic diseases, with stronger associations observed for VAT as compared to SAT (15).

In this study we evaluated the associations between urinary phthalate biomarker concentrations and dual energy x-ray absorptiometry (DXA)-estimated measures of VAT and SAT in a subset of participants enrolled in the Women's Health Initiative (WHI).

Materials and Methods

Study Population

As previously described, the WHI recruited 161,808 postmenopausal women ages 50 to 79 years old from 40 clinical centers across the U.S. between October 1, 1993, and December 21, 1998 (16,17). Participants at three WHI sites (Birmingham, AL; Pittsburgh, PA; Tucson/Phoenix, AZ) were enrolled in a bone density substudy and provided first-morning void urine samples at baseline, annual visit (AV) 1 and AV3 (N=11,020).

A prior nested case-control study evaluating urinary phthalate biomarkers and breast cancer selected cases of invasive breast cancer diagnosed after AV3 and 1:2 matched controls (matched on enrollment date, length of follow-up, age at enrollment, and study arm) from participants at these three sites (N=1,257) (18). A total of 419 invasive breast cancer cases and 838 controls, 1:2 matched on, were selected. For the present analysis, we selected participants from the nested breast cancer case-control study who also had DXA-derived visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) measurements at baseline, AV3, and/or AV6 and who had non-missing data on needed covariates. Our final analytic sample included 1,125 participants.

Participants provided written informed consent upon WHI enrollment. Institutional review boards (IRB) at each WHI clinical center approved the study, and the University of Massachusetts Amherst IRB additionally approved the current analysis. The involvement of

the Centers for Disease Control and Prevention (CDC) laboratory in the analysis of samples did not constitute an engagement in human subjects' research.

Quantification of Urinary Phthalate Metabolites

WHI followed a standard urine collection, processing, and storage protocol at each clinical center. First morning void urine samples were collected by participants at home and processed within 30 minutes after clinic arrival. Urine samples were centrifuged for 5 minutes at 1330 x g; 1.8mL aliquots were frozen and shipped to McKesson Bioservices packed in dry ice via overnight FedEx then stored at −70°C.

Phthalate metabolites were used as biomarkers to ensure that measured concentrations related to endogenous exposures, which are generally accepted to reflect short-term exposures (i.e. days) (19). The CDC quantified thirteen phthalate metabolites in urine samples provided at baseline (mono-n-butyl phthalate [MBP], monobenzyl phthalate [MBzP], MCNP, mono-carboxyoctyl phthalate [MCOP], MCPP, mono(2-ethyl-5-carboxypentyl) phthalate [MECPP], mono-(2-ethyl-5-hydroxyhexyl) phthalate [MEHHP], mono-(2-ethylhexyl) phthalate [MEHP], mono(2-ethyl-5-oxohexyl) phthalate [MEOHP], monoethyl phthalate [MEP], mono-hydroxybutyl phthalate [MHBP], mono-hydroxyisobutyl phthalate [MHiBP], and monoisobutyl phthalate [MiBP]), with limits of detection (LOD) ≤0.5 mg/mL. The glucuronidated phthalate metabolites underwent enzymatic deconjugation followed by on-line solid phase extraction and high-performance liquid chromatography-electrospray ionization-tandem mass spectrometry.

Samples were randomly distributed through the batches, with all replicates from cases and matched controls analyzed together. A blinded 10% quality control sample was included and used to estimate CVs: MBP 5.4%, MBzP 6.1%, MCNP 4.7%, MCOP 6.3%, MCPP 5.8%, MECPP 4.3%, MEHHP 5.4%, MEHP 19.5%, MEOHP 6.0%, MEP 3.1%, MHBP 9.0%, MHiBP 21.9%, MiBP 10.3%. Laboratory staff were blinded to the identity, disease status, and demographic and risk factor characteristics of the samples. Urinary creatinine was measured using a Roche Modular P Chemistry Analyzer (Indianapolis, IN) and an enzymatic assay. The LOD for creatinine was 1 mg/dL and the CV was 2.5%. We previously calculated intraclass correlation coefficients for the phthalate biomarkers across three years, which ranged from 0.01-0.12 (18).

Adiposity Measurement

Participants underwent DXA measurements using Hologic machines (QDR2000, 2000+, or 4500 Hologic) at baseline, AV3, and AV6 clinic visits. These DXA scans were reanalyzed to measure VAT (cm^2) and SAT (cm^2) as previously described (20). Briefly, DXA-VAT and DXA-SAT were measured in a 5-cm wide region placed across the entire abdomen above the iliac crest at a level that approximately corresponded with the 4^{th} lumbar vertebrae on the whole-body DXA scan. The delimited lateral SAT on each side of the abdominal cavity, measured via DXA, was used to model the anterior and posterior amount of SAT over the visceral cavity. The estimated SAT over the visceral cavity was added to the measured lateral SAT to calculate the total abdominal SAT, which was then subtracted from the total abdominal fat mass to calculate VAT. In a validation study within the WHI

cohort, DXA-derived measures of VAT and SAT demonstrated strong correlations with those measured by MRI (r>0.90). Calibration of measurements across DXA machine models was carefully applied and described previously (20).

Covariates and Potential Confounders

Participants provided extensive data via self-reported questionnaires at annual clinic visits. We selected covariates for our statistical models based on prior knowledge of associations between these variables and phthalate exposure and adiposity; this resulted in the following list of covariates assessed at baseline, with updates at subsequent clinic visits for time-varying covariates: age (continuous; time-varying), region (Northeast, South, West), race (White, Black, Hispanic/Latina, Other), education (less than high school, high school/some college, college graduate, graduate degree), neighborhood socioeconomic status (below median, at/above median) (Griffin et al. 2013), smoking status (never, past, current; time-varying), current alcohol intake (non-drinker, past drinker, <1 drink per month, <1 drink per week, 1-<7 drinks per week, 7+ drinks per week; time-varying), total energy intake (continuous, kcal; time-varying), Healthy Eating Index (HEI) score (continuous; time-varying) (21,22), , and Dietary Modification trial arm (DM arm) (not randomized to DM, intervention, control).

Statistical Analysis

We imputed phthalate metabolite concentrations reported <LOD (<1% of observations) as the LOD/√2. Molar sums of the metabolites of di-n-butyl phthalate (ΣDBP), di-isobutyl phthalate (ΣDiBP), and di(2-Ethylhexyl) phthalate (ΣDEHP) were calculated as follows: ΣDBP (MBP and MHBP), ΣDiBP (MiBP and MHiBP), ΣDEHP (MEHP, MEHHP, MEOHP, and MECPP). Phthalate biomarker concentrations were natural log-transformed to limit the influence of outliers. To facilitate comparison of effect size across phthalates with differing biologic exposure ranges, phthalate biomarkers were z-score standardized (i.e., each phthalate biomarker was subtracted from their mean and divided by their respective standard deviation) and analyzed as continuous and as quartile variables. VAT and SAT measures were analyzed continuously.

