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

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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 $\log_2$-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,

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Appendix A. Supplementary data

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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-choloro-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, meta-bolite 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/cm^2), normal weight(18.5 ≤ BMI < 25.0 kg/cm^2), overweight (25.0 ≤ BMI < 30.0 kg/cm^2), or obese (BMI ≥ 30.0 kg/cm^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

range. 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/√2 for OPE metabolites detected in ≥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) ≥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. ≥ 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 (≤ 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 ≥ 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 $\log_2$-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 ($p_{EMM} = 0.03$) 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 (β: 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 ($p_{trends} \leq 0.04$, 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; ($p_{trend} < 0.001$)].

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), β: −0.46, 95% CI: −0.95, 0.03; high vs. normal WC, aPOR: 0.93, 95% CI: 0.81, 1.060); 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.

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Abbreviations:

BCPP	bis(1-choloro-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-pcresyl 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

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Table 1

Study population characteristics for children (6–19 years) and adults (20+ years), NHANES 2013–2014.[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[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[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)[d]		
Normal	-	762 (44.6)
High	-	910 (55.4)
Screen time		
< 2 h/day	205 (29.9)	395 (23.1)
≥ 2h/day	579 (70.2)	1277 (76.9)
Physical activity level[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/m^2)	-	28.9 (6.9)
BMI z-score	0.56 (1.2)	–
Waist circumference (cm)	73.2 (15.6)	99.0 (16.6)

[a]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]

	Children (N = 784)							Adults (N = 1672)					
OPE metabolite	**DF%**	**LOD (μg/L)**	**GM[b]**	**p25**	**p50**	**p75**	**Max**	**DF%**	**GM[b]**	**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)	90.6	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.

[a]Values in parentheses represent summary statistics based on creatinine-adjusted concentrations (μg/gCre).

[b]Geometric 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)												
	All children crude POR	**95% CI**	**p-Value**	**All children aPOR**	**95% CI**	**p-Value**	**Male (*N* = 333)**			**Female (*N* = 274)**			
							aPOR	**95% CI**	**p-Value**	**aPOR**	**95% CI**	**p-Value**	**EMM p-value**
BCPP (< LOD vs. ≥ LOD)	1.21	0.67, 2.21	0.50	1.39	0.79, 2.45	0.24	0.63	0.32, 1.24	0.18	1.62	0.46, 5.80	0.45	0.20
DPHP (log_2)	0.97	0.81, 1.17	0.75	0.98	0.81, 1.19	0.84	1.45	0.83, 2.51	0.19	0.85	0.58, 1.23	0.39	0.10
BDCPP (log_2)	0.95	0.84, 1.06	0.33	0.98	0.86, 1.12	0.72	1.41	0.89, 2.23	0.15	0.87	0.64, 1.18	0.37	0.08
BCEP (log_2)	1.04	0.93, 1.16	0.43	1.05	0.93, 1.19	0.40	1.20	0.91, 1.59	0.19	0.97	0.72, 1.29	0.82	0.40
DBUP (log_2)	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
Overweight vs. normal weight (*N* = 609)													
	All children crude POR	**95% CI**	**p-Value**	**All children aPOR**	**95% CI**	**p-Value**	**Male (*N*= 331)**			**Female (*N* = 278)**			
							aPOR	**95% CI**	**p-Value**	**aPOR**	**95% CI**	**p-Value**	**EMM p-value**
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 (log_2)	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 (log_2)	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 (log_2)	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 (log_2)	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
BMI z-score (N = 784)													
							Male (*N* = 430)		**Female (*N* = 354)**				
	All children crude β	**95% CI**	**p-Value**	**All children β**	**95% CI**	**p-Value**	**β**	**95% CI**	**p-Value**	**β**	**95% CI**	**p-Value**	**EMM p-value**
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 (log_2)	−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 (log_2)	−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)												
	All children crude POR	**95% CI**	**p-Value**	**All children aPOR**	**95% CI**	**p-Value**	**Male (*N* = 333)**			**Female (*N* = 274)**			
							aPOR	**95% CI**	**p-Value**	**aPOR**	**95% CI**	**p-Value**	**EMM p-value**
BCEP (log_2)	0.02	−0.05, 0.10	0.53	0.03	0.04, 0.10	0.39	0.04	−0.02, 0.11	0.22	0.02	−0.10, 0.14	0.76	0.76
DBUP (log_2)	−0.08	−0.15, −0.01	0.04 *	−0.08	0.17, 0.01	0.07	−0.16	−0.39, 0.07	0.17	−0.04	−0.21, 0.13	0.61	0.49
Waist circumference (cm) (N = 784)													
									Male (*N* = 430)		**Female (*N* = 354)**		
	All children crude β	**95% CI**	**p-Value**	**All children β**	**95% CI**	**p-Value**	**β**	**95% CI**	**p-Value**	**β**	**95% CI**	**p-Value**	**EMM p-value**
BCPP (< LOD vs. ≥ LOD)	−6.05	−9.60, −2.50	0.002 *	0.31	− 2.44, 3.06	0.81	−3.64	−7.36, 0.09	0.06	2.25	−2.73, 7.23	0.38	0.08
DPHP (log_2)	−2.35	−3.21, −1.49	< 0.001 *	−0.20	−0.89, 0.48	0.53	0.99	−1.29, 3.26	0.40	−0.73	−1.82, 0.36	0.19	0.22
BDCPP (log_2)	−2.70	−3.57, −1.82	< 0.001 *	−0.29	−0.90, 0.33	0.34	0.77	−1.01, 2.54	0.40	−0.58	−1.73, 0.57	0.32	0.25
BCEP (log_2)	−1.13	−1.77, −0.49	0.002	0.19	−0.46, 0.85	0.54	0.60	−0.54, 1.74	0.30	−0.20	−1.34, 0.95	0.74	0.40
DBUP (log_2)	−2.78	−3.71, −1.84	< 0.001 *	−0.71	−1.49, 0.07	0.07	−1.53	−4.20, 1.13	0.26	0.20	−2.05, 2.46	0.86	0.40

