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Parabens and measures of adiposity among adults and children from the U.S. general population: NHANES 2007-2014.

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Abstract

Background.—Emerging experimental studies suggest that parabens could affect metabolism by altering the microbiome or signaling pathways involved in adipocyte differentiation. While human exposure to parabens is widespread, epidemiologic studies assessing the role of these chemicals on adiposity measures are scarce.

Objective.—We examined associations of parabens with adiposity measures among adults and children in the U.S. general population.

Methods.—We conducted covariate-adjusted linear and logistic regression models to examine associations between urinary biomarker concentrations of four parabens (butyl-BP, ethyl-EP, methyl-MP, and propyl paraben-PP) and measures of adiposity (obesity; body mass index, BMI or BMI z-score; and waist circumference) among 4730 adults (2007–2014) and 1324 children (2007–2012), participating in the National Health and Nutrition Examination Survey. We also assessed heterogeneity of associations by gender.

Results.—We generally observed significant inverse associations between adiposity measures and paraben biomarker concentrations among adults (BP, EP, MP, PP) and children (MP). For example, adjusted prevalence odds ratios (95% confidence intervals, CI) for obesity per a tenfold increase in MP concentrations were 0.64 (95% CI: 0.55, 0.73) for adults and 0.71(95% CI: 0.52, 0.95) for children. Strength of inverse associations typically increased monotonically with increasing paraben exposure quartiles; and, in general, inverse associations were more pronounced among females. Associations remained when controlling for other phenolic compounds previously linked with adiposity measures.

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Conclusions.—In this cross-sectional study of adiposity measures and parabens, we observed consistent inverse associations in a representative sample of U.S adults and children. Further studies are warranted to confirm our findings, examine the potential role of paraben sequestration in adipose tissue, and elucidate mechanisms by which parabens could alter metabolism.

Keywords

parabens; children; adults; adiposity; obesity; body mass index

Introduction

Obesity is a pressing and prevalent public health problem in the U.S., affecting an estimated 35% of adults and 17% of children and adolescents (Centers for Disease Control and Prevention 2017a; Ogden et al. 2014). While genetics, lack of physical activity, poor diet, insufficient sleep, and built environment are recognized risk factors for obesity, these factors alone do not explain the high obesity prevalence observed today. Mounting evidence from animal and human studies suggests that exposures to “metabolism-disrupting chemicals”, a subclass of endocrine disrupting compounds that affect energy homeostasis, could play a role on human metabolism by disrupting hormonally-mediated metabolic processes via dysregulation of lipid metabolism and/or adipogenesis (Grun and Blumberg 2006; Heindel et al. 2015). Another potential mechanism by which such compounds could alter metabolism includes alteration of the gut microbiome although research in this area is still nascent (Claus et al. 2016; Ley et al. 2006; Nadal et al. 2017; Snedeker and Hay 2012).

Parabens are a group of alkyl esters of *p*-hydroxybenzoic acid and suspected metabolism-disrupting chemicals (Hu et al. 2013; Hu et al. 2016; Hu et al. 2017). They are widely used as preservatives in consumer products, including cosmetics, personal care products, medications, and foods. Exposure to parabens in the U.S general population is widespread and occurs mainly via ingestion and dermal absorption from consuming or using products containing these agents (Centers for Disease Control and Prevention 2016; Soni et al. 2005). Parabens are considered non-persistent chemicals as they are generally excreted in urine within the first 24 hours post exposure (Janjua et al. 2008; Moos et al. 2016) though emerging evidence suggests that they may also deposit in adipose tissue (Artacho-Cordon et al. 2017; Wang et al. 2015).