Generalized Estimating Equation (GEE) models were fit using the identity link and Gaussian (normal) distribution to estimate cross-sectional associations between phthalate biomarkers and VAT and SAT.

We then fit multilevel mixed-effects models with a random-intercept to estimate the associations of phthalate biomarkers with changes in VAT and SAT. Phthalate biomarker concentrations at the beginning of a 3-year interval (i.e. baseline or AV3) were analyzed for association with VAT and SAT measures at the end of the 3-year interval (i.e. AV3 or AV6). Controls each contributed up to two 3-year intervals (baseline to AV3 and AV3 to AV6), and cases contributed only a single 3-year interval (baseline to AV3) to exclude the potential effects of cancer treatment on adiposity, for a total of 985 participants. We evaluated the stability of our results when adjusting for the other adipose tissue measurement (i.e. adjust for SAT at beginning of 3-year interval in models for VAT, and vice versa). We also repeated our analyses with stratification on age (<65 vs ≥65 years) at baseline.

All analyses were performed using Stata version 16.0 (Stata Corporation LLC, College Station, TX). Two-sided *P* values ≤0.05 were considered statistically significant, although our interpretations are based on the general pattern and consistency, and not solely on p-values.

Results

The age- and creatinine-adjusted geometric mean (95% CI) of each phthalate biomarker across descriptive characteristics at baseline are presented in Table 1. From this we observed differences by race, with women identifying as Black having higher MEP concentrations yet lower concentrations of other phthalate biomarkers compared to women in other racial groups. Hispanic/Latina women had the highest adjusted MEP concentrations, while concentrations of other phthalate biomarkers were generally similar to those of White women. In general, phthalate biomarker concentrations also were higher among those with less than a high school education. Past and current smokers had higher concentrations of ΣDBP, and concentrations of ΣDBP, ΣDiBP, and MCNP were positively associated with higher levels of alcohol intake.

Estimates of the multivariable-adjusted cross-sectional associations of measured phthalates with VAT and SAT are reported in Table 2. We observed positive associations between concentrations of MCPP (Q4 vs Q1 6.35 cm^2 higher VAT 95% CI −0.32-13.01) and ΣDEHP (Q4 vs Q1 7.18 cm^2 higher VAT, 95% CI 0.77-13.60) with VAT, as well as a positive association between MCOP and VAT (Q4 vs Q1 5.15 cm^2 higher VAT, 95% CI −0.96-11.25). ΣDiBP (Q4 vs Q1 10.00 cm^2 higher SAT, 95% CI −0.87-20.88) and ΣDEHP (Q4 vs Q1 8.89 cm^2 higher SAT, 95% CI −1.10-18.89) concentrations were positively associated with SAT. Higher concentrations of MEP, ΣDiBP, MBzP, and MCNP were not associated with VAT, as well as MCPP and SAT.

Table 3 shows the associations between urinary phthalate biomarker concentrations and adiposity measures 3 years later. We observed positive associations between concentrations of ΣDiBP (Q4 vs Q1 7.15 cm^2 higher VAT, 95% CI −1.76-16.06; Q3 vs Q1 10.94 cm^2 higher VAT, 95% CI 3.55-18.33) and MCNP (Q4 vs Q1 10.50 cm^2 higher VAT, 95% CI 3.11-17.90). ΣDEHP concentrations also were positively associated with VAT (3.83 cm^2 higher VAT per 1 SD increase, 95% CI 0.82-6.83), although results were not statistically significant when ΣDEHP was categorized by quartiles. ΣDiBP also non-significantly associated with SAT after 3 years, with a non-linear trend noted (Q4 vs Q1 8.51 cm^2 higher SAT, 95% CI −3.69-20.71; Q3 vs Q1 12.71 cm^2 higher SAT, 1.46-23.96). MBzP concentrations were positively associated with SAT 3 years later (Q4 vs Q1 11.71 cm^2 higher SAT, 95% CI 0.03-23.38). In models additionally adjusted for SAT at the beginning of the 3-year interval, urinary concentrations of ΣDiBP, ΣDEHP, and MCNP were somewhat attenuated yet remained positively associated with VAT (Table 4). No statistically significant associations were observed between any phthalate biomarkers and SAT in models additionally adjusted for VAT at the beginning of the 3-year interval (Table 4).

Interestingly, we observed some differences in associations when we repeated our results stratified on age (<65, ≥65; Table 5). For example, ΣDBP concentrations were negatively

associated with VAT among women younger than 65 (Q4 vs Q1 18.31 cm^2 lower VAT, 95% CI −29.36—7.25) yet were positively associated with both VAT (Q4 vs Q1 20.91 cm^2 higher VAT, 95% CI 8.13-33.7) and SAT (Q4 vs Q1 18.27 cm^2 higher SAT, 95% CI 2.20-34.34) among women 65 and older. Likewise, the positive associations between ΣDiBP and SAT and between ΣDEHP and VAT were apparent only among women ages 65 and older.

Discussion

In this prospective analysis of postmenopausal women, we observed many positive associations between some phthalate biomarkers and measures of VAT and SAT. For example, women in the third quartile of urinary ΣDiBP concentrations had 10.9 cm^2 greater VAT and 12.7 cm^2 greater SAT three years later compared to women in the first quartile of urinary ΣDiBP. We observed non-linear associations between urinary ΣDiBP concentrations and VAT and SAT. While these estimates could reflect random statistical error, non-monotonic dose-response curves are characteristic of endocrine-disrupting chemicals (23). Together, our findings suggest that certain phthalates may contribute to adiposity, potentially with a greater impact on VAT than SAT among postmenopausal women. These results call for a replication of findings in other cohort samples.

Our findings are largely consistent with prior studies evaluating adiposity measured via BMI and WC, which generally demonstrate positive associations between metabolites of DEHP and DBP and these obesity measures (5–8). Importantly, these findings add rigor in estimation of adiposity and particularly VAT, which is considered a major driver of obesity-associated inflammation and chronic disease risk (24).

Because metabolism and accumulation of adiposity changes with aging, we repeated our analyses with stratification on age. Importantly, the associations between phthalate biomarkers and VAT and SAT were stronger and significant only among women ages 65 and older, while some statistically significant negative associations were observed among women younger than 65. These findings suggest that phthalates may be an important contributory factor to adiposity among older women but not those who are younger than 65 y. These novel findings will require confirmation by future studies, yet they underscore the importance of considering how environmental exposures may differentially affect health across the life course.