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

[a]Crude models adjusted for log_{10} 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)												
	All adults crude POR	**95% CI**	**p-Value**	**All adults aPOR**	**95% CI**	**p-Value**	**Male (*N* = 497)**			**Female (*N* = 600)**			
							aPOR	**95% CI**	**p-Value**	**aPOR**	**95% CI**	**p-Value**	**EMM *p*-value**
BCPP (< LOD vs. ≥ LOD)	1.41	0.98, 2.03	0.06	1.70	1.21, 2.38	0.004*	2.09	1.31, 3.33	0.002*	1.38	0.91, 2.12	0.13	0.21
DPHP (log_2)	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 (log_2)	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 (log_2)	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 (log_2)	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
Overweight vs. normal weight (*N* = 1040)													
	All adults crude POR	**95% CI**	**p-Value**	**All adults aPOR**	**95% CI**	**p-Value**	**Male (*N* = 537)**			**Female (*N* = 503)**			
							aPOR	**95% CI**	**p-Value**	**aPOR**	**95% CI**	**p-Value**	**EMM p-value**
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 (log_2)	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 (log_2)	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 (log_2)	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 (log_2)	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
BMI (kg/m^2) (N = 1672)													
	All adults crude β	**95% CI**	**p-Value**	**All adults β**	**95% CI**	**p-Value**	**Male (*N*= 818)**			**Female (*N* = 854)**			
							β	**95% CI**	**p-Value**	**β**	**95% CI**	**p-Value**	**EMM p-value**
BCPP (< LOD vs. ≥ LOD)	1.10	0.03, 2.17	0.04*	1.31	0.30, 2.33	0.02*	0.95	−0.16, 2.07	0.09	1.50	0.30, 2.69	0.01*	0.51
DPHP (log_2)	−0.03	−0.26, 0.19	0.75	−0.14	−0.38, 0.10	0.24	0.21	−0.21, 0.64	0.32	−0.33	−0.62, −0.04	0.03	0.08
BDCPP (log_2)	0.13	−0.15, 0.41	0.33	0.12	−0.20, 0.44	0.44	0.28	−0.12, 0.68	0.17	−0.01	−0.48, 0.46	0.97	0.35
BCEP (log_2)	0.20	−0.08, 0.47	0.15	0.16	−0.10, 0.41	0.21	0.01	−0.22, 0.23	0.95	0.34	−0.15, 0.83	0.18	0.31

OPE metabolite													
	Obese vs. normal weight (*N* = 1097)												
	All adults crude POR	**95% CI**	**p-Value**	**All adults aPOR**	**95% CI**	**p-Value**	**Male (*N* = 497)**			**Female (*N* = 600)**			
							aPOR	**95% CI**	**p-Value**	**aPOR**	**95% CI**	**p-Value**	**EMM *p*-value**
DBUP (log_2)	−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**	**Male (N = 818)**			**Female (N = 854)**			
							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 (log_2)	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 (log_2)	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 (log_2)	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 (log_2)	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 log_{10} 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.

* $p < 0.05$.