Associations between urinary organophosphate ester metabolites and measures of adiposity among U.S. children and adults: NHANES 2013–2014

M. Boyle\textsuperscript{a,1}, J.P. Buckley\textsuperscript{b}, L. Quirós-Alcalá\textsuperscript{a,*,1}
\textsuperscript{a}Maryland Institute of Applied Environmental Health, School of Public Health, University of Maryland, College Park, MD, USA
\textsuperscript{b}Johns Hopkins University, Department of Environmental Health & Engineering, Department of Epidemiology, Baltimore, MD, USA

Abstract

Background: Organophosphate esters (OPEs) are synthetic chemicals found in many consumer products, including furniture, electronics, processed foods, and building materials. Emerging in vitro and in vivo studies suggest that OPEs are metabolism disrupting compounds; however, epidemiologic studies investigating their associations with adiposity markers are sparse.

Objective: We examined cross-sectional associations between OPE biomarkers and adiposity measures among U.S. children and adults participating in the National Health and Nutrition Examination Survey (NHANES: 2013–2014).

Methods: Concentrations of five OPE metabolites were quantified in urine: diphenyl phosphate (DPHP), bis(1,3-dichloro-2-propyl) phosphate (BDCPP), bis(2-chloroethyl) phosphate (BCEP), dibutyl phosphate (DBUP), and bis (1-chloro-2-propyl) phosphate (BCPP). We conducted covariate-adjusted logistic and linear regressions to examine associations between log₂-transformed and dichotomized OPE metabolite concentrations and obesity, body mass index (BMI), and waist circumference (WC), separately among 784 children (6–19 years) and 1672 adults (≥20 years). We also assessed heterogeneity of associations by sex.

Results: DBUP concentrations were inversely associated with the prevalence odds of being obese vs. normal weight in children (adjusted Prevalence Odds Ratio, aPOR: 0.82, 95% Confidence Interval, 95% CI: 0.70, 0.95) and adults (aPOR: 0.83, 95% CI: 0.72, 0.96). DBUP was also significantly associated with lower BMI z-scores (β:−0.08, 95% CI:−0.17, 0.01) and WC (β:−0.71, 95% CI: −1.49, 0.07) in children. BCEP concentrations were associated with increased prevalence odds of being overweight vs. normal weight (aPOR: 1.15, 95% CI: 1.01, 1.30).

This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/BY-NC-ND/4.0/).

*Corresponding author at: 2234U School of Public Health Building, University of Maryland, College Park, MD 20742, USA.
lquiros@umd.edu (L. Quirós-Alcalá).

1 Both authors contributed equally.

Financial interests
The authors declare no competing financial interests.

Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2019.03.055.
1.32) among children; similar, albeit not statistically significant, relationships were observed with other child adiposity outcomes. Among adults, detectable BCPP concentrations were associated with increased prevalence odds of being obese vs. normal weight (aPOR: 1.70, 95% CI: 1.21, 2.38) and having a high vs. normal WC (aPOR: 1.51, 95% CI: 1.11, 2.07) as well as higher BMI (β: 1.31, 95% CI: 0.30, 2.33). Other OPE metabolites were not consistently associated with adiposity measures among adults. Although associations of BCPP exposure with adiposity outcomes were generally inverse among boys, but not girls, we did not observe consistent evidence of sexually-dimorphic associations for other OPE metabolites.

**Conclusions:** Exposure to select OPEs may be differentially associated with body size among children and adults. Given the cross-sectional design of the present study, future prospective studies are needed to confirm these findings.

**Keywords**
Organophosphate esters; Adiposity; Body mass index; Flame retardants; Children; Adults

---

1. **Introduction**

Organophosphate esters (OPEs) are synthetic chemicals found in consumer products, including furniture, electronics, plastics, building materials, and processed foods (Ballesteros-Gómez et al., 2014; Bello et al., 2018, 2010; Kajiwara et al., 2011; Poma et al., 2017; Stapleton et al., 2009; Wang et al., 2017; Yang et al., 2019). National biomonitoring data indicate that exposure to OPEs is widespread in the U.S. general population (Ospina et al., 2018). While there are various uses for OPEs (Supplementary Material, Table S1), several of them were introduced as replacements for polybrominated diphenyl ether flame retardants (PBDEs), which were voluntarily withdrawn from the U.S. market in the mid-2000s due to concerns about toxicity, bioaccumulation, and environmental persistence (National Institute of Environmental Health Sciences, n.d.). However, there are emerging concerns that OPEs may not be safer alternatives given the lack of toxicity testing requirements for manufacturers (Hansson et al., 2011; Howard, 2014), their structural similarity to neurotoxic organophosphorus pesticides (Dishaw et al., 2011), their endocrine disrupting properties (Kojima et al., 2013; Liu et al., 2012a; Schang et al., 2016), and toxicological evidence on carcinogenic potential (Faust and Meehan, 2011).

OPEs are also hypothesized to be metabolism-disrupting compounds (Heindel et al., 2017; Patisaul et al., 2013), which are chemicals that interfere with energy homeostasis, lipid metabolism, satiety, and insulin sensitivity leading to metabolic dysregulation or increased body fat (Heindel et al., 2017, 2015). Metabolism-disrupting compounds are increasingly recognized to play a role in obesity, as established risk factors (e.g., poor diet, physical inactivity, and genetic predisposition) do not fully account for the rapid increase in obesity prevalence rates. Consequently, identifying contributing environmental factors may inform mitigation strategies to help reduce the burden of obesity estimated to affect 17% of children and 35% of adults in the U.S. (Hales et al., 2018; Heindel and vom Saal, 2009; Keith et al., 2006; Ogden et al., 2014).
Several biological mechanisms by which OPEs could alter metabolism have been proposed. Emerging laboratory and human evidence indicates that OPEs may interfere with sex steroid and thyroid hormones (Farhat et al. 2013; Kim et al. 2015; Krivoshiev et al. 2016; Liu et al. 2012b; Meeker and Stapleton 2010; Preston et al. 2017; Schang et al. 2016; Wang et al. 2015; Zhang et al., 2016a), peroxisome proliferator-activated receptors (PPARs) (Belcher et al. 2014; Fang et al. 2015; Hu et al. 2017; Kojima et al. 2013; Pillai et al. 2014), and induce oxidative stress (Arukwe et al. 2016; Chen et al. 2015; Jin et al. 2016; Lu et al. 2017; Yan et al. 2017). These biologic pathways serve well-known roles in adipose tissue development and obesity risk. Two independent studies also demonstrated that perinatal exposure to select OPEs in rodents increases body mass, fat mass, fasting glucose, leptin, and total energy intake (Green et al. 2017; Patisaul et al. 2013).

Despite accumulating in vitro and in vivo evidence, epidemiologic studies evaluating relationships between OPE exposures and adiposity are extremely limited. Two cross-sectional studies examining predictors of OPE biomarker concentrations in pregnant women reported positive associations with body mass index (BMI) (Hoffman et al. 2017; Romano et al. 2017). However, these studies were not designed to assess etiologic relationships, did not account for known obesity risk factors, and did not include children and men. To address existing data gaps, the present study aimed to examine associations between urinary bio-marker concentrations of five OPEs and markers of adiposity in a U.S. population-based sample of children and adults.

2. Methods

2.1. Data source and study participants

Our study sample included children 6 to 19 years and adults ≥20 years who participated in the 2013–2014 National Health and Nutrition Examination Survey (NHANES). The NHANES is a cross-sectional population-based, multistage, stratified survey of the civilian, non-institutionalized U.S. general population conducted in 2-year cycle waves. The survey is conducted by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC) to assess the general health and nutritional status of the U.S. population. To ensure a representative sample of the U.S. general population, select subgroups including Mexican Americans, non-Hispanic blacks, and individuals of low socioeconomic status, are oversampled. All NHANES protocols were reviewed by the NCHS research ethics board and written informed consent and child assent was obtained prior to any data collection (Zipf et al. 2013). Publicly-available information on study participants was obtained from questionnaires, laboratory, diet, and physical examination components of the NHANES. Selection of the 2013–2014 cycle years was based on availability of OPE bio-marker data; OPE data was only available on a random one-third subset of NHANES participants 6 years of age and older during this period. Pregnant women (n = 16) were excluded from our analyses since pregnancy can alter bodyweight and xenobiotic metabolism (Abduljalil et al. 2012).
2.2. Exposure assessment of organophosphate esters

Concentrations of the following 9 OPE metabolites of 10 parent compounds were quantified in spot urine samples provided by study participants: diphenyl phosphate (DPHP, metabolite of triphenyl phosphate and 2-ethylhexyl diphenyl phosphate); bis(1,3-dichloro-2-propyl) phosphate [BDCPP, metabolite of tris(1,3-dichloro-2-propyl) phosphate]; bis(1-chloro-2-propyl) phosphate [BCPP, metabolite of tris(1-chloro-2-propyl)phosphate]; bis(2-chloroethyl) phosphate [BCEP, metabolite of tris(2-chloroethyl) phosphate]; di-p-cresyl phosphate (DpCP, metabolite of tri-p-cresyl phosphate); di-o-cresyl phosphate (DoCP, metabolite of tri-o-cresylphosphate); dibutyl phosphate (DBUP, metabolite of tri-n-butyl phosphate); dibenzyl phosphate (DBzP, metabolite of tri-benzyl-phosphate); and 2,3,4,5-tetrabromobenzoic acid (TBBA, metabolite of 2-ethylhexyl-2,3,4,5-tetrabromobenzoate).