Our prospective findings of associations between ΣDiBP and ΣDEHP and VAT are consistent with prior reports of adult weight gain associated with metabolites of these phthalates (10). Weight gain was also positively associated with MBzP in a prior study (25), which is consistent with our findings of positive prospective associations between MBzP and SAT. We note, however, that our analysis utilized direct measures of adiposity, and so are not directly comparable to prior work evaluating weight change.

Additionally, the heterogeneity of our findings across the phthalate biomarkers explored highlights the need to consider a broad panel of chemicals within a single chemical class. Various phthalates and their metabolites differ in their mechanisms of action. Multiple experimental studies provide evidence that certain phthalates and/or their metabolites (e.g.,

DEHP, MEHP, MBzP, MBP) may induce adipogenesis through the activation of PPARs whereas others do not (4,26–28); such a mechanism may explain our findings of significant associations between ΣDEHP, ΣDBP, and ΣDiBP with adiposity while other phthalate biomarkers (e.g., MEP) were not associated with adiposity in this study. Additionally, a recent study using a bioassay demonstrated that extracts from plastic consumer products, including those containing the phthalates DBP and DEHP induced adipogenesis in a bioassay through mechanisms other than activation of PPARγ (29). Additional research will be helpful in understanding the mechanisms by which phthalates trigger adipogenesis and why they appear to preferentially affect VAT, the more metabolically active component, than SAT as we observed in our analysis.

Our results must be interpreted in light of relevant limitations. Because phthalate biomarkers have a short metabolic half-life, there is substantial within-person variability (ICC range 0.01-0.12). While we had up to three repeated phthalate biomarker measurements per participant, we chose to utilize only the measurements from baseline to be consistent with our prior analyses of body weight (10) and to maximize our use of the VAT and SAT data collected at baseline and the years 3 and 6 visits. However, we acknowledge that a single measurement of the phthalate biomarkers reflects only fairly recent exposure; there is a substantial potential for non-differential misclassification of exposure that would most likely attenuate our results toward the null. Also, there is the potential for type I error, given the large number of statistical comparisons performed, which were not adjusted for the multiple comparisons. However, we base our interpretation on general patterns along with the p values, and the general consistency of our findings across phthalate biomarkers and similarity of our findings with those reported in prior literature supports the validity of our findings. Future studies will be useful in either confirming or refuting our findings. We also note that our analytic sample is a highly selected convenience sample derived from a breast cancer nested case-control study. While this selection would not affect the internal validity of our results, our findings could be limited in the external validity and application to populations beyond this sample, which we also note has limited racial/ethnic diversity and includes only postmenopausal women. However, we did observe similar phthalate metabolite concentrations and patterns of association with age and race as reported by contemporary NHANES measurements, thus supporting that the associations we report here are likely to be reflective of those within the general population.

Important strengths of our study include a well-characterized sample of women, quantification of a broad panel of phthalate metabolites in first-morning void urine samples using an established analytic method with proven reliability and validity, and the measurement of adiposity via DXA-derived measures of VAT and SAT. These DXA-derived measurements are more robust and accurate than BMI or WC and have been validated against the gold standard measurement of adiposity via magnetic resonance imaging (20). Finally, our repeated, prospective assessments of urinary phthalate biomarkers and VAT/SAT are unique aspects of our study and support the rigor of our findings.

The growing evidence supporting obesogenic effects of environmental chemicals, including phthalates, is compelling. Our prospective evaluation to explore phthalate exposure in relation to VAT and SAT finds evidence that some phthalates may have important effects

on accumulation of adipose tissue, especially VAT and among women over the age of 65 years. Replication of our findings in other populations with prospective data on phthalate exposure and VAT/SAT will be important for clarifying associations between phthalate exposure and adiposity. If such future studies support our reported results, interventions to reduce phthalate exposure could offer an additional approach for addressing adiposity within the population.

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Research Approval

Written informed consent was provided by participants upon WHI enrollment. Institutional review boards at each clinical site approved the WHI, and this particular analysis was approved by the University of Massachusetts Amherst IRB. The involvement of the Centers for Disease Control and Prevention (CDC) laboratory in the analysis of samples did not constitute engagement in human subjects research.

Declaration of interests

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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Highlights

- Phthalates are environmental chemicals that may act as obesogens
- Urinary concentrations of select phthalate biomarkers were positively associated with visceral and subcutaneous adipose tissue
- Phthalates may preferentially impact visceral versus subcutaneous adipose tissue

Table 1.

Age- and creatinine-adjusted geometric means of phthalate biomarkers by descriptive characteristics at baseline, N=1125