Although results remain inconclusive, recent experimental studies indicate that parabens could play a role in altering metabolism, with either pro- or anti-adipogenic effects. For example, one *in vitro* study reported that exposure to several parabens at environmentally relevant doses (i.e., doses in the range of typical human exposure) promotes adipogenesis (Hu et al. 2013). The authors also reported that exposure to either butyl or methyl paraben induces changes in gene expression related to adipocyte differentiation and lipogenesis in adipose tissue in female mice (Hu et al. 2016), and that parabens alter multipotent mesenchymal stem cell fates towards adipocyte lineage (Hu et al. 2017). In contrast, a recent *in vivo* study reported that postnatal exposure to methyl paraben at environmentally relevant doses was inversely associated with bodyweight among adolescent rats (Hu J. et al. 2016),

while one *in vitro* study reported no adipogenic activity for several parabens (Kassotis et al. 2017).

To date, epidemiologic studies on the role of parabens on adiposity measures are scarce and findings are inconsistent. For example, prenatal exposure to parabens has been reported to be positively associated with birth weight among boys (Philippat et al. 2014). Conversely, postnatal exposure to parabens in one U.S. study (Deierlein et al. 2017) was not associated with adiposity measures among girls from ages 7 through 15 years. Similarly, Guo et al. (Guo et al. 2017) did not observe associations between body mass index z-scores and exposure to parabens among three-year-olds in Korea; however, researchers reported a positive link between weight z-scores and ethyl paraben biomarker concentrations among boys. To our knowledge, no other studies have examined these associations among U.S. adults or in children of other ages. In the present study, we sought to fill these critical knowledge gaps and examine whether urinary concentrations of four commonly used parabens were associated with adiposity measures among children and adults in a representative sample from the U.S. general population. We also examined whether associations varied by gender given prior studies on endocrine disrupting compounds have reported sex differences for health outcomes, including obesity (Braun et al. 2014; Buckley et al. 2016a; Buser et al. 2014; Heindel et al. 2015; Li et al. 2017).

Methods

Study Population

Our study population consisted of children between the ages of 6 and 19 years and adults ≥ 20 years, participating in the National Health and Nutrition Examination Survey (NHANES) between 2007 and 2012 (children) and between 2007 and 2014 (adults). NHANES is a multi-stage probability sample survey of the non-institutionalized U.S. general population conducted to assess general health and nutritional status and is administered by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC). All information and samples from individual participants are collected at one time point during two-year cycle waves with different individuals participating in each wave. All protocols were reviewed by the NCHS research ethics board and written informed consent and child assent was obtained prior to any data and sample collection (Zipf et al. 2013). Information on study participants was extracted from publicly-available questionnaires, laboratory, diet, and physical examination components of the NHANES. Selection of cycle years (2007–2012 for children and 2007–2014 for adults) was based on availability of exposure and outcome data, as well as data on important covariates used in our analyses.

Exposure assessment of parabens

Four parabens commonly used in consumer products, including butyl (BP), ethyl (EP), methyl (MP), and propyl paraben (PP), were measured in a one-third subsample of the NHANES participants ≥ 6 years of age in spot urine samples. Total individual paraben concentrations (free plus conjugated) were measured in urine samples using a validated laboratory method published previously (Ye et al. 2006). Currently, concentrations of total urinary species of the parent parabens (i.e., BP, EP, MP, and PP) are considered valid human

exposure biomarkers (Calafat et al. 2010; Ye et al. 2006). Limits of detection (LOD) were 1.0 μg/L (EP, MP) and 0.2 Mg/L (BP, PP). Concentrations below the LOD for frequently detected parabens (i.e., >90% detection) were imputed to $\mathrm{LOD}/\sqrt{2}$. We examined concentrations of individual parabens and also created a molar sum of paraben concentrations to allow for comparison of our results to a prior study (Deierlein et al. 2017). Concentrations of parabens were summed based on molecular weight, expressed as propyl paraben (molecular weight 180.2 g/mol) as done previously (Deierlein et al. 2017; Wolff et al. 2010). Urinary creatinine (mg/dL) concentrations were also measured in urine samples using an automated colorimetric method based on a modified Jaffe reaction on a Beckman Synchron AS/ASTRA clinical analyzer (Beckman Instruments, Inc., Brea, CA) and used to correct for urine dilution in our statistical models.