OPE metabolites were quantified using a validated laboratory method described in detail elsewhere (Jayatilaka et al. 2017). Briefly, the analytical method entailed using solid-phase extraction coupled with isotope dilution high-performance liquid chromatography-tandem mass spec-trometry after enzymatic hydrolysis of OPE conjugates. Limits of detection (LOD) for the OPE metabolites were: 0.16 μg/L for DPHP, 0.11 μg/L for BDCPP, 0.10 μg/L for BCPP, 0.08 μg/L for BCEP, and 0.05 μg/L for DpCP, DoCP, DBUP, DBzP, and TBBA.

Urinary creatinine concentrations were also measured in urine samples using the Jaffe rate reaction with a CX3 analyzer (Beckman Instruments, Brea, CA, USA) to account for dilution-dependent sample variation in biomarker concentrations. For the present analyses, we excluded OPEs that were not widely detected in urine samples (i.e., detection frequency < 20%), including DpCP, DoCP, DBzP, and TBBA.

2.3. Adiposity measures

Anthropometric measurements for study participants, including height (m), weight (kg), and waist circumference (cm) were collected by trained technicians following standard procedures (Lohman et al. 1988). Body mass index (BMI) was calculated as the ratio of weight in kilograms to height in meters squared (kg/m^2). For children, we calculated age- and sex-standardized BMI percentiles and BMI z-scores (i.e., the number of standard deviations by which a child differs from the average BMI of a reference pediatric population of the same age and sex) in accordance with CDC guidelines using the zanthro function in Stata/SE 14.2 for Mac (StataCorp, College Station, TX) (Vidmar et al. 2004). We then used age- and sex-standardized BMI percentiles to classify children as underweight (< 5th BMI percentile), normal weight (5th ≤ BMI percentile ≤ 85th), overweight (85th < BMI percentile ≤ 95th) or obese (≥95th BMI percentile). Similarly, we used BMI to classify adults as underweight (BMI ≤ 18.5 kg/m^2), normal weight (18.5 ≤ BMI < 25.0 kg/m^2), overweight (25.0 ≤ BMI < 30.0 kg/m^2), or obese (BMI ≥ 30.0 kg/m^2). For adults, we also generated waist circumference categories (normal vs. high) in accordance with guidelines developed by the North American Association for the Study of Obesity and the National Heart, Lung, and Blood Institute (National Institutes of Health; National Heart, Lung, 2000).

2.4. Statistical analysis

We calculated descriptive statistics for concentrations of OPE metabolites detected among children and adults, including weighted geometric means (GMs), percentiles, and
Biomarker concentrations of frequently detected OPE metabolites (i.e., DPHP, BDCPP, BCEP, and DBUP) were log-normally distributed and modeled as continuous log\(_2\)-transformed variables in subsequent statistical tests and models. To increase statistical power and precision of effect estimates, biomarker concentrations below the LOD were replaced with LOD/\(\sqrt{2}\) for OPE metabolites detected in \(\geq 80\%\) of the study participants (Cole et al. 2009; Hornung and Reed 1990). To assess if concentrations for frequently detected OPE metabolites differed based on select demographic characteristics (e.g., gender; children vs. adults; normal weight vs. overweight/obese), we conducted linear regressions where the independent variable was the demographic characteristic of interest and the dependent variable was the OPE metabolite concentration. These models were also adjusted for urinary creatinine to adjust for dilution; results were similar when conducting separate \(t\)-tests using log\(_2\)-transformed creatinine-corrected and uncorrected OPE biomarker concentrations (not shown). We conducted Chi-square tests to assess demographic differences between participants who were included vs. excluded in our analysis to assess the potential for selection bias. To estimate correlations between OPE biomarker concentrations and account for the complex survey design, we calculated Kendall’s Tau rank correlation coefficients using the somersd package in Stata (Newson, 1998).

To examine associations between OPE biomarker concentrations and continuous measures of adiposity, including BMI z-score (children), BMI (adults), and waist circumference, we conducted crude and covariate-adjusted linear regression models. We also conducted crude and covariate-adjusted logistic regression models for dichotomized outcomes, including obese compared to normal weight, overweight compared to normal weight, and, for adults, normal compared to high waist circumference. OPE metabolites with a detection frequency (DF) \(\geq 80\%\) (i.e., DPHP, BDCPP, BCEP, and DBUP) were modeled as continuous log\(_2\)-transformed independent variables in separate models as previously specified. Because BCPP was detected in approximately 67\% and 58\% of child and adult urine samples, respectively, BCPP was modeled as a dichotomous exposure variable (< LOD vs. \(\geq\) LOD).

All crude and covariate-adjusted regression models included log\(10\) transformed urinary creatinine concentrations to account for urinary dilution as recommended by Barr et al. (Barr et al. 2005). Models using creatinine-corrected concentrations did not materially affect our results (not shown). Adjusted models included variables selected using a directed acyclic graph (DAG) to identify potential confounders associated with both OPE exposure and adiposity. Demographic variables included age (years); gender; race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, and Other, which included other Hispanic, other races, and multi-racial); and poverty income ratio (\(\leq 1.85\), > 1.85 to < 3.50, and > 3.50 (Johnson et al. 2013). We also included known predictors of adiposity to increase precision of our effect estimates and rule out potential residual confounding given that information on sources of OPE exposure is sparse. These additional variables included screen time, physical activity, and diet. The screen time variable included time spent watching television or videos, playing video games, and using a computer and was coded as < 2 h/day and \(\geq 2\) h/day (American Academy of Pediatrics. Committee on Public Education 2001). Using the Healthy People 2020 guidelines, we coded physical activity for adults as inactive, moderate, or vigorous based on self-reported activity levels (U.S. Department of Health and Human Services 2008). Data on self-reported physical activity levels was only considered for adults.
as this information was not available for children under 12 years. We additionally included several variables to address general dietary habits and behaviors for both children and adults that could impact an individual’s adiposity, including the number of meals from fast food or pizza restaurants consumed in the past seven days, the number of ready-to-eat foods consumed in the past 30 days, and the number of frozen meals or pizza consumed in the past 30 days.

Because the effects of metabolism-disrupting compounds may vary by sex (Heindel et al. 2017), we also evaluated effect measure modification (EMM) by sex using an augmented product term approach (Buckley et al. 2017). This approach entailed including cross product terms between gender and biomarker concentration as well as between gender and each covariate in the model (Buckley et al. 2017; Quirós-Alcalá et al. 2018).

In sensitivity analyses, we examined dose-response relationships. For frequently detected OPE metabolites (DPHP, BDCPP, BCEP, and DBUP) we ran models using creatinine-adjusted quartiles of exposure. To assess potential dose-response relationships for BCPP, which was less frequently detected, we modeled concentrations as a three-level categorical variable (< LOD, below the median of detected concentrations, and above the median of detected concentrations). These models were run overall and stratified by sex for both children and adults and were considered secondary analyses due to the large number of statistical tests.

We applied NCHS-created sampling weights, strata, and primary sampling units in our statistical analyses in accordance with NCHS guidelines to yield robust standard errors and unbiased point estimates, and to account for the complex, stratified multistage probability sample design of NHANES. All analyses were conducted using Stata/SE 14.2 for Mac (StataCorp, College Station, TX) and the threshold for statistical significance was set at $p < 0.05$ for main effects and at $p < 0.10$ for effect measure modification by sex. Given our target outcome measures are not completely independent of one another and the exploratory nature of our study, we did not perform adjustment for multiple comparisons.

3. Results

A total of 820 children and 1702 adults had complete data available on OPEs and our target outcomes (BMI and waist circumference). The proportion of participants excluded from our analyses due to missing data was 4% for children ($n = 36$) and 2% for adults ($n = 30$). Thus, our final study sample included 784 children and 1672 adults with complete data on OPE biomarkers, target outcomes, and covariates. We did not observe any differences in demographic characteristics between individuals who were included in our analyses compared to those who were excluded due to missing data (not shown).

3.1. Participant characteristics

Demographic characteristics for children and adults included in our analysis are presented in Table 1. A little over half of the children and nearly two-thirds of adults self-identified as non-Hispanic white. Over half of the participants (62.1% of children, 59.0% of adults) reported consuming at least one fast food meal in the prior week. A little over one-third
(34.0%) of children and the majority of adults (69.3%) were either overweight or obese based on their BMI.

### 3.2. OPE biomarker concentrations

Overall, four of the five OPE metabolites included in our analysis were detected in ≥80% of children and adults (Table 2). BCPP was less frequently detected among children (DF = 67%) and adults (DF = 58%) compared to other OPE metabolites. Geometric mean (GM) concentrations of DPHP, BDCPP, BCEP, and DBUP were significantly higher (p < 0.003) in children than in adults. Among children, GM concentrations of DPHP and BDCPP were significantly higher in females compared to males (DPHP females: 1.69 μg/L vs. males 1.37 μg/L, p = 0.001; BDCPP females: 1.89 μg/L vs. males 1.57 μg/L, p = 0.02); while the opposite was observed for BDCPP among adults (males: 0.79 μg/L vs. females: 0.65 μg/L, p = 0.03; not shown). Biomarker concentrations of the four OPE metabolites widely detected (DPHP, BDCPP, BCEP, and DBUP) were weakly to moderately correlated (p < 0.05) with Kendall τ correlation coefficients ranging from 0.23 to 0.38 (Supplemental Material, Table S2).

For children, GM concentrations of DBUP were higher among normal vs. obese weight children (DBUP: 0.231 μg/L vs. 0.228 μg/L, p = 0.03; Supplemental Material, Table S3).