Characteristic	N(%)	MEP	DBP	DiBP	MBzP	MCPP	DEHP	MCOP	MCNP
					Geometric Mean (95% CI)				
Age, years									
<65	691 (61.4)	92.3 (81.9, 104.0)	0.126 (0.115, 0.139)	0.013 (0.012, 0.014)	11.8 (10.8, 13.0)	3.2 (3.0, 3.5)	0.186 (0.171, 0.202)	4.2 (3.8, 4.5)	3.0 (2.8, 3.3)
65+	434 (38.6)	78.0 (65.8, 92.4)	0.129 (0.113, 0.147)	0.012 (0.011, 0.014)	12.3 (10.8, 14.1)	3.6 (3.3, 4.1)	0.181 (0.161, 0.204)	3.7 (3.3, 4.2)	2.8 (2.5, 3.2)
		0.19	0.85	0.38	0.67	0.16	0.77	0.21	0.38
Race/Ethnicity									
White	932 (82.8)	81.7 (75.8, 88.1)	0.131 (0.124, 0.139)	0.012 (0.012, 0.013)	12.5 (11.8, 13.2)	3.6 (3.4, 3.7)	0.190 (0.180, 0.200)	4.1 (3.9, 4.3)	3.1 (2.9, 3.2)
Black	118 (10.5)	113.6 (91.6, 141.1)	0.097 (0.082, 0.115)	0.013 (0.011, 0.015)	9.3 (7.8, 11.0)	2.3 (2.0, 2.6)	0.141 (0.121, 0.164)	2.9 (2.5, 3.4)	2.2 (1.9, 2.6)
Hispanic/Latina	55 (4.9)	126.9 (93.2, 172.9)	0.135 (0.106, 0.173)	0.015 (0.012, 0.019)	11.6 (9.1, 14.8)	3.4 (2.8, 4.1)	0.199 (0.161, 0.247)	4.8 (3.9, 6.0)	3.2 (2.6, 4.0)
Other	20 (1.8)	85.6 (51.2, 143.1)	0.118 (0.079, 0.177)	0.012 (0.008, 0.017)	11.0 (7.4, 16.5)	3.4 (2.5, 4.8)	0.160 (0.111, 0.228)	4.1 (2.8, 5.9)	2.7 (1.9, 3.8)
		0.003	0.01	0.53	0.01	<0.001	0.002	<0.001	0.001
Education									
Less than high school	302 (26.8)	102.0 (89.4, 116.3)	0.119 (0.107, 0.132)	0.012 (0.010, 0.013)	12.1 (10.9, 13.5)	3.3 (3.0, 3.6)	0.190 (0.173, 0.209)	4.1 (3.8, 4.5)	2.9 (2.6, 3.1)
High school/some college	408 (36.3)	93.7 (83.8, 104.9)	0.132 (0.121, 0.144)	0.013 (0.012, 0.014)	12.6 (11.6, 13.8)	3.6 (3.3, 3.8)	0.181 (0.168, 0.196)	3.9 (3.6, 4.3)	2.9 (2.7, 3.2)
College or higher	415 (36.9)	70.8 (63.4, 79.2)	0.128 (0.117, 0.140)	0.013 (0.012, 0.014)	11.4 (10.4, 12.4)	3.3 (3.0, 3.5)	0.183 (0.169, 0.198)	3.9 (3.6, 4.3)	3.1 (2.8, 3.3)
		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
SES index									
Below median	563 (50.0)	93.5 (84.9, 103.0)	0.125 (0.116, 0.135)	0.012 (0.012, 0.013)	12.4 (11.5, 13.4)	3.4 (3.2, 3.6)	0.182 (0.170, 0.194)	3.8 (3.6, 4.1)	2.7 (2.5, 2.8)
At or above median	562 (50.0)	80.0 (72.6, 88.1)	0.129 (0.120, 0.139)	0.013 (0.012, 0.014)	11.7 (10.8, 12.6)	3.4 (3.2, 3.6)	0.187 (0.175, 0.200)	4.2 (3.9, 4.5)	3.3 (3.1, 3.5)
		0.03	0.61	0.61	0.27	0.73	0.58	0.08	<0.001
Smoking status									
Never smoked	639 (56.8)	83.8 (76.6, 91.8)	0.118 (0.110, 0.127)	0.012 (0.011, 0.013)	11.7 (10.9, 12.6)	3.3 (3.1, 3.5)	0.179 (0.168, 0.190)	4.0 (3.7, 4.3)	2.9 (2.8, 3.1)

Characteristic	N(%)	MEP	DBP	DiBP	MBzP	MCPP	DEHP	MCOP	MCNP
					Geometric Mean (95% CI)				
Past smoker	419 (37.2)	87.8 (78.6, 98.2)	0.141 (0.129, 0.154)	0.013 (0.012, 0.015)	12.6 (11.6, 13.8)	3.6 (3.3, 3.8)	0.197 (0.182, 0.212)	4.1 (3.8, 4.4)	3.0 (2.8, 3.3)
Current smoker	67 (6.0)	104.7 (79.0, 138.8)	0.129 (0.103, 0.160)	0.012 (0.010, 0.015)	11.5 (9.2, 14.3)	3.2 (2.7, 3.9)	0.164 (0.134, 0.199)	3.5 (2.9, 4.3)	2.4 (2.0, 2.9)
		0.32	0.01	0.18	0.39	0.18	0.08	0.46	0.10
Alcohol intake, drinks/week									
None	361 (32.1)	84.4 (74.7, 95.3)	0.110 (0.100, 0.121)	0.012 (0.011, 0.013)	11.8 (10.8, 13.0)	3.1 (2.9, 3.3)	0.177 (0.162, 0.192)	3.9 (3.6, 4.2)	2.7 (2.5, 2.9)
<1	397 (35.3)	85.0 (75.7, 95.4)	0.125 (0.114, 0.137)	0.012 (0.011, 0.013)	11.7 (10.7, 12.8)	3.3 (3.1, 3.6)	0.176 (0.163, 0.191)	4.1 (3.7, 4.4)	3.0 (2.8, 3.3)
1-6	265 (23.6)	88.2 (76.7, 101.3)	0.148 (0.133, 0.165)	0.014 (0.013, 0.016)	12.1 (10.9, 13.5)	3.7 (3.4, 4.0)	0.203 (0.184, 0.223)	4.1 (3.7, 4.5)	3.0 (2.7, 3.3)
7+	102 (9.1)	95.4 (76.0, 119.8)	0.150 (0.126, 0.179)	0.014 (0.012, 0.016)	13.9 (11.7, 16.6)	3.9 (3.4, 4.6)	0.195 (0.167, 0.229)	3.9 (3.3, 4.6)	3.4 (2.9, 4.0)
		0.79	0.00	0.02	0.36	0.004	0.10	0.86	0.05
Daily energy intake, kcal									
<1560	542 (48.2)	93.1 (84.5, 102.5)	0.134 (0.124, 0.145)	0.013 (0.012, 0.013)	11.6 (10.8, 12.6)	3.4 (3.2, 3.6)	0.187 (0.175, 0.200)	3.8 (3.6, 4.1)	2.9 (2.7, 3.1)
1560+	542 (48.2)	80.5 (73.1, 88.6)	0.121 (0.112, 0.130)	0.013 (0.012, 0.014)	12.4 (11.5, 13.4)	3.4 (3.2, 3.6)	0.181 (0.169, 0.194)	4.2 (3.9, 4.5)	3.0 (2.8, 3.3)
		0.04	0.05	0.93	0.23	0.88	0.51	0.10	0.18
Healthy eating index									
Below median	542 (48.2)	88.6 (80.3, 97.6)	0.129 (0.120, 0.140)	0.013 (0.012, 0.014)	12.6 (11.7, 13.6)	3.5 (3.3, 3.7)	0.193 (0.181, 0.207)	4.2 (3.9, 4.5)	3.0 (2.8, 3.2)
At or above median	542 (48.2)	84.6 (76.7, 93.3)	0.125 (0.116, 0.135)	0.013 (0.012, 0.013)	11.5 (10.6, 12.4)	3.3 (3.1, 3.5)	0.175 (0.164, 0.188)	3.8 (3.5, 4.1)	2.9 (2.7, 3.1)
Dietary modification (DM) trial arm		0.52	0.52	0.85	0.10	0.29	0.05	0.06	0.27
Not in DM trial	738 (65.6)	85.0 (78.1, 92.4)	0.126 (0.118, 0.135)	0.012 (0.012, 0.013)	12.0 (11.2, 12.8)	3.3 (3.2, 3.5)	0.181 (0.171, 0.192)	4.0 (3.8, 4.3)	2.9 (2.8, 3.1)
Intervention	143 (12.7)	88.1 (72.6, 107.0)	0.133 (0.114, 0.155)	0.014 (0.013, 0.017)	13.0 (11.2, 15.2)	3.6 (3.1, 4.0)	0.185 (0.161, 0.212)	3.7 (3.2, 4.3)	2.9 (2.6, 3.4)
Control	244 (21.7)	90.3 (77.7, 105.0)	0.126 (0.112, 0.142)	0.012 (0.011, 0.014)	11.7 (10.4, 13.1)	3.4 (3.1, 3.8)	0.193 (0.174, 0.215)	4.1 (3.6, 4.5)	3.0 (2.7, 3.3)
		0.77	0.84	0.12	0.49	0.65	0.59	0.55	0.90

Table 2.