Outcome assessment: Measures of adiposity

Trained technicians collected anthropometric measurements for study participants, including height (m), weight (kg), and waist circumference (cm), 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). Because BMI is known to vary by age and sex among 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 mean BMI of a reference population of children of the same age and sex) following CDC guidelines (Centers for Disease Control and Prevention 2017b). For children, we used age- and sex-standardized BMI percentiles to classify individuals as underweight ($<5^{th}$ BMI percentile), normal weight ($5^{th} \leq$ BMI percentile $< 85^{th}$), overweight ($85^{th} <$ BMI percentile $\leq 95^{th}$) or obese ($\geq 95^{th}$ BMI percentile). For adults, we used BMI to classify individuals as underweight (BMI $\leq$18.5 kg/cm^2), normal weight (18.5 $\leq$BMI <25.0 kg/cm^2), overweight (25.0 $\leq$BMI <30.0 kg/cm^2), or obese (BMI $\geq$ 30.0 kg/cm^2).

Covariates

We controlled for several covariates *a priori* in our models that were identified as potential confounders using directed acyclic graphs (not shown) or that were expected to be strong predictors of our outcome measures, but not in the causal pathway. These covariates included age, gender, race/ethnicity, poverty income ratio, cycle year, creatinine concentrations, total caloric intake, physical activity (for adults only as data were not available for children aged 6–11 years), smoking status, and a series of covariates related to dietary consumption behaviors as detailed below. Race/ethnicity was coded as non-Hispanic white, non-Hispanic black, Mexican American, and Other where the latter category included participants reporting “other Hispanic” and “other race”, including multi-racial. Poverty income ratio (PIR) was used as a measure of socioeconomic status and coded as 0 to 1.85, >1.85 to <3.50, and ≥3.50 based on CDC guidelines (Centers for Disease Control and Prevention 2013). Physical activity was coded as inactive, moderate, or vigorous according to the Healthy People 2020 guidelines (U.S. Department of Health and Human Services. 2008). Briefly, an individual’s physical activity was coded as inactive if they reported not engaging in moderate or vigorous activity or engaged in less than 150 minutes of moderate activity and less than 75 minutes of vigorous activity, moderate if they reported engaging in moderate activity at least 150 minutes per week, and vigorous if they reported engaging in at

least 75 minutes of vigorous activity per week. We included serum cotinine as a marker of smoking status in our models because smoking has been linked to weight in prior studies (Dare et al. 2015; Ginawi et al. 2016; Perkins 1992). We classified individuals as non/passive smokers if serum cotinine concentrations were between 0 and <3.0 μg/L and as active smokers if they fell at or above 3.0 μg/L (Benowitz et al. 2009). Total caloric intake (kcal/day) was determined by averaging self-reported calorie intake captured over two examination days. We also included covariates based on self-reported dietary consumption habits which could serve as proxies for general eating habits and healthy behaviors that could impact weight and/or exposure to parabens, including the number of meals consumed that were not prepared at home in the prior seven days, the number of meals from fast food or pizza restaurants consumed over the prior seven days, and the number of ready-to-eat foods and frozen meals or pizza consumed in the prior 30 days. For adults, we also included how healthy was the participant's diet (i.e., excellent, very good, good, fair, and poor), which was only available for participants over 15 years.

Among 5216 adults and 1584 children with data on parabens and our target outcomes, the proportion of participants that were excluded due to missing covariate data was small for adults (n=486, 9%) and children (n=260, 16%). We excluded pregnant women (n=70) from the eligible pool of participants given pregnancy can alter bodyweight and affect disposition of xenobiotics (Perera and Herbstman 2011). Most of the missing data for children was due to lack of serum available for cotinine analysis (n=179). When comparing children with and without complete covariate data, children with complete covariate data had a higher mean waist circumference, but there were no significant differences in other adiposity outcomes or urinary paraben concentrations (not shown). No significant differences for adiposity measures or paraben concentrations were observed between adults with and without complete covariate data (not shown). Our final analytic sample consisted of 4730 adults and 1324 children with complete data on parabens, main covariates, and outcomes of interest.