### 3.3. Associations between OPE biomarkers and adiposity measures among children age 6–19 years

Results from covariate-adjusted regression models for children are presented in Table 3. We observed a statistically significant inverse association between log₂-transformed DBUP concentrations and the prevalence odds of being obese vs. normal weight (adjusted Prevalence Odds Ratio, aPOR: 0.82, 95% Confidence Interval, 95% CI: 0.70, 0.95). Similar inverse associations, albeit not statistically significant, were observed when assessing BMI z-scores (β: −0.08, 95% CI: −0.17, 0.01) and WC (β: −0.71, 95% CI: −1.49, 0.07).

In sensitivity analyses, we observed a borderline and statistically significant inverse dose-response trend when modeling DBUP concentrations in quartiles for associations with BMI z-scores (p_trend = 0.05) and waist circumference (p_trend = 0.02; see Supplemental Material, Table S4a). We also observed increased prevalence odds of being overweight versus normal weight for every doubling of BCEP concentrations (aPOR: 1.15, 95%, CI: 1.01, 1.32) among all children; however, no statistically significant associations were observed with other outcomes. Overall, we did not observe statistically significant findings or strong evidence of non-linear dose-response trend among all children with other OPE metabolites (BCPP, BDCPP, and DPHP).

We observed suggestive evidence of EMM by sex for associations between detectable concentrations of BCPP and BMI z-scores (p_EM = 0.03) whereby detectable concentrations of BCPP were inversely associated with BMI z-scores among boys but not girls (BMI z-scores = β boys: −0.45, 95% CI: −0.80, −0.09 vs. β girls: 0.18, 95% CI: −0.21, 0.57). Overall, similar patterns (albeit generally not statistically significant) were observed for most outcomes and when modeling BCPP as a three-level categorical variable (see Supplementary Material, Table S4b). For other OPE metabolites, we did not observe strong and consistent...
evidence of EMM by sex; results were not robust across outcomes (Table 4) or when modeling exposures as categories (Supplementary Material, Table S4a–b).

3.4. Associations between OPE metabolites and adiposity measures among adults age 20 years and older

Among adults, those with detectable BCPP concentrations had increased prevalence odds of being obese vs. normal weight (aPOR: 1.70, 95% CI: 1.21, 2.38) and having high vs. normal WC (aPOR: 1.51, 95% CI: 1.11, 2.07) compared to those with undetectable concentrations (Table 4). Similarly, we observed positive associations among those with detectable BCPP metabolite concentrations when BMI was modeled as a continuous dependent variable ($\beta$: 1.31, 95% CI: 0.30, 2.33). Additionally, we observed a monotonic increasing trend of associations for categories of BCPP biomarker concentrations and several outcomes ($p_{\text{trend}} \leq 0.04$, Supplemental Material, Table S5a). For example, compared to adults with BCPP concentrations < LOD, we observed increased prevalence odds of being obese vs. normal weight among those with BCPP concentrations below the median of detectable concentrations (aPOR: 1.88, 95% CI: 1.17, 3.03) and above the median of detectable concentrations [aPOR: 2.07, 95% CI: 1.67, 2.56; ($p_{\text{trend}} < 0.001$)].

Similar to results observed among children, DBUP biomarker concentrations were inversely, albeit generally not statistically significantly, associated with adiposity outcomes [(e.g., obese vs. normal weight, aPOR: 0.83, 95% CI: 0.72, 0.96; BMI (kg/m$^2$), $\beta$: −0.46, 95% CI: −0.95, 0.03; high vs. normal WC, aPOR: 0.93, 95% CI: 0.81, 1.06); Table 4]. We did not observe any consistent statistically significant associations with other OPEs or consistent evidence of dimorphic associations by sex. In addition, we did not observe evidence of non-linear dose-response relationships overall or by sex (Table 4 and Supplemental Material, Table S5b).

4. Discussion

In the present study, we examined cross-sectional associations between several adiposity measures and urinary biomarker concentrations of five OPE metabolites among children and adults from a representative sample of the U.S. general population. Similar to prior studies (Butt et al. 2016, 2014; Carignan et al. 2013; Cequier et al. 2015; He et al. 2018a; Saillenfait et al. 2018; Van Den Eede et al. 2015), several OPE metabolites were frequently detected in urine samples and GM concentrations were generally higher among children compared to adults and among females compared to males. Among children, we observed a significant inverse association between DBUP biomarker concentrations and the prevalence odds of being obese vs. normal weight. Similar inverse trends were observed with BMI z-scores and waist circumference. Among adults, we observed increased BMI and increased prevalence odds of being obese and having a high waist circumference for individuals with detectable levels of BCPP and significant positive dose-response trends. With the exception of BCPP in children, we did not observe consistent and robust evidence of dimorphic effects by sex for most OPE biomarkers among children or adults.

While laboratory studies of OPEs and metabolic outcomes are limited and have focused on prenatal or early postnatal exposures, there is some indication from in vivo and in
vitro studies that OPEs may be associated with adiposity. For example, an in vitro study of tributyl phosphate (TBUP) and tris (2-butoxyethyl) phosphate (TBOEP) administered at high doses reported high PPAR γ ligand binding potential, indicating that these OPEs may promote the development of obesity (Fang et al. 2015). Patisaul et al. reported that both prenatal and early postnatal exposure at environmentally-relevant levels to Firemaster 550 (FM 550), a flame retardant mixture which contains TBUP, was significantly associated with elevated body weight in both male and female rats (Patisaul et al. 2013). In another rat study, perinatal exposure to triphenyl phosphate (TPHP), a component of FM 550, was significantly associated with increased body weight, which became more pronounced with age (Green et al. 2017). Pillai et al. also reported that in vitro exposure to Firemaster 550 initiated adipocyte differentiation (Pillai et al. 2014).

No epidemiologic studies to date have examined associations between exposure to OPEs and adiposity markers, while controlling for important confounders. Still, two U.S. studies in pregnant women reported positive correlations of select OPE biomarker concentrations with pre-pregnancy BMI and weight (Romano et al. 2017; Hoffman et al., 2017). In a small study of 59 pregnant women in Rhode Island, Romano and colleagues reported that biomarker concentrations of BDCPP and DPHP were both significantly associated with higher pre-pregnancy maternal BMI, while BCEP and BDCPP were significantly associated with higher maternal pre-pregnancy weight (Romano et al. 2017). Hoffman et al. (2017) also reported that in a cohort of 349 pregnant women from North Carolina participating in the Pregnancy Infection and Nutrition Study, women classified as overweight or obese prior to pregnancy had higher biomarker concentrations of BDCPP and DPHP compared to women classified as normal weight. In the present study, higher urinary BCPP metabolite concentrations were associated with increased BMI and WC among adults, and with increased prevalence odds of being obese vs. normal weight after controlling for several covariates, including physical activity and dietary behaviors.

However, we did not observe any significant adjusted associations between adiposity markers and BDCPP, DPHP or BCEP biomarker concentrations. Compared to adults in our study sample, median concentrations of DPHP and BDCPP were 1.5 to 2.7 times higher in both cohorts of pregnant women, while median BCEP concentrations were comparable to those reported in pregnant women from Rhode Island (Romano et al. 2017; Hoffman et al., 2017). Comparisons across these studies should be interpreted with caution as pregnancy can alter xenobiotic metabolism (Abduljalil et al. 2012).

In children, we did not observe a positive association between BCPP biomarker concentrations and adiposity markers as was observed among adults. It is not immediately clear why BCPP associations differed between children and adults, though differing biological susceptibility or biomarker metabolism by age, residual confounding, low power due to small sample size, or spurious findings may have played a role. We observed statistically significant (or borderline significant) inverse relationships with DBUP and adiposity markers among children. This inverse trend was also observed among adults, albeit associations were generally not statistically significant. While speculative, OPE bioaccumulation in adipose tissue could lead to decreased urinary biomarker concentrations and explain the general inverse trends observed among children and adults for DBUP.
Tributyl phosphate, the parent compound of DBUP, has been detected in human adipose tissue as have other select OPEs like tris(1,3-dichloro-2-propyl)phosphate (TDCPP) (LeBel et al. 1989). It is plausible that different OPEs have varying pharmacokinetic processes controlling metabolism and storage that would affect interpretation of our findings. Further studies evaluating bioaccumulation and metabolism of OPEs in humans are needed to determine how these factors, including differences in metabolism based on age, gender, and adiposity, may affect biomarker interpretation. Alternatively, we cannot rule out spurious findings.

It is unclear whether the relationship between OPEs and adiposity among children is sexually dimorphic given that results for effect measure modification were generally not consistent across outcomes or robust to model adjustments for most OPEs. To our knowledge, no previous studies have assessed sexually dimorphic associations between postnatal exposure to OPEs and measures of adiposity, so further research is currently needed to determine if the potential effects of OPEs differ by sex.