Cross-sectional association between phthalate biomarkers and adiposity, N=1125

	VAT	P-value	SAT	
Phthalate biomarker	**Beta (95% CI)**		**Beta (95% CI)**	**P-value**
MEP				
Per 1 SD	−1.00 (−3.96 , 1.96)	0.51	0.65 (−3.38 , 4.68)	0.75
≤32.8	ref		ref	
32.9 - 68.1	−1.59 (−6.85 , 3.67)	0.55	0.04 (−8.16 , 8.24)	0.99
68.2 - 163	−1.57 (−7.32 , 4.17)	0.59	−0.95 (−9.91 , 8.02)	0.84
≥164	−4.74 (−11.10 , 1.62)	0.14	−0.44 (−10.37 , 9.48)	0.93
P trend	0.17		0.89	
ΣDBP				
Per 1 SD	−0.77 (−3.74 , 2.20)	0.61	1.64 (−2.37 , 5.66)	0.42
≤0.0586	ref		ref	
0.0587 - 0.116	1.59 (−3.77 , 6.95)	0.56	7.38 (−0.97 , 15.72)	0.08
0.117 - 0.231	2.46 (−3.36 , 8.27)	0.41	5.75 (−3.31 , 14.80)	0.21
≥0.231	−1.20 (−7.97 , 5.57)	0.73	3.41 (−7.15 , 13.96)	0.53
P trend	0.84		0.59	
ΣDiBP				
Per 1 SD	4.02 (0.70 , 7.34)	0.02	6.93 (2.42 , 11.45)	0.003
≤0.0061	ref		ref	
0.0062 - 0.0124	1.98 (−3.29 , 7.24)	0.46	4.32 (−3.87 , 12.50)	0.30
0.0125 - 0.0249	3.13 (−2.74 , 9.01)	0.30	10.11 (0.97 , 19.26)	0.03
≥0.025	3.54 (−3.43 , 10.51)	0.32	10.00 (−0.87 , 20.88)	0.07
P trend	0.28		0.04	
MBzP				
Per 1 SD	1.57 (−1.53 , 4.67)	0.32	0.70 (−3.50 , 4.89)	0.74
≤6	ref		ref	
6.1 - 11.8	3.73 (−1.63 , 9.08)	0.17	7.20 (−1.14 , 15.53)	0.09
11.9 - 22	4.99 (−0.77 , 10.76)	0.09	3.46 (−5.52 , 12.43)	0.45
≥22.1	3.74 (−2.93 , 10.41)	0.27	1.62 (−8.77 , 12.02)	0.76
P trend	0.24		0.91	
MCPP				
Per 1 SD	1.63 (−1.38 , 4.64)	0.29	0.24 (−3.82 , 4.31)	0.91
≤1.7	ref		ref	
1.8 - 3.1	2.88 (−2.35 , 8.11)	0.28	3.45 (−4.69 , 11.59)	0.41
3.2 - 5.5	6.44 (0.81 , 12.07)	0.02	5.93 (−2.84 , 14.70)	0.19
≥5.6	6.35 (−0.32 , 13.01)	0.06	6.48 (−3.91 , 16.88)	0.22
P trend	0.03		0.19	
ΣDEHP				
Per 1 SD	3.75 (0.77 , 6.74)	0.01	4.86 (0.83 , 8.88)	0.02
≤0.101	ref		ref	

	VAT	P-value	SAT	
Phthalate biomarker	**Beta (95% CI)**		**Beta (95% CI)**	**P-value**
0.102 - 0.181	4.72 (−0.54 , 9.99)	0.08	5.23 (−2.97 , 13.43)	0.21
0.182 - 0.333	5.78 (0.21 , 11.36)	0.04	9.85 (1.18 , 18.53)	0.03
≥0.334	7.18 (0.77 , 13.60)	0.03	8.89 (−1.10 , 18.89)	0.08
P trend	0.03		0.05	
MCOP				
Per 1 SD	3.31 (0.48 , 6.14)	0.02	2.46 (−1.37 , 6.29)	0.21
≤2.1	ref		ref	
2.2 - 3.6	2.66 (−2.52 , 7.84)	0.31	2.18 (−5.87 , 10.24)	0.59
37 - 6.5	6.36 (0.70 , 12.02)	0.03	5.73 (−3.09 , 14.54)	0.20
≥6.6	5.15 (−0.96 , 11.25)	0.10	3.64 (−5.86 , 13.14)	0.45
P trend	0.06		0.37	
MCNP				
Per 1 SD	0.20 (−2.41 , 2.80)	0.88	−0.05 (−3.54 , 3.44)	0.98
≤1.6	ref		ref	
1.7 - 2.7	2.57 (−2.62 , 7.77)	0.33	5.52 (−2.55 , 13.58)	0.18
2.8 - 4.8	3.43 (−2.14 , 9.00)	0.23	6.08 (−2.56 , 14.73)	0.17
≥4.9	3.98 (−1.97 , 9.93)	0.19	5.14 (−4.10 , 14.37)	0.28
P trend	0.19		0.31	

Adjusted for age, creatinine, race, education, SES index, smoking status, alcohol use, daily energy intake, Healthy Eating Index score, Dietary Modification Trial arm

Table 3.