Statistical Analysis

We calculated descriptive statistics on urinary paraben concentrations (e.g., weighted geometric mean (GM), percentiles, range) and visually inspected the distribution of concentrations for frequently detected parabens. We examined the associations of paraben concentrations with measures of adiposity several ways. First, we conducted linear regression models to test associations between individual parabens or the molar sum and continuous measures of BMI (adults), BMI z-scores (children), and waist circumference. For adults, we also modeled waist circumference dichotomized as low (≤ 88 cm for females and ≤102 cm for males) vs. high (> 88 cm for females and > 102 cm for males) based on guidelines developed by the North American Association for the Study of Obesity and the National Heart and the National Heart, Lung, and Blood Institute (National Institutes of Health 2000) in logistic regression models. We did not dichotomize waist circumference for children as, to our knowledge, similar guidelines are not available. In addition, we conducted logistic regression models to examine whether exposure to individual parabens or the molar sum increased the prevalence odds of being obese, compared to normal weight and the prevalence odds of being overweight compared to normal weight in both children and adults. We modeled parabens with low detection frequencies (i.e., <50% detection frequency; BP

and EP) as dichotomous variables (detect vs. not detected), and modeled widely detected parabens (>90% detection frequency; MP and PP) and the molar sum as continuous log10-transformed variables. Crude models included log-10 transformed creatinine concentrations to account for urinary dilution. Adjusted models included log-10 transformed creatinine concentrations and covariates described above. We also evaluated effect measure modification by gender by including in the models a cross product term for gender*biomarker, as well as cross product terms between gender and each covariate, as outlined previously (Buckley et al. 2017). To examine exposure-response relationships for MP, PP, and the molar sum, we created categorical variables for quartiles of exposure based on creatinine-adjusted concentrations (biomarker concentration/creatinine).

As part of our sensitivity analyses to examine the robustness of our results, we also ran our main models adjusting for log10-concentrations of other phenolic compounds (bisphenol A, triclosan, 2,4-dichlorophenol, and 2,5-dichlorophenol) previously linked with adiposity measures (Braun et al. 2014; Buser et al. 2014; Carwile and Michels 2011; Corbasson et al. 2016; Lankester et al. 2013; Li et al. 2017; Li et al. 2015).

We conducted all analyses using STATA/SE 14.2 for Mac (StataCorp, College Station, TX) and applied sampling weights to account for the complex survey design. Our statistical significance criteria for main effects and effect measure modification by gender included p-values<0.05 and p<0.20, respectively.

Results

Participant characteristics

In our study population, adult participants had a mean age of 50 years (SD: 17.4 years) and children had a mean age of 12 years (SD: 4.0 years) (Table 1). Nearly half of the adults (48%) and one-third (30%) of the children in our study population self-identified as non-Hispanic white, and the majority of participants (>70%) were non-smokers. Obesity prevalence was approximately 37% for adults and 22% for children. In addition, at least half of the adults and children reported consuming at least one meal not prepared at home in the previous month or a fast food meal in the prior week.

Butyl (BP) and ethyl (EP) paraben were not widely detected (detection frequencies, DF, adults: BP 38.8%, EP 51.9%; children: BP 40.0%, EP 39.2%); while methyl (MP) and propyl (PP) paraben were widely detected in both adults and children (DF, adults: MP 99.6%, PP 95.0%; children: MP 99.4%, PP 95.4%) (Table 2). The geometric mean (GM) concentration of MP was 5.8 μg/L in adults and 5.4 μg/L in children and the GM concentration for PP was 2.4 μg/L in adults and 2.1 μg/L in children. GM concentrations for the molar paraben sum was 7.0 μg/L and 6.4 μg/L for adults and children, respectively, and largely driven by methyl paraben concentrations. In adults and children, GM concentrations for MP, PP, and the molar sum were lower among obese individuals compared to those who were normal weight (adults: MP GM: 5.64 μg/L vs. 6.16 μg/L; PP GM: 2.23 μg/L vs. 2.62 μg/L; molar sum GM: 6.78 μg/L vs. 7.56 μg/L; children: MP GM: 5.22 μg/L vs. 5.53 μg/L; PP GM: 2.16 μg/L vs. 2.20 μg/L; molar sum GM: 6.27 μg/L vs. 6.62 μg/L; all p<0.001).