Our findings should be interpreted with caution in light of study limitations. First, our cross-sectional study design precludes us from adequately assessing temporality of associations. We relied on a single spot urine sample to assess exposure to OPEs, which may not accurately represent long-term exposures to some OPEs. Limited experimental studies suggest that select OPEs are quickly metabolized and excreted in urine with half-lives of several hours (Burka et al. 1991; Carignan et al. 2016; Lynn et al. 1981; Nomeir et al. 1981). Studies examining temporal variability of OPE urinary biomarkers (Supplemental Material, Table S8), including DPHP, BCDPP, and BCEP have generally reported moderate to strong intraclass correlation coefficients (ICC = 0.50–0.81) among pregnant women and non-pregnant adults in repeated urine samples collected within about 1 week up to 12 months (Cequier et al. 2015; Gibson et al. 2018; Hoffman et al. 2015, 2014; Meeker et al. 2013; Romano et al. 2017). However, some studies have reported poor agreement across multiple urine measurements for some OPE bio-markers. For example, a study of 51 office workers in Massachusetts reported poor agreement across three measurements of urinary DPHP collected over the course of ~12 months (ICC = 0.19, 95% CI: 0.06, 0.45 (Preston et al. 2017), while another study conducted on adult men over a 3-month period reported moderate agreement between DPHP concentrations (ICC = 0.51, 95% CI: 0.32, 0.70) (Meeker et al. 2013). Altogether, findings suggest that reliability for some OPE metabolites may be poor over longer periods for select OPEs. Thus, it is possible that concentrations measured at the time of outcome assessment in our cross-sectional study do not represent exposures that led to accumulation of body fat, and we cannot rule out reverse causation. For example, obesity may lead to increased OPE concentrations if obese individuals consume more OPE-contaminated foods or spend more time in contact with OPE-containing furniture than lean individuals.

While little is known about dietary predictors of urinary OPE concentrations, findings from two small studies suggest that intake of fresh foods, certain vegetables, citrus fruit, eggs, or meats may be associated with lower concentrations of several OPE metabolites (Romano et al. 2017; Thomas et al. 2017). OPEs have been measured in food packaging materials (Wang and Kannan 2018) and food samples including seafood, meat, dairy, fats, oils, grains, rice,
cheese, cereals, pastries, sugar/sweets, vegetables, and beverages (Ding et al. 2018; He et al. 2018b; Poma et al. 2018, 2017; Wang and Kannan 2018; Zhang et al., 2016b). Notably, Poma et al. (Poma et al. 2018) reported that 89% of the processed foods assessed contained OPEs as compared with only 11% of non-processed foods. While we tried to account for several diet variables, some of which reflect consumption of processed foods, and other important covariates and confounders, we relied on information available in NHANES and cannot rule out unmeasured or residual confounding.

Despite these limitations, our study has several strengths. To our knowledge, this is the first study to examine the relationship between OPE biomarkers and adiposity measures among children or non-pregnant adults. We also examined associations in a large nationally representative sample of the U.S. general population. In addition, we examined associations between OPE biomarkers and adiposity outcomes while controlling for important confounders, including several dietary behavior and physical activity covariates. We also found similar results for several adiposity markers.

In summary, our study suggests that exposure to select OPEs may be differentially associated with increased or decreased general and central obesity in children and adults. Given the cross-sectional design of the present study, our findings must be interpreted with caution as we were unable to measure OPE concentrations prior to the development of adiposity outcomes. Future prospective epidemiologic studies and laboratory studies designed to elucidate biological mechanisms for OPE-induced metabolic changes are needed. Human studies examining additional susceptible periods, including gestation, are particularly important as there is substantial evidence demonstrating that early life exposures to endocrine disrupting compounds could alter adipogenesis and energy balance leading to changes in obesity risk (Grün and Blumberg 2006; Heindel et al. 2017).

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

**Acknowledgements**

Lesliam Quirós-Alcalá was supported by a NHLBI Career Development Award (K01HL138124). Jessie Buckley received funding from a Mid-Atlantic Nutrition Obesity Research Center Pilot & Feasibility Grant (P30DK072488). The findings and conclusions in this manuscript are those of the authors and do not necessarily represent the official position or views of the NIH.

**Abbreviations:**

- **BCPP**: bis(1-chloro-2-propyl) phosphate
- **BCEP**: bis(2-chloroethyl) phosphate
- **BDCPP**: bis(1,3-dichloro-2-propyl) phosphate
- **BMI**: body mass index
- **CDC**: centers for disease control and prevention
CI  confidence Interval
DBzP  dibenzyl phosphate
DBUP  dibutyl phosphate
DF  detection frequency
DpCP  di-peresyl phosphate
DPHP  diphenyl phosphate
DoCP  di-o-cresyl phosphate
GM  geometric mean
ICC  intraclass correlation coefficient
NCHS  National Center for Health Statistics
NHANES  National Health and Nutrition Examination Survey
OPEs  organophosphate esters
PBDEs  polybrominated diphenyl ether flame retardants
TBBA  2,3,4,5-tetrabromobenzoic acid
WC  waist circumference

References

Abduljalil K, Furness P, Johnson TN, Rostami-Hodjegan A, Soltani H, 2012. Anatomical, physiological and metabolic changes with gestational age during Normal pregnancy. Clin. Pharmacokinet 51, 365–396. 10.2165/11597440-000000000-00000. [PubMed: 22515555]

American Academy of Pediatrics. Committee on Public Education, 2001. American Academy of Pediatrics: children, adolescents, and television. Pediatrics 107, 423–426. [PubMed: 11158483]

Arukwe A, Carteny CC, Eggen T, 2016. Lipid peroxidation and oxidative stress responses in juvenile salmon exposed to waterborne levels of the organophosphate compounds tris(2-butoxyethyl)- and tris(2-chloroethyl) phosphates. J. Toxicol. Environ. Heal. Part A 79, 515–525. 10.1080/15287394.2016.1171978.

Ballesteros-Gómez A, Brandsma SH, De Boer J, Leonards PEG, 2014. Analysis of two alternative organophosphorus flame retardants in electronic and plastic consumer products: resorcinol bis-(diphenylphosphate) (PBDPP) and bisphenol A bis (diphenylphosphate) (BPA-BDPP). Chemosphere 116, 10–14. 10.1016/j.chemosphere.2013.12.099. [PubMed: 24556545]

Barr DB, Wilder LC, Caudill SP, Gonzalez AJ, Needham LL, Pirkle JL, 2005. Urinary creatinine concentrations in the U.S. population: implications for urinary biologic monitoring measurements. Environ. Health Perspect 113, 192–200. 10.1289/ehp.7337. [PubMed: 15687057]

Belcher SM, Cookman CJ, Patisaul HB, Stapleton HM, 2014. In vitro assessment of human nuclear hormone receptor activity and cytotoxicity of the flame retardant mixture FM 550 and its triarylphtate and brominated components. Toxicol. Lett 228, 93–102. 10.1016/j.toxlet.2014.04.017. [PubMed: 24786373]

Bello A, Quinn MM, Perry MJ, Milton DK, 2010. Quantitative assessment of airborne exposures generated during common cleaning tasks: a pilot study. Environ. Heal. a Glob. access Sci source 9, 76. 10.1186/1476-069X-9-76.
Bello A, Carignan CC, Xue Y, Stapleton HM, Bello D. 2018. Exposure to organo-phosphate flame retardants in spray polyurethane foam applicators: role of dermal exposure. Environ. Int 113, 55–65. 10.1016/j.envint.2018.01.020. [PubMed: 29421408]

Buckley JP, Doherty BT, Keil AP, Engel SM. 2017. Statistical approaches for estimating sex-specific effects in endocrine disruptors research. Environ. Health Perspect 125. 10.1289/EHP334.

Burka LT, Sanders JM, Herr DW, Matthews HB. 1991. Metabolism of tris(2-chloroethyl) phosphate in rats and mice. Drug Metab. Dispos 19, 443–447. [PubMed: 1676651]

Butt CM, Congleton J, Hoffman K, Fang M, Stapleton HM. 2014. Metabolites of Organophosphate Flame Retardants and 2-Ethylhexyl Tetrabromobenzoate in Urine from Paired Mothers and Toddlers. 10.1021/es5025299.

Butt CM, Hoffman K, Chen A, Lorenzo A, Congleton J, Stapleton H, Author EI, 2016. Regional comparison of organophosphate flame retardant (PFRs) urinary metabolites and Tetrabromobenzoic acid (TBBA) in mother-toddler pairs from California and New Jersey HHS public access Author manuscript. Env. Int 94, 627–634. 10.1016/j.envint.2016.06.029. [PubMed: 27397928]

Carignan CC, McClean MD, Cooper EM, Fraser AJ, Heiger-Bernays W, Stapleton HM, Webster TF. 2013. Predictors of tris(1,3-dichloro-2-propyl) phosphate metabolite in the urine of office workers. Environ. Int 55, 56–61. 10.1016/j.envint.2013.02.004. [PubMed: 23523854]

Carignan CC, Fang M, Stapleton HM, Heiger-Bernays W, McClean MD, Webster TF. 2016. Urinary biomarkers of flame retardant exposure among collegiate U.S. gymnasts. Environ. Int 94, 362–368. 10.1016/j.ENVINT.2016.06.030. [PubMed: 27395335]

Cequier E, Sakhi AK, Marcé RM, Becher G, Thomsen C. 2015. Human exposure pathways to organophosphate triesters - a biomonitoring study of mother-child pairs. Environ. Int 75, 159–165. 10.1016/j.envint.2014.11.009. [PubMed: 25461425]

Chen G, Jin Y, Wu Y, Liu L, Fu Z. 2015. Exposure of male mice to two kinds of organophosphate flame retardants (OPFRs) induced oxidative stress and endocrine disruption. Environ. Toxicol. Pharmacol 40, 310–318. 10.1016/j.etap.2015.06.021. [PubMed: 26183808]

Cole SR, Chu H, Nie L, Schisterman EF. 2009. Estimating the odds ratio when exposure has a limit of detection. Int. J. Epidemiol 38, 1674–1680. 10.1093/ije/dyp269. [PubMed: 19667054]

Ding J, Deng T, Xu M, Wang S, Yang F. 2018. Residuals of organophosphate esters in foodstuffs and implication for human exposure. Environ. Pollut 233, 986–991. 10.1016/j.envpol.2017.09.092. [PubMed: 29037495]