Longitudinal associations between phthalate biomarkers and adiposity, N=985

	VAT		SAT	
Phthalate biomarker	**VAT Beta (95% CI)**	**P-value**	**SAT Beta (95% CI)**	**P-value**
MEP				
Per 1 SD	−1.10 (−4.10 , 1.91)	0.47	−2.31 (−7.09 , 2.46)	0.34
≤32.8	ref		ref	
32.9 - 68.1	−7.00 (−13.73 , −0.28)	0.04	−10.45 (−21.07 , 0.16)	0.05
68.2 - 163	−5.80 (−13.14 , 1.53)	0.12	−9.61 (−20.87 , 1.66)	0.09
≥164	−2.78 (−10.75 , 5.20)	0.50	−3.31 (−14.90 , 8.28)	0.58
P trend	0.63		0.54	
ΣDBP				
Per 1 SD	−0.88 (−3.87 , 2.12)	0.57	0.66 (−4.10 , 5.43)	0.79
≤0.0586	ref		ref	
0.0587 - 0.116	−0.60 (−7.27 , 6.07)	0.86	0.85 (−9.66 , 11.36)	0.87
0.117 - 0.231	2.98 (−4.26 , 10.22)	0.42	3.00 (−8.01 , 14.02)	0.59
≥0.231	−1.94 (−10.44 , 6.57)	0.66	2.50 (−9.20 , 14.19)	0.68
P trend	0.92		0.77	
ΣDiBP				
Per 1 SD	2.93 (−0.46 , 6.33)	0.09	2.64 (−2.76 , 8.04)	0.34
≤0.0061	ref		ref	
0.0062 - 0.0124	5.62 (−0.93 , 12.17)	0.09	4.97 (−5.35 , 15.30)	0.35
0.0125 - 0.0249	10.94 (3.55 , 18.33)	0.00	12.71 (1.46 , 23.96)	0.03
≥0.025	7.15 (−1.76 , 16.06)	0.12	8.51 (−3.69 , 20.71)	0.17
P trend	0.04		0.09	
MBzP				
Per 1 SD	2.23 (−0.94 , 5.40)	0.17	4.54 (−0.50 , 9.58)	0.08
≤6	ref		ref	
6.1 - 11.8	0.55 (−6.13 , 7.23)	0.87	6.08 (−4.44 , 16.60)	0.26
11.9 - 22	4.76 (−2.62 , 12.13)	0.21	10.39 (−0.81 , 21.59)	0.07
≥22.1	5.43 (−3.03 , 13.90)	0.21	11.71 (0.03 , 23.38)	0.05
P trend	0.14		0.04	
MCPP				
Per 1 SD	1.53 (−1.54 , 4.60)	0.33	2.76 (−2.12 , 7.65)	0.27
≤1.7	ref		ref	
1.8 - 3.1	2.60 (−3.87 , 9.08)	0.43	1.39 (−8.75 , 11.53)	0.79
3.2 - 5.5	0.65 (−6.40 , 7.71)	0.86	0.92 (−9.67 , 11.51)	0.86
≥5.6	3.98 (−4.52 , 12.49)	0.36	6.61 (−5.10 , 18.32)	0.27
P trend	0.51		0.39	
ΣDEHP				
Per 1 SD	3.83 (0.82 , 6.83)	0.01	3.13 (−1.65 , 7.91)	0.20

	VAT		SAT	
Phthalate biomarker	**VAT Beta (95% CI)**	**P-value**	**SAT Beta (95% CI)**	**P-value**
≤0.101	ref		ref	
0.102 - 0.181	2.17 (−4.61 , 8.95)	0.53	3.48 (−7.12 , 14.09)	0.52
0.182 - 0.333	2.09 (−4.87 , 9.04)	0.56	3.24 (−7.29 , 13.77)	0.55
≥0.334	7.60 (−0.61 , 15.81)	0.07	7.08 (−4.35 , 18.51)	0.22
P trend	0.10		0.31	
MCOP				
Per 1 SD	1.60 (−1.29 , 4.49)	0.28	1.28 (−3.32 , 5.87)	0.59
≤2.1	ref		ref	
2.2 - 3.6	−1.08 (−7.60 , 5.44)	0.75	−6.74 (−16.97 , 3.49)	0.20
3.7 - 6.5	2.99 (−4.17 , 10.14)	0.41	4.25 (−6.58 , 15.08)	0.44
≥6.6	3.84 (−4.09 , 11.77)	0.34	4.85 (−6.52 , 16.23)	0.40
P trend	0.22		0.15	
MCNP				
Per 1 SD	2.14 (−0.51 , 4.79)	0.11	0.50 (−3.73 , 4.73)	0.82
≤1.6	ref		ref	
1.7 - 2.7	7.51 (1.06 , 13.96)	0.02	6.77 (−3.42 , 16.97)	0.19
2.8 - 4.8	7.17 (−0.02 , 14.37)	0.05	4.27 (−6.69 , 15.23)	0.44
≥4.9	10.50 (3.11 , 17.90)	0.01	7.24 (−3.60 , 18.07)	0.19
P trend	0.01		0.34	

Adjusted for age, creatinine, race, education, SES index, smoking status, alcohol use, daily energy intake, Healthy Eating Index score, Dietary Modification Trial arm

Table 4.

Longitudinal associations between phthalate biomarkers and adiposity, adjusting for VAT/SAT, N=985

	VAT		SAT	
Phthalate biomarker	**Beta (95% CI)**	**P value**	**Beta (95% CI)**	**P value**
MEP				
Per 1 SD	−0.76 (−3.73 , 2.22)	0.62	−0.49 (−5.16 , 4.18)	0.84
<=32.8	ref		ref	
32.9 - 68.1	−2.01 (−8.95 , 4.93)	0.57	−7.85 (−18.72 , 3.02)	0.16
68.2 - 163	0.34 (−6.91 , 7.60)	0.93	−10.95 (−22.30 , 0.41)	0.06
>=164	1.76 (−5.61 , 9.14)	0.64	−3.12 (−14.67 , 8.43)	0.60
P trend	0.84		0.96	
ΣDBP				
Per 1 SD	−1.57 (−4.61 , 1.47)	0.31	2.38 (−2.39 , 7.16)	0.33
<=0.0586	ref		ref	
0.0587 - 0.116	−1.79 (−8.68 , 5.10)	0.61	−0.18 (−11.00 , 10.64)	0.97
0.117 - 0.231	5.45 (−1.63 , 12.53)	0.13	−2.55 (−13.69 , 8.58)	0.65
>=0.231	0.69 (−6.65 , 8.03)	0.85	−0.13 (−11.65 , 11.40)	0.98
P trend	0.68		0.55	
ΣDiBP				
Per 1 SD	0.01 (−3.29 , 3.31)	0.99	0.28 (−4.89 , 5.45)	0.92
<=0.0061	ref		ref	
0.0062 - 0.0124	2.98 (−3.76 , 9.73)	0.39	4.46 (−6.14 , 15.06)	0.41
0.0125 - 0.0249	7.36 (0.23 , 14.49)	0.04	8.25 (−2.93 , 19.43)	0.15
>=0.025	4.87 (−2.66 , 12.40)	0.20	1.46 (−10.35 , 13.27)	0.81
P trend	0.56		0.20	
MBzP				
Per 1 SD	1.74 (−1.41 , 4.89)	0.28	3.73 (−1.20 , 8.67)	0.14
<=6	ref		ref	
6.1 - 11.8	0.46 (−6.40 , 7.32)	0.90	0.82 (−9.97 , 11.62)	0.88
11.9 - 22	5.13 (−2.01 , 12.28)	0.16	2.47 (−8.78 , 13.72)	0.67
>=22.1	8.07 (0.76 , 15.39)	0.03	3.87 (−7.64 , 15.37)	0.51
P trend	0.12		0.12	
MCPP				
Per 1 SD	1.61 (−1.49 , 4.71)	0.31	2.42 (−2.44 , 7.29)	0.33
<=1.7	ref		ref	
1.8 - 3.1	3.83 (−2.85 , 10.50)	0.26	−4.75 (−15.23 , 5.73)	0.37
3.2 - 5.5	1.82 (−5.08 , 8.72)	0.61	−6.28 (−17.12 , 4.56)	0.26
>=5.6	7.46 (0.11 , 14.82)	0.05	−0.77 (−12.32 , 10.77)	0.90
P trend	0.50		0.64	
ΣDEHP				
Per 1 SD	3.20 (0.15 , 6.25)	0.04	1.70 (−3.09 , 6.50)	0.49
<=0.101	ref		ref	