Associations between markers of adiposity and exposure to parabens among adults

Results from covariate-adjusted logistic and linear regression models for adults and children are presented in Tables 3 and 4, respectively. Among adults, we observed statistically significant and consistently inverse associations between detection (BP and EP) and log10-transformed concentrations of parabens (MP, PP, molar sum) with most adiposity measures. For example, we observed inverse associations between detection (BP, EP) or log10-transformed concentrations (MP, PP, molar sum) of parabens with the prevalence odds of being obese vs. normal weight (BP- adjusted prevalence odds ratio, aPOR: 0.78; 95% Confidence Interval, CI: 0.64, 0.94; EP-aPOR: 0.52; CI: 0.41, 0.66; MP-aPOR: 0.64; 95% CI: 0.55, 0.73; PP-aPOR: 0.74; 95% CI: 0.67, 0.83; molar sum - aPOR: 0.62; 95%CI: 0.54, 0.71). While we also observed this inverse pattern among overweight compared to normal weight adults, results were only statistically significant for BP and EP. Also, consistent with results for dichotomous waist circumference (Table 3), we observed statistically significant inverse associations when we modeled waist circumference as a continuous outcome (BP-β: −2.73, 95% CI: −3.97, −1.48; EP-β: −3.62, CI: −4.73, −2.51; MP-β: −3.10, CI: −3.92, −2.27; PP-β: −2.13, CI: −2.74, −1.53; and molar sum – β: −3.28; 95%CI: −4.07, −2.49).

We also observed statistically significant effect measure modification by gender, with more pronounced inverse associations among females compared to males for associations of MP, PP, and molar sum concentrations with most adiposity measures (Table 3). This pattern was also observed among overweight compared to normal weight adults; however, results were not statistically significant upon stratification. In contrast, we observed a more pronounced statistically significant inverse association among males for EP and the prevalence odds of being obese vs. normal weight (Males: aPOR: 0.46; CI: 0.35, 0.60 vs. Females: aPOR: 0.60; CI: 0.45, 0.82); but not for EP and other outcomes.

Creatinine-adjusted quartiles of paraben concentrations (MP, PP or molar sum) revealed inverse linear exposure-response relationships, with statistically significant p-trends for obesity, BMI, and waist circumference outcomes in most models of adults (see Supplemental Table S1).

Associations between markers of adiposity and exposure to parabens among children

Similar to adults, we generally observed an inverse trend of associations between urinary paraben concentrations (i.e., either individual or summed molar paraben concentrations) and adiposity measures among children, although findings were statistically significant or borderline significant only for MP, PP, and/or the molar sum (Table 4). For example, statistically significant inverse associations were observed between MP concentrations and the prevalence odds of being obese vs. normal weight (aPOR: 0.71; 95% CI: 0.52, 0.95) and a decreased waist circumference (β=−2.36; CI:−3.91, −0.82). Although p-values for effect measure modification by gender were mostly ≥0.20, we generally observed more pronounced inverse associations among girls, with some statistically significant associations, while associations among boys were null. In addition, we generally observed the same overall patterns of association when using creatinine-adjusted quartiles, with more pronounced sex-differences in some instances (see Supplemental Material, Table S2).

Sensitivity analysis

Inclusion of log10-tranformed bisphenol A, triclosan, 2,4-dichlorophenol, and 2,5-dichlorophenol concentrations did not alter the inference of our results (i.e., effect estimates were similar and patterns of association remained) for adults or children, suggesting that associations observed were independent of exposure to other phenolic compounds previously linked to adiposity measures (see Supplemental Material, Tables S3 and S4).

Discussion.