Dishaw LV, Powers CM, Ryde IT, Roberts SC, Seidler FJ, Slotkin TA, Stapleton HM, 2011. Is the PentaBDE replacement, tris (1,3-dichloro-2-propyl) phosphate (TDCPP), a developmental neurotoxicant? Studies in PC12 cells. Toxicol. Appl. Pharmacol 256, 281–289. 10.1016/j.taap.2011.01.005. [PubMed: 21255595]

Fang M, Webster TF, Stapleton HM. 2015. Activation of human peroxisome proliferator-activated nuclear receptors (PPARγ1) by semi-volatile compounds (SVOCs) and chemical mixtures in indoor dust. Environ. Sci. Technol 49, 10057–10064. 10.1021/acs.est.5b01523. [PubMed: 26172262]

Farhat A, Crump D, Chiu S, Williams KL, Letcher RJ, Gauthier LT, Kennedy SW. 2013. In Ovo effects of two organophosphate flame retardants—TCPP and TDCPP—on pipping success, development, mRNA expression, and thyroid hormone levels in chicken embryos. Toxicol. Sci 134, 92–102. 10.1093/toxsci/kft100. [PubMed: 23629516]

Faust JB, Meehan L. 2011. Evidence on the Carcinogenicity of Tris(1,3-dichloro-2-propyl) Phosphate. California Environmental Protection Agency. Reprod. Cancer Hazard Assess. Branch

Gibson EA, Stapleton HM, Calero L, Holmes D, Burke K, Martínez R, Cortes B, Nematollahi A, Evans D, Herbstritt JB. 2018. Flame retardant exposure assessment: findings from a behavioral intervention study. J. Expo. Sci. Environ. Epidemiol. 10.1038/s41370-018-0049-6.

Green AJ, Graham JL, Gonzalez EA, La Frano MR, Petropoulou SSE, Park JS, Newman JW, Stanhope KL, Havel PJ, La Merrill MA. 2017. Perinatal triphenyl phosphate exposure accelerates type 2 diabetes onset and increases adipose accumulation in UCD-type 2 diabetes mellitus rats. Reprod. Toxicol 68, 119–129. 10.1016/j.reprotox.2016.07.009. [PubMed: 27421578]

Environ Int. Author manuscript; available in PMC 2020 June 01.
Grün F, Blumberg B, 2006. Environmental Obesogens: Organotins and endocrine disruption via nuclear receptor signaling. Endocrinology 147, s50–s55. 10.1210/en.2005-1129. [PubMed: 16690801]

Hales CM, Fryar CD, Carroll MD, Freedman DS, Ogden CL, 2018. Trends in obesity and severe obesity prevalence in US youth and adults by sex and age, 2007–2008 to 2015–2016. JAMA 319, 1723. 10.1001/jama.2018.3060. [PubMed: 29570750]

Hansson SO, Molander L, Rudén C, 2011. The substitution principle. Regul. Toxicol. Pharmacol 59, 454–460. 10.1016/j.yrtph.2011.01.011. [PubMed: 21295097]

He C, English K, Baduel C, Thai P, Jagals P, Ware RS, Li Y, Wang X, Sly PD, Mueller JF, 2018a. Concentrations of organophosphate flame retardants and plasticizers in urine from young children in Queensland, Australia and associations with environmental and behavioural factors. Environ. Res 164, 262–270. 10.1016/j.envres.2018.02.040. [PubMed: 29525639]

He C, Wang X, Tang S, Thai P, Li Z, Baduel C, Mueller JF, 2018b. Concentrations of organophosphate esters and their specific metabolites in food in Southeast Queensland, Australia: is dietary exposure an important pathway of organophosphate esters and their metabolites? Environ. Sci. Technol 52, 12765–12773. 10.1021/acs.est.8b03043. [PubMed: 30303374]

Heindel JJ, vom Saal FS, 2009. Role of nutrition and environmental endocrine disrupting chemicals during the perinatal period on the aetiology of obesity. Mol. Cell. Endocrinol 304, 90–96. 10.1016/j.mce.2009.02.025. [PubMed: 19433253]

Heindel JJ, vom Saal FS, Blumberg B, Bovolopin L, Calamandrei G, Ceresini G, Cohn BA, Fabbri E, Gioiosa L, Kassotis C, Legler J, La Merrill M, Rizzir L, Machtung R, Mantovani A, Mendez MA, Montanini L, Molteni L, Nagel SC, Parmiggiani S, Panzica G, Paterlini S, Pomatto V, Ruzzin J, Sartor G, Schug TT, Street ME, Suzorov A, Volpi R, Zoeller RT, Palanza P, 2015. Parma consensus statement on metabolic disruptors. Environ. Health 14, 54. 10.1186/s12940-015-0042-7. [PubMed: 26092037]

Hoffman K, Daniels JL, Stapleton HM, 2014. Urinary metabolites of organophosphate flame retardants and their variability in pregnant women. Environ. Int 63, 169–172. 10.1016/j.envint.2013.11.003. [PubMed: 24316320]

Hoffman K, Garantziotis S, Birnbaum LS, Stapleton HM, 2015. Monitoring indoor exposure to organophosphate flame retardants: hand wipes and house dust. Environ. Health Perspect 123, 160–165. 10.1289/ehp.1408669. [PubMed: 25343780]

Hoffman K, Lorenzo A, Butt CM, Adair L, Herring AH, Stapleton HM, Daniels JL, 2017. Predictors of urinary flame retardant concentration among pregnant women. Environ. Int 98, 96–101. 10.1016/j.envint.2016.10.007. [PubMed: 27745946]

Howard GJ, 2014. Chemical alternatives assessment: the case of flame retardants. Chemosphere 116, 112–117. 10.1016/j.chemosphere.2014.02.034. [PubMed: 24703012]

Hu W, Gao F, Zhang H, Hiromori Y, Arakawa S, Nagase H, Nakamishi T, Hu J, 2017. Activation of peroxisome proliferator-activated receptor gamma and disruption of progesterone synthesis of 2-Ethylhexyl diphenyl phosphate in human placental Choriocarcinoma cells: comparison with Triphenyl phosphate. Environ. Sci. Technol 51, 4061–4068. 10.1021/acs.est.7b00872. [PubMed: 28282128]

Jayatiaka NK, Restrepo P, Williams L, Ospina M, Valentin-Blasini L, Calafat AM, 2017. Quantification of three chlorinated dialkyl phosphates, diphenyl phosphate, 2,3,4,5-tetrabromobenzoic acid, and four other organophosphates in human urine by solid phase extraction-high performance liquid chromatography-tandem mass spec-trometry. Anal. Bioanal. Chem 409, 1323–1332. 10.1007/s00216-016-0661-4. [PubMed: 27838756]

Jin Y, Chen G, Fu Z, 2016. Effects of TBEP on the induction of oxidative stress and endocrine disruption in Tm3 Leydig cells. Environ. Toxicol 31, 1276–1286. 10.1002/tox.22137. [PubMed: 25808963]
Johnson CJ, Paulose-Ram R, Ogden CL, Carroll MD, Kruszon-Moran D, Doehrmann SM, Curtin LR, 2013. National Health and Nutrition Examination Survey: Analytical Guidelines, 1999–2010.

Kajiwara N, Noma Y, Takigami H, 2011. Brominated and organophosphate flame retardants in selected consumer products on the Japanese market in 2008. J. Hazard. Mater 192, 1250–1259. 10.1016/j.jhazmat.2011.06.043. [PubMed: 21783321]

Keith SW, Redden DT, Katzmarzyk PT, Boggiano MM, Hanlon EC, Benca RM, Ruden D, Pietrobelli A, Bargel JL, Fontaine KR, Wang C, Aronne LJ, Wright SM, Baskin M, Dhurandhar NV, Lijoi MC, Grilo CM, DeLuca M, Westfall AO, Allison DB, 2006. Putative contributors to the secular increase in obesity: exploring the roads less traveled. Int. J. Obes 30, 1585–1594. 10.1038/sj.ijo.0803326.

Kim S, Jung J, Lee I, Jung D, Youn H, Choi K, 2015. Thyroid disruption by triphenyl phosphate, an organophosphate flame retardant, in zebrafish (Danio rerio) embryos/larvae, and in GH3 and FRTL-5 cell lines. Aquat. Toxicol 160, 188–196. 10.1016/j.aquatox.2015.01.016. [PubMed: 25646720]

Kojima H, Takeuchi S, Itoh T, Iida M, Kobayashi S, Yoshida T, 2013. In vitro endocrine disruption potential of organophosphate flame retardants via human nuclear receptors. Toxicology 314, 76–83. 10.1016/j.tox.2013.09.004. [PubMed: 24051214]

Krivoshiev BV, Dardenne F, Covaci A, Blust R, Husson SJ, 2016. Assessing in-vitro estrogenic effects of currently-used flame retardants. Toxicol. Vit 33, 153–162. 10.1016/j.tiv.2016.03.006.

LeBel GL, Williams DT, Berard D, 1989. Triaryl/alkyl phosphate residues in human adipose autopsy samples from six Ontario municipalities. Bull. Environ. Contam. Toxicol 43, 225–230. [PubMed: 2775890]

Liu X, Ji K, Choi K, 2012a. Endocrine disruption potentials of organophosphate flame retardants and related mechanisms in H295R and MVLN cell lines and in zebrafish. Aquat. Toxicol 114–115, 173–181. 10.1016/j.aquatox.2012.02.019.

Liu X, Ji K, Choi K, 2012b. Endocrine disruption potentials of organophosphate flame retardants and related mechanisms in H295R and MVLN cell lines and in zebrafish. Aquat. Toxicol 114–115, 173–181. 10.1016/j.aquatox.2012.02.019.