	VAT		SAT	
Phthalate biomarker	**Beta (95% CI)**	**P value**	**Beta (95% CI)**	**P value**
0.102 - 0.181	2.34 (−4.52 , 9.21)	0.50	−3.15 (−13.95 , 7.64)	0.57
0.182 - 0.333	2.32 (−4.59 , 9.22)	0.51	−1.61 (−12.46 , 9.25)	0.77
>=0.334	8.66 (1.40 , 15.92)	0.02	−1.22 (−12.64 , 10.20)	0.83
P trend	0.18		0.56	
MCOP				
Per 1 SD	1.41 (−1.50 , 4.33)	0.34	1.14 (−3.44 , 5.72)	0.62
<=2.1	ref		ref	
2.2 - 3.6	0.03 (−6.68 , 6.73)	0.99	−8.11 (−18.63 , 2.40)	0.13
3.7 - 6.5	4.73 (−2.27 , 11.73)	0.19	0.18 (−10.80 , 11.16)	0.97
>=6.6	6.79 (−0.44 , 14.03)	0.07	1.20 (−10.15 , 12.54)	0.84
P trend	0.18		0.15	
MCNP				
Per 1 SD	1.66 (−1.09 , 4.41)	0.24	1.61 (−2.71 , 5.93)	0.47
<=1.6	ref		ref	
1.7 - 2.7	6.29 (−0.36 , 12.95)	0.06	−0.02 (−10.51 , 10.46)	1.00
2.8 - 4.8	5.95 (−1.13 , 13.04)	0.10	−0.82 (−11.98 , 10.35)	0.89
>=4.9	8.99 (2.04 , 15.93)	0.01	2.68 (−8.25 , 13.62)	0.63
P trend	0.11		0.28	

Adjusted for age, creatinine, race, education, SES index, smoking status, alcohol use, daily energy intake, Healthy Eating Index score, Dietary Modification Trial arm

Table 5.

Longitudinal associations between phthalate biomarkers and adiposity, with stratification by age, N=985

	VAT					SAT				
	Age <65 years N=640		Age >=65 years N=381			Age <65 years N=640		Age >=65 years N=381		
Phthalate biomarker	Beta (95% CI)	P value	Beta (95% CI)	P value	P interaction	Beta (95% CI)	P value	Beta (95% CI)	P value	P interaction
MEP										
Per 1 SD	−0.84 (−4.95 , 3.26)	0.69	−1.06 (−5.45 , 3.32)	0.63	0.68	−4.16 (−11.06 , 2.73)	0.24	0.12 (−6.21 , 6.45)	0.97	0.25
<=32.8	ref		ref		0.62	ref		ref		0.33
32.9 - 68.1	−10.20 (−19.24 , −1.16)	0.03	−4.02 (−14.05 , 6.01)	0.43		−14.57 (−29.77 , 0.62)	0.06	−6.72 (−21.03 , 7.58)	0.36	
68.2 - 163	−9.79 (−19.96 , 0.37)	0.06	−0.80 (−11.38 , 9.77)	0.88		−18.88 (−34.98 , −2.79)	0.02	1.10 (−14.00 , 16.19)	0.89	
>=164	−4.84 (−15.31 , 5.62)	0.36	0.01 (−12.42 , 12.43)	1.00		−8.33 (−24.41 , 7.74)	0.31	3.04 (−13.29 , 19.37)	0.72	
P trend	0.58		0.89			0.38		0.78		
ΣDBP										
Per 1 SD	−4.97 (−9.03 , −0.92)	0.02	3.94 (−0.42 , 8.30)	0.08	0.06	−2.28 (−9.15 , 4.60)	0.52	4.05 (−2.27 , 10.36)	0.21	0.42
<=0.0586	ref		ref		<0.001	ref		ref		0.02
0.0587 - 0.116	−2.17 (−10.72 , 6.39)	0.62	−0.35 (−10.61 , 9.90)	0.95		3.51 (−10.98 , 18.00)	0.63	−5.44 (−20.10 , 9.23)	0.47	
0.117 - 0.231	−6.01 (−15.55 , 3.52)	0.22	14.19 (3.51 , 24.87)	0.01		−3.51 (−18.96 , 11.95)	0.66	11.40 (−3.51 , 26.31)	0.13	
>=0.231	−18.31 (−29.36 , −7.25)	<0.01	20.91 (8.13 , 33.70)	0.00		−8.56 (−24.80 , 7.69)	0.30	18.27 (2.20 , 34.34)	0.03	
P trend	<0.01		<0.01			0.16		0.01		
ΣDiBP										
Per 1 SD	2.18 (−2.27 , 6.63)	0.34	4.16 (−1.03 , 9.36)	0.12	0.29	0.00 (−7.49 , 7.49)	0.99	6.43 (−1.08 , 13.94)	0.09	0.04
<=0.0061	ref		ref		0.99	ref		ref		0.75
0.0062 - 0.0124	5.59 (−3.33 , 14.50)	0.22	5.58 (−3.95 , 15.11)	0.25		3.66 (−11.22 , 18.54)	0.63	6.60 (−7.09 , 20.29)	0.34	
0.0125 - 0.0249	10.91 (1.11 , 20.71)	0.03	12.39 (1.13 , 23.65)	0.03		11.63 (−4.08 , 27.33)	0.15	14.80 (−0.91 , 30.51)	0.06	
>=0.025	6.89 (−5.04 , 18.82)	0.26	8.08 (−5.18 , 21.34)	0.23		3.41 (−13.71 , 20.53)	0.70	15.43 (−1.31 , 32.17)	0.07	
P trend	0.15		0.11			0.42		0.07		
MBzP										