Lohman TG, Roche AF, Martorell R, 1988. Anthropometric Standardization Reference Manual.

Lu S, Li Y, Zhang T, Cai D, Ruan J, Huang M, Wang L, Zhang J, Qiu R, 2017. Effect of E-waste recycling on urinary metabolites of organophosphate flame retardants and plasticizers and their association with oxidative stress. Environ. Sci. Technol 51, 2427–2437. 10.1021/acs.est.6b05462. [PubMed: 28094923]

Lynn RK, Wong K, Garvie-Gould C, Kennish JM, 1981. Disposition of the flame retardant, tris(1,3-dichloro-2-propyl) phosphate, in the rat. Drug Metab. Dispos 9.

Meeker JD, Stapleton HM, 2010. House dust concentrations of organophosphate flame retardants in relation to hormone levels and semen quality parameters. Environ. Health Perspect 118, 318–323. 10.1289/ehp.0901332. [PubMed: 20194068]

Meeker JD, Cooper EM, Stapleton HM, Hauser R, 2013. Urinary metabolites of organophosphate flame retardants: temporal variability and correlations with house dust concentrations. Environ. Health Perspect 121, 580–585. 10.1289/ehp.1205907. [PubMed: 23461877]

National Institute of Environmental Health Sciences, n.d. Flame Retardants [WWWDocument]. URL https://www.niehs.nih.gov/health/topics/agents/flame_retardants/index.cfm (accessed 12.16.17).

National Institutes of Health, National Heart, Lung, and B.I, 2000. The Practical Guide Identification, Evaluation, and Treatment of Overweight and Obesity in Adults.

Newson R, 1998. SOMERSD: Stata module to calculate Kendall’s tau-a, Somers’ D and median differences. In: Statistical Software Components S336401, Boston College Department of Economics, revised 12 Jan 2019.

Nomeir AA, Kato S, Matthews HB, 1981. The metabolism and disposition of tris(1,3-dichloro-2-propyl) phosphate (Fyrol FR-2) in the rat. Toxicol. Appl. Pharmacol 57, 401–413. [PubMed: 7222047]

Ogden CL, Carroll MD, Kit BK, Flegal KM, 2014. Prevalence of childhood and adult obesity in the United States, 2011–2012. JAMA 311, 806–814. 10.1001/jama.2014.732. [PubMed: 24570244]
Ospina M, Jayatilaka NK, Wong LY, Restrepo P, Calafat AM, 2018. Exposure to organophosphate flame retardant chemicals in the U.S. general population: data from the 2013–2014 National Health and nutrition examination survey. Environ. Int 110, 32–41. 10.1016/j.envint.2017.10.001. [PubMed: 29102155]

Patisaul HB, Roberts SC, Mabrey N, Mccaffrey KA, Gear RB, Braun J, Belcher SM, Stapleton HM, 2013. Accumulation and endocrine disrupting effects of the flame retardant mixture firemaster?? 550 in rats: an exploratory assessment. J. Biochem. Mol. Toxicol 27, 124–136. 10.1002/jbt.21439. [PubMed: 23139171]

Pillai HK, Fang M, Beglov D, Kozakov D, Vajda S, Stapleton HM, Webster TF, Schlezinger JJ, 2014. Ligand binding and activation of PPARgamma by Firemaster(R) 550: effects on adipogenesis and osteogenesis in vitro. Env. Heal. Perspect 122, 1225–1232. 10.1289/ehp.1408111.

Poma G, Glynn A, Malarvannan G, Covaci A, Darnerud PO, 2017. Dietary intake of phosphorus flame retardants (PFRs) using Swedish food market basket estimations. Food Chem. Toxicol 100, 1–7. 10.1016/j.fct.2016.12.011. [PubMed: 27965106]

Poma G, Sales C, Bruyland B, Christia C, Goscinny S, Van Loco J, Covaci A, 2018. Occurrence of organophosphorus flame retardants and plasticizers (PFRs) in Belgian foodstuffs and estimation of the dietary exposure of the adult population. Environ. Sci. Technol 52, 2331–2338. 10.1021/acs.est.7b06341.

Preston EV, McClean MD, Claus Henn B, Stapleton HM, Braverman LE, Pearce EN, Makey CM, Webster TF, 2017. Associations between urinary diphenyl phosphate and thyroid function. Environ. Int 101, 158–164. 10.1016/j.envint.2017.01.020. [PubMed: 28162782]

Quirós-Alcalá L, Buckley JP, Boyle M, 2018. Parabens and measures of adiposity among adults and children from the U.S. general population: NHANES 2007–2014. Int. J. Hyg. Environ. Health 10.1016/j.ijheh.2018.03.006.

Romano ME, Hawley NL, Eliot M, Calafat AM, Jayatilaka NK, Kelsey K, McGarvey S, Phipps MG, Savitz DA, Werner EF, Braun JM, 2017. Variability and predictors of urinary concentrations of organophosphate flame retardant meta-bolites among pregnant women in Rhode Island. Environ. Health 16, 40. 10.1186/s12940-017-0247-z. [PubMed: 28399857]

Saillenfait A-M, Ndaw S, Robert A, Sabaté J-P, 2018. Recent biomonitoring reports on phosphate ester flame retardants: a short review. Arch. Toxicol 92, 2749–2778. 10.1007/s00204-018-2275-z. [PubMed: 30097699]

Schang G, Robaire B, Hales BF, 2016. Organophosphate flame retardants act as endocrine-disrupting chemicals in MA-10 mouse tumor Leydig cells. Toxicol. Sci 150, 499–509. 10.1093/toxsci/kfw012. [PubMed: 26794138]

Stapleton HM, Klosterhaus S, Eagle S, Fuh J, Meeker JD, Blum A, Webster TF, 2009. Detection of organophosphate flame retardants in furniture foam and U.S. house dust. Environ. Sci. Technol 43, 7490–7495. 10.1021/es9014019. [PubMed: 19848166]

Thomas MB, Stapleton HM, Dills RL, Violette HD, Christakis DA, Sathyanarayana S, 2017. Demographic and dietary risk factors in relation to urinary metabolites of organophosphate flame retardants in toddlers. Chemosphere 185, 918–925. 10.1016/j.chemosphere.2017.07.015. [PubMed: 28763939]

U.S. Department of Health and Human Services, 2008. 2008 Physical Activity Guidelines for Americans.

Van Den Eede N, Hefferman AL, Aylward LL, Hobson P, Neels H, Mueller JF, Covaci A, 2015. Age as a determinant of phosphate flame retardant exposure of the Australian population and identification of novel urinary PFR metabolites. Environ. Int 74, 1–8. 10.1016/j.envint.2014.09.005. [PubMed: 25277340]

Vidmar S, Carlin J, Hesketh K, 2004. Standardizing anthropometric measures in children and adolescents with new functions for egen. Stat A 4 (1), 50–55.

Wang Q, Lam JCW, Han J, Wang X, Guo Y, Lam PKS, Zhou B, 2015. Developmental exposure to the organophosphorus flame retardant tris(1,3-dichloro-2-propyl) phosphate: estrogenic activity, endocrine disruption and reproductive effects on zebrafish. Aquat. Toxicol 160, 163–171. 10.1016/j.aquatox.2015.01.014. [PubMed: 25637911]
Wang Y, Kannan K, 2018. Concentrations and dietary exposure to organophosphate esters in foodstuffs from Albany, New York, United States. J. Agric. Food Chem 66, 13525–13532. 10.1021/acs.jafc.8b06114. [PubMed: 30525574]

Wang Y, Hou M, Zhang Q, Wu X, Zhao H, Xie Q, Chen J, 2017. Organophosphorus flame retardants and plasticizers in building and decoration materials and their potential burdens in newly decorated houses in China. Environ. Sci. Technol 51, 10991–10999. 10.1021/acs.est.7b03367. [PubMed: 28866882]

Yan S, Wu H, Qin J, Zha J, Wang Z, 2017. Halogen-free organophosphorus flame retardants caused oxidative stress and multixenobiotic resistance in Asian freshwater clams (Corbicula fluminea). Environ. Pollut 225, 559–568. 10.1016/j.envpol.2017.02.071. [PubMed: 28318792]

Yang C, Harris SA, Jantunen LM, Siddique S, Kubwabo C, Tsirlin D, Latifovic L, Fraser B, St-Jean M, De La Campa R, You H, Kulka R, Diamond ML, 2019. Are cell phones an indicator of personal exposure to organophosphate flame retardants and plasticizers? Environ. Int 122, 104–116. 10.1016/J.ENVIRONT.2018.10.021. [PubMed: 30522823]

Zhang Q, Ji C, Yin X, Yan L, Lu M, Zhao M, 2016a. Thyroid hormone-disrupting activity and ecological risk assessment of phosphorus-containing flame retardants by in vitro, in vivo and in silico approaches. Environ. Pollut 210, 27–33. 10.1016/j.envpol.2015.11.051. [PubMed: 26701863]

Zhang X, Zou W, Mu L, Chen Y, Ren C, Hu X, Zhou Q, 2016b. Rice ingestion is a major pathway for human exposure to organophosphate flame retardants (OPFRs) in China. J. Hazard. Mater 318, 686–693. 10.1016/j.jhazmat.2016.07.055. [PubMed: 27484948]

Zipf G, Chiappa M, Porter KS, Ostchega Y, Lewis BG, Dostal J, 2013. National health and nutrition examination survey: plan and operations, 1999–2010. Vital Health Stat. 1, 1–37.

Environ Int. Author manuscript; available in PMC 2020 June 01.
Table 1

Study population characteristics for children (6–19 years) and adults (20+ years), NHANES 2013–2014.\textsuperscript{a}

| Characteristic                  | Children (n = 784) | Adults (n = 1672) |
|--------------------------------|-------------------|-------------------|
|                                | N (%)             | N (%)             |
| Gender                         |                   |                   |
| Male                           | 430 (52.6)        | 818 (48.8)        |
| Female                         | 354 (47.4)        | 854 (51.2)        |
| Race/ethnicity                 |                   |                   |
| Non-Hispanic White             | 215 (53.8)        | 722 (65.8)        |
| Non-Hispanic Black             | 205 (13.5)        | 327 (11.2)        |
| Mexican                        | 181 (16.2)        | 217 (8.2)         |
| Other\textsuperscript{b}       | 183 (16.5)        | 406 (14.1)        |
| Poverty income ratio           |                   |                   |
| 0–1.85                         | 431 (42.4)        | 681 (31.2)        |
| 1.85–3.49                      | 134 (22.9)        | 383 (23.7)        |
| ≥3.50                          | 219 (34.7)        | 608 (45.1)        |
| Body mass index (BMI) categories\textsuperscript{c} | | |
| Underweight                    | 33 (4.9)          | 25 (1.6)          |
| Normal                         | 465 (61.1)        | 490 (29.1)        |
| Overweight                     | 144 (15.9)        | 550 (32.2)        |
| Obese                          | 142 (18.1)        | 607 (37.1)        |
| Waist circumference (cm)\textsuperscript{d} | | |
| Normal                         | -                 | 762 (44.6)        |
| High                           | -                 | 910 (55.4)        |
| Screen time                    |                   |                   |
| < 2 h/day                      | 205 (29.9)        | 395 (23.1)        |
| ≥2 h/day                       | 579 (70.2)        | 1277 (76.9)       |
| Physical activity level\textsuperscript{e} | | |
| Inactive                       | -                 | 1075 (62.1)       |
| Moderate activity              | -                 | 251 (14.4)        |
| Vigorous activity              | -                 | 346 (23.6)        |
| Number of fast food meals in the past 7 days | | |
| None                           | 299 (37.9)        | 758 (41.0)        |
| 1–2 meals                      | 344 (43.4)        | 569 (37.2)        |
| 3 or more meals                | 141 (18.7)        | 345 (21.8)        |
| Number of ready-to-eat meals in the past 30 days | | |
| None                           | 590 (73.8)        | 1142 (66.1)       |
| 1–2 meals                      | 96 (12.8)         | 262 (17.8)        |
| 3 or more meals                | 98 (13.5)         | 268 (16.1)        |
| Number of frozen meals or pizza in the past 30 days | | |
| None                           | 431 (53.0)        | 1075 (61.1)       |
| Characteristic       | Children (n = 784) | Adults (n = 1672) |
|---------------------|--------------------|-------------------|
|                     | N (%)              | N (%)             |
| 1–2 meals           | 147 (19.3)         | 256 (16.0)        |
| 3 or more meals     | 206 (27.7)         | 341 (22.9)        |
| Mean (SD)           |                    |                   |
| Age (years)         | 11.8 (3.9)         | 48.5 (17.3)       |
| Total calories (kcal)| 1890.3 (679.0)     | 2093.3 (871.7)    |
| Body mass index (kg/m²)| -                  | 28.9 (6.9)        |
| BMI z-score         | 0.56 (1.2)         | -                 |
| Waist circumference (cm) | 73.2 (15.6)       | 99.0 (16.6)       |

*d* Percent values presented are weighted to account for the NHANES complex survey design.

*b* The race/ethnic category “Other” represents participants who self-identify as other Hispanic, other races, and multi-racial.

*c* BMI (kg/m²) was used to classify adults and BMI z-score was used to classify children.

*d* Waist circumference (WC) categories based on guidelines from North American Association for the Study of Obesity and NHLBI.

*e* Data was not available for children. Notation and abbreviations: -: data not available; SD: standard deviation.
Table 2

Summary statistics for urinary OPE metabolite concentrations among children and adults in μg/L (μg/gCre).a

| OPE metabolite | DF% | LOD (μg/L) | GMb | p25  | p50  | p75  | Max   | DF% | GMb | p25  | p50  | p75  | Max   |
|----------------|-----|------------|------|------|------|------|-------|-----|------|------|------|------|-------|
| DPHP          | 96.4| 0.16       | 1.51 (1.57) | 0.73 (0.77) | 1.43 (1.41) | 2.97 (2.66) | 193 (235.4) | 90  | 0.72 (0.79) | 0.32 (0.40) | 0.72 (0.68) | 1.44 (1.28) | 102 (112.1) |
| BDCPP         | 98.7| 0.11       | 1.71 (1.78) | 0.72 (0.76) | 1.57 (1.60) | 3.50 (3.26) | 169 (75.8)  | 90  | 0.72 (0.78) | 0.27 (0.35) | 0.69 (0.70) | 1.74 (1.41) | 88.9 (67.9)  |
| BCEP          | 94.8| 0.08       | 0.63 (0.65) | 0.26 (0.28) | 0.57 (0.59) | 1.34 (1.26) | 97.4 (44.2) | 87.3| 0.37 (0.40) | 0.15 (0.19) | 0.36 (0.35) | 0.85 (0.73) | 110 (60.4)   |
| DBUP          | 83.7| 0.05       | 0.23 (0.24) | 0.11 (0.13) | 0.29 (0.24) | 0.45 (0.43) | 70.3 (42.3) | 79.7| 0.18 (0.19) | 0.07 (0.11) | 0.23 (0.20) | 0.35 (0.33) | 7.33 (15.9)  |
| BCPP          | 67.2| 0.10       | 0.22 (0.23) | < LOD | 0.20 (0.21) | 0.43 (0.41) | 46.7 (50.8) | 58.4| 0.18 (0.20) | < LOD | 0.14 (0.18) | 0.33 (0.32) | 14.6 (18.5) |

Abbreviations: DF% - detection frequency; LOD - limit of detection; and GM - geometric mean.

aValues in parentheses represent summary statistics based on creatinine-adjusted concentrations (μg/gCre).

bGeometric mean values reported were calculated using the LOD/√2 for values below the LOD.
### Table 3

Associations between urinary OPE metabolite concentrations and adiposity measures among children 6–19 years (NHANES 2013–2014). *a*

| OPE metabolite | Obese vs. normal weight (N = 607) | Overweight vs. normal weight (N = 609) | BMI z-score (N = 784) |
|----------------|----------------------------------|--------------------------------------|----------------------|
|                | All children crude POR 95% CI p-Value | All children aPOR 95% CI p-Value | Male (N = 333) Female (N = 274) |
|                |                                  |                                      |                      |
|                |                                  |                                      |                      |
| BCPP (< LOD vs. ≥ LOD) | 1.21 0.67, 2.21 0.50 0.50 | 0.79 0.24 0.79 0.24 | 0.63 0.32 1.24 0.18 1.62 0.46 5.80 0.45 0.20 |
| DPHP (log2)    | 0.97 0.81, 1.17 0.75 0.98 | 0.81 0.84 1.45 0.83 2.51 0.19 0.85 0.88 1.23 0.39 0.10 |
| BDCPP (log2)   | 0.95 0.84, 1.06 0.33 0.98 | 0.86 1.12 1.41 0.89 2.23 0.15 0.87 0.64 1.18 0.37 0.08 |
| BCEP (log2)    | 1.04 0.93, 1.16 0.43 1.05 | 0.93 1.19 1.20 0.91 1.59 0.19 0.97 0.72 1.29 0.82 0.40 |
| DBUP (log2)    | 0.84 0.74, 0.96 0.02* 0.82 | 0.70 0.95 0.02* 0.69 0.44 1.10 0.12 1.14 0.68 1.91 0.62 0.20 |
|                |                                  |                                      |                      |
|                | All children crude POR 95% CI p-Value | All children aPOR 95% CI p-Value | Male (N = 331) Female (N = 278) |
|                |                                  |                                      |                      |
|                |                                  |                                      |                      |
| BCPP (< LOD vs. ≥ LOD) | 0.68 0.46, 1.01 0.06 0.72 | 0.48 1.08 0.10 0.41 0.16 1.05 0.06 0.82 0.47 1.43 0.49 0.30 |
| DPHP (log2)    | 0.92 0.79, 1.07 0.27 0.90 | 0.70 1.15 0.37 0.97 0.53 1.76 0.91 0.81 0.56 1.18 0.28 0.57 |
| BDCPP (log2)   | 0.96 0.83, 1.11 0.58 1.01 | 0.83 1.23 0.91 1.04 0.65 1.65 0.88 0.85 0.58 1.23 0.39 0.53 |
| BCEP (log2)    | 1.12 0.99, 1.28 0.07 1.15 | 1.01 1.32 0.04* 1.08 0.91 1.29 0.38 1.14 0.84 1.55 0.41 0.79 |
| DBUP (log2)    | 1.00 0.82, 1.22 1.00 1.03 | 0.79 1.33 0.83 1.20 0.91 1.59 0.19 0.64 0.44 0.91 0.01* 0.02 |
|                |                                  |                                      |                      |
|                | All children crude β 95% CI p-Value | All children β 95% CI p-Value | Male (N = 430) Female (N = 354) |
|                |                                  |                                      |                      |
|                |                                  |                                      |                      |
| BCPP (< LOD vs. ≥ LOD) | −0.09 −0.34, 0.16 0.45 −0.03 | 0.26 0.20 0.81 −0.45 −0.80 −0.09 0.01* 0.18 −0.21 0.57 0.38 0.03 |
| DPHP (log2)    | −0.02 −0.08, 0.05 0.55 −0.02 | 0.08 0.05 0.64 0.09 −0.08 0.26 0.29 −0.02 −0.12 0.07 0.60 0.29 |
| BDCPP (log2)   | −0.02 −0.10, 0.06 0.65 0.01 | 0.08 0.09 0.84 0.08 −0.07 0.23 0.28 0.02 −0.11 0.14 0.80 0.51 |
### OPE metabolite