	VAT					SAT				
	Age <65 years N=640		Age >=65 years N=381			Age <65 years N=640		Age >=65 years N=381		
Phthalate biomarker	**Beta (95% CI)**	**P value**	**Beta (95% CI)**	**P value**	**P interaction**	**Beta (95% CI)**	**P value**	**Beta (95% CI)**	**P value**	**P interaction**
Per 1 SD	2.67 (−1.56 , 6.89)	0.22	1.89 (−2.85 , 6.64)	0.43	0.86	4.82 (−2.30 , 11.93)	0.18	4.26 (−2.59 , 11.12)	0.22	0.89
<=6	ref		ref		0.99	ref		ref		0.99
6.1 - 11.8	1.50 (−7.44 , 10.44)	0.74	−0.96 (−10.92 , 8.99)	0.85		6.14 (−8.74 , 21.02)	0.42	5.30 (−9.02 , 19.62)	0.47	
11.9 - 22	5.26 (−4.55 , 15.07)	0.29	5.00 (−6.14 , 16.14)	0.38		10.31 (−5.43 , 26.06)	0.20	10.06 (−5.36 , 25.49)	0.20	
>=22.1	6.94 (−4.54 , 18.42)	0.24	4.34 (−8.07 , 16.74)	0.49		10.28 (−6.34 , 26.90)	0.23	13.47 (−2.26 , 29.21)	0.09	
P trend	0.19		0.37			0.13		0.13		
MCPP										
Per 1 SD	−0.74 (−4.87 , 3.38)	0.72	4.95 (0.41 , 9.49)	0.03	0.57	0.18 (−6.77 , 7.13)	0.96	6.67 (0.09 , 13.24)	0.05	0.56
<=1.7	ref		ref		0.21	ref		ref		0.70
1.8 - 3.1	−2.58 (−11.32 , 6.17)	0.56	9.85 (0.28 , 19.43)	0.04		−2.14 (−16.63 , 12.36)	0.77	6.77 (−6.89 , 20.44)	0.33	
3.2 - 5.5	−3.35 (−12.63 , 5.94)	0.48	5.97 (−4.80 , 16.74)	0.28		−1.41 (−16.24 , 13.41)	0.85	3.88 (−10.74 , 18.51)	0.60	
>=5.6	−2.54 (−13.74 , 8.66)	0.66	13.35 (0.37 , 26.34)	0.04		0.82 (−15.54 , 17.18)	0.92	15.33 (−0.87 , 31.53)	0.06	
P trend	0.62		0.08			0.85		0.19		
ΣDEHP										
Per 1 SD	2.36 (−1.48 , 6.20)	0.23	6.86 (2.02 , 11.69)	0.01	0.50	3.16 (−3.32 , 9.64)	0.34	3.97 (−3.00 , 10.93)	0.26	0.95
<=0.101	ref		ref		0.14	ref		ref		0.48
0.102 - 0.181	3.11 (−5.70 , 11.92)	0.49	0.12 (−10.40 , 10.64)	0.98		7.61 (−7.09 , 22.31)	0.31	−3.31 (−18.14 , 11.52)	0.66	
0.182 - 0.333	−2.27 (−11.07 , 6.53)	0.61	10.24 (−1.02 , 21.51)	0.07		3.51 (−10.75 , 17.77)	0.63	3.82 (−11.47 , 19.10)	0.62	
>=0.334	6.18 (−4.37 , 16.73)	0.25	12.77 (−0.27 , 25.81)	0.06		5.06 (−10.39 , 20.52)	0.52	13.10 (−3.57 , 29.78)	0.12	
P trend	0.57		0.02			0.62		0.16		
MCOP										
Per 1 SD	1.23 (−2.45 , 4.91)	0.51	2.55 (−2.12 , 7.23)	0.28	0.70	0.13 (−6.06 , 6.33)	0.97	3.70 (−3.06 , 10.45)	0.28	0.20
<=2.1	ref		ref		0.74	ref		ref		0.70
2.2 - 3.6	0.82 (−7.78 , 9.42)	0.85	−3.96 (−13.93 , 6.01)	0.44		−8.32 (−22.52 , 5.87)	0.25	−4.35 (−18.69 , 9.98)	0.55	
3.7 - 6.5	4.28 (−5.21 , 13.77)	0.38	3.27 (−7.59 , 14.13)	0.56		5.92 (−9.29 , 21.14)	0.45	1.78 (−13.08 , 16.64)	0.81	
>=6.6	3.41 (−6.79 , 13.62)	0.51	7.04 (−5.62 , 19.71)	0.28		1.87 (−13.54 , 17.28)	0.81	10.87 (−5.77 , 27.50)	0.20	

	VAT					SAT				
	Age <65 years N=640		Age >=65 years N=381			Age <65 years N=640		Age >=65 years N=381		
Phthalate biomarker	**Beta (95% CI)**	**P value**	**Beta (95% CI)**	**P value**	**P interaction**	**Beta (95% CI)**	**P value**	**Beta (95% CI)**	**P value**	**P interaction**
P trend	0.40		0.22			0.25		0.30		
MCNP										
Per 1 SD	1.97 (−1.37 , 5.32)	0.25	2.38 (−2.01 , 6.77)	0.29	0.76	0.22 (−5.43 , 5.88)	0.94	1.58 (−4.77 , 7.93)	0.63	0.67
<=1.6	ref		ref		0.36	ref		ref		0.38
1.7 - 2.7	5.37 (−3.13 , 13.88)	0.22	10.29 (0.50 , 20.08)	0.04		1.70 (−12.57 , 15.98)	0.82	14.50 (0.52 , 28.48)	0.04	
2.8 - 4.8	2.22 (−7.00 , 11.45)	0.64	15.69 (4.31 , 27.06)	0.01		−3.04 (−17.96 , 11.87)	0.69	16.61 (0.89 , 32.34)	0.04	
>=4.9	8.44 (−1.16 , 18.04)	0.09	13.49 (1.79 , 25.18)	0.02		3.88 (−11.21 , 18.97)	0.61	13.38 (−1.82 , 28.58)	0.08	
P trend	0.16		0.02			0.74		0.15		

Adjusted for age, creatinine, race, education, SES index, smoking status, alcohol use, daily energy intake, Healthy Eating Index score, Dietary Modification Trial arm