#### Obese vs. normal weight (N = 607)

| OPE metabolite | All children crude POR | 95% Cl | p-Value | All children aPOR | 95% Cl | p-Value | Male (N = 333) | Female (N = 274) |
|----------------|------------------------|--------|---------|-------------------|--------|---------|---------------|------------------|
| BCEP (log₂)    | 0.02                   | -0.05, 0.10 | 0.53 | 0.03              | 0.04, 0.10 | 0.39 | 0.04 | -0.02, 0.11 | 0.22 |
| DBUP (log₂)    | -0.08                  | -0.15, -0.01 | 0.04 | -0.08             | 0.17, 0.01 | 0.07 | -0.16 | -0.39, 0.07 | 0.17 |

#### Waist circumference (cm) (N = 784)

| OPE metabolite | All children crude β | 95% Cl | p-Value | All children β | 95% Cl | p-Value | Male (N = 430) | Female (N = 354) |
|----------------|----------------------|--------|---------|----------------|--------|---------|---------------|------------------|
| BCPP (< LOD vs. ≥ LOD) | -6.05 | -9.60, -2.50 | 0.002 | -2.44, 3.06 | 0.81 | -3.64 | -7.36, 0.09 | 0.06 |
| DPHP (log₂)    | -2.35                 | -3.21, -1.49 | < 0.001 | -0.89, 0.48 | 0.53 | 0.99 | -1.29, 3.26 | 0.40 |
| BDCPP (log₂)   | -2.70                 | -3.57, -1.82 | < 0.001 | -0.90, 0.33 | 0.34 | 0.77 | -1.01, 2.54 | 0.40 |
| BCEP (log₂)    | -1.13                 | -1.77, -0.49 | 0.002 | 0.19             | -0.46, 0.85 | 0.54 | 0.60 | -0.54, 2.17 | 0.30 |
| DBUP (log₂)    | -2.78                 | -3.71, -1.84 | < 0.001 | -1.49, 0.07 | 0.07 | -1.53 | -3.00, 1.13 | 0.26 |

**Abbreviations:**
- **aPOR:** Adjusted prevalence odds ratio
- **EMM p-value:** p-value for effect measure modification (EMM) by sex.
- **Crude models adjusted for log₁₀ creatinine concentrations and multivariable models additionally adjusted for age, sex, race, poverty income ratio, screen time, number of fast food meals, number of ready-to-eat meals, number of frozen meals or pizza.

* p < 0.05
Table 4

Associations between urinary OPE metabolite concentrations and adiposity measures among adults ≥20 years (NHANES 2013–2014).a

| OPE metabolite | Obese vs. normal weight (N = 1097) | Overweight vs. normal weight (N = 1040) | BMI (kg/m²) (N = 1672) |
|----------------|------------------------------------|----------------------------------------|------------------------|
|                | All adults | 95% CI | p-Value | All adults | 95% CI | p-Value | All adults | 95% CI | p-Value | Male (N = 497) | Female (N = 600) | Male (N = 537) | Female (N = 503) | Male (N = 818) | Female (N = 854) | |
|                | crude POR  |         |         | aPOR      | 95% CI   | p-Value | aPOR      | 95% CI   | p-Value | aPOR      | 95% CI   | p-Value | aPOR      | 95% CI   | p-Value |          |          |          |
| BCPP (≤ LOD vs. ≥ LOD) | 1.41 | 0.98, 2.03 | 0.06 | 1.70 | 1.21, 2.38 | 0.006 | 2.09 | 1.31, 3.33 | 0.002 | 1.38 | 0.91, 2.12 | 0.13 | 0.21 |
| DPHP (log₂)  | 0.95 | 0.81, 1.11 | 0.48 | 0.94 | 0.80, 1.12 | 0.47 | 1.02 | 0.81, 1.30 | 0.85 | 0.89 | 0.73, 1.09 | 0.26 | 0.38 |
| BDCPP (log₂) | 0.95 | 0.87, 1.04 | 0.23 | 0.99 | 0.90, 1.10 | 0.90 | 1.05 | 0.84, 1.31 | 0.64 | 0.95 | 0.84, 1.08 | 0.44 | 0.48 |
| BCEP (log₂)  | 1.04 | 0.89, 1.21 | 0.61 | 1.05 | 0.90, 1.22 | 0.54 | 1.01 | 0.83, 1.23 | 0.90 | 1.09 | 0.92, 1.28 | 0.32 | 0.55 |
| DBUP (log₂)  | 0.91 | 0.82, 1.01 | 0.07 | 0.83 | 0.72, 0.96 | 0.02 | 0.93 | 0.73, 1.18 | 0.54 | 0.76 | 0.62, 0.93 | 0.009 | 0.29 |
| BCPP (< LOD vs. ≥ LOD) | 1.21 | 0.78, 1.86 | 0.37 | 1.35 | 0.83, 2.19 | 0.20 | 1.49 | 0.81, 2.76 | 0.20 | 1.18 | 0.71, 1.95 | 0.52 | 0.45 |
| DPHP (log₂)  | 0.91 | 0.79, 1.04 | 0.15 | 0.96 | 0.84, 1.09 | 0.48 | 1.00 | 0.83, 1.20 | 0.97 | 0.94 | 0.82, 1.08 | 0.37 | 0.60 |
| BDCPP (log₂) | 0.87 | 0.79, 0.97 | 0.02 | 0.91 | 0.83, 1.00 | 0.04 | 0.94 | 0.84, 1.06 | 0.29 | 0.89 | 0.79, 1.00 | 0.04 | 0.44 |
| BCEP (log₂)  | 0.99 | 0.87, 1.14 | 0.93 | 1.00 | 0.87, 1.15 | 0.99 | 0.96 | 0.82, 1.13 | 0.66 | 1.06 | 0.88, 1.27 | 0.53 | 0.42 |
| DBUP (log₂)  | 1.02 | 0.88, 1.18 | 0.79 | 0.99 | 0.85, 1.16 | 0.92 | 0.96 | 0.77, 1.20 | 0.74 | 1.03 | 0.80, 1.34 | 0.80 | 0.71 |

*a* Denotes statistical significance at the 0.05 level.
| OPE metabolite | Obese vs. normal weight (N = 1097) |  |  |  | Male (N = 497) | Female (N = 600) |  |  |  |  |
|----------------|----------------------------------|---|---|---|----------------|-----------------|---|---|---|---|
|                | All adults crude POR             | 95% CI | p-Value | All adults aPOR | 95% CI | p-Value | aPOR | 95% CI | p-Value | aPOR | 95% CI | p-Value | EMM p-value |
| DBUP (log₂)    | -0.26                           | -0.78, 0.25 | 0.28 | -0.46          | -0.95, 0.03 | 0.06 | -0.13 | -0.75, 0.50 | 0.69 | -0.67 | -1.14, -0.21 | 0.004* | 0.11 |
| High vs. normal waist circumference \( b \) (N = 1672) | All adults crude POR             | 95% CI | p-Value | All adults aPOR | 95% CI | p-Value | aPOR | 95% CI | p-Value | aPOR | 95% CI | p-Value | EMM p-value |
| BCPP (< LOD vs. ≥ LOD) | 1.42                           | 1.06, 1.89 | 0.02* | 1.51          | 1.11, 2.07 | 0.01* | 1.53 | 1.00, 2.34 | 0.05* | 1.42 | 0.93, 2.15 | 0.10 | 0.82 |
| DPHP (log₂)    | 1.05                           | 0.97, 1.14 | 0.20 | 0.96          | 0.88, 1.05 | 0.38 | 1.04 | 0.87, 1.25 | 0.67 | 0.90 | 0.78, 1.04 | 0.15 | 0.32 |
| BDCPP (log₂)   | 1.03                           | 0.95, 1.12 | 0.41 | 1.06          | 0.97, 1.15 | 0.19 | 1.11 | 0.96, 1.29 | 0.16 | 1.00 | 0.91, 1.10 | 0.99 | 0.25 |
| BCEP (log₂)    | 1.09                           | 0.98, 1.23 | 0.12 | 1.07          | 0.94, 1.22 | 0.31 | 1.05 | 0.91, 1.20 | 0.53 | 1.12 | 0.96, 1.30 | 0.16 | 0.41 |
| DBUP (log₂)    | 1.08                           | 0.98, 1.18 | 0.10 | 0.93          | 0.81, 1.06 | 0.26 | 0.90 | 0.73, 1.11 | 0.31 | 0.96 | 0.83, 1.12 | 0.63 | 0.59 |

Abbreviations: aPOR: Adjusted prevalence odds ratio; EMM p-value: p-value for effect measure modification (EMM) by sex.

\( a \) Crude models adjusted for log₁₀ creatinine concentrations and multivariable models additionally adjusted for age, sex, race, poverty income ratio, physical activity, screen time, number of fast food meals, number of ready-to-eat meals, number of frozen meals or pizza.

\( b \) Waist circumference was dichotomized as normal vs. high based on guidelines developed by the North American Association for the Study of Obesity and the NHLBI.

* \( p < 0.05 \).