In this study, we examined the cross-sectional associations between markers of adiposity and urinary biomarker concentrations of four parabens commonly used in consumer products among a nationally representative sample of adults and children from the U.S. general population. We observed consistent and statistically significant inverse associations between urinary concentrations for all parabens and most measures of adiposity among adults. These inverse trends were also observed among children, but only statistically significant for MP and select adiposity measures (i.e., prevalence odds of being obese and waist circumference). We also observed more pronounced inverse associations among females, although for children, most associations were null upon stratification.

To date, few epidemiologic studies have examined the effects of parabens on measures of adiposity and results are generally inconsistent. Deierlein et al. investigated longitudinal associations of childhood exposures to several phenols, including parabens, and subsequent measures of adiposity among girls enrolled in The Breast Cancer and Environment Research Program (BCERP) (Deierlein et al. 2017). Although the authors reported inverse trends between measures of adiposity and the molar sum of urinary paraben concentrations in their population, effect sizes were small and results were not statistically significant. When we examined associations between paraben concentrations, expressed as the molar sum, and adiposity measures among children in our study population, we observed statistically significant inverse associations with obesity and waist circumference, and a borderline significant inverse association when examining the prevalence odds of being overweight vs normal weight as well as BMI z-scores. Overall, this inverse trend was stronger among girls in our study population although, in general, effect measure modification by gender was not statistically significant for the molar sum. The median creatinine-adjusted concentration for the molar sum of parabens among girls 6–8 years old in our study population was comparable to that reported by Deierlein et al. among girls of the same age range (96.5 μg/gCr vs. 90.8 μg/gCr, respectively) but higher when including all girls in our target age range (girls 6–19 years: 137.6 μg/gCr). In another study, exposure to parabens among three-year old Korean children was not associated with BMI z-scores, although authors did report that ethyl paraben was positively associated with weight and height z-scores among boys (Guo et al. 2017). Geometric mean paraben concentrations reported in Korean children were higher than those observed among children in our study (MP- GM: 12.6 ug/gCre vs. 5.9 ug/gCre; MP GM-: 7.1 ug/gCre vs. 2.4 ug/gCre). Still, comparisons across these studies should be interpreted with caution given differences in study design (longitudinal vs. cross-sectional), and demographic characteristics of the study populations, including age, and potential product use patterns.

While no other epidemiologic studies have examined associations of paraben exposures with adiposity, BMI has been assessed as a predictor of paraben concentrations in several cross-sectional studies. Among adults, exposure to methyl and propyl paraben has been reported to be positively correlated with BMI in Korean adults (Kang et al. 2016), while exposure to these and other parabens were inversely correlated with BMI in two other U.S. studies (Koeppe et al. 2013; Meeker et al. 2011). However, the focus of prior studies in adults was not adiposity measures, hence they did not control for several important covariates included in our analyses.

Recent *in vitro* studies by Hu et al. examined the effects of exposure to parabens in murine 3T3-L1 cells (a widely used *in vitro* cell model for adipocyte differentiation) and reported that exposure to parabens promotes adipogenesis, as revealed by adipocyte morphology, lipid accumulation, and mRNA expression of adipocyte-specific markers (Hu et al. 2013). The authors also found that the adipogenic potency of parabens increased with increasing length of the linear alkyl chain; and that parabens activate glucocorticoid receptor and/or peroxisome proliferator-activated receptor (PPAR)γ in preadipocytes, the two established signaling pathways in adipocyte differentiation. The authors also reported that parabens induce changes in gene expression related to adipocyte differentiation and lipogenesis in adipose tissue among female mice (Hu et al. 2016), and that parabens alter multipotent mesenchymal stem cell fates towards adipocyte lineage (Hu et al. 2017). Based on these findings, the authors suggest that parabens could potentially play a role in the development of obesity. Our results of an inverse association between exposure to parabens and markers of adiposity; however, are more in line with a recent *in vivo* study from another research group that reported a statistically significant reduction in body weight among female adolescent rats and adult rats (albeit not statistically significant among adult rats) exposed postnatally to methyl paraben at environmentally relevant doses (Hu J. et al. 2016). These authors also reported changes in the gut microbiome among adolescent rats exposed to methyl paraben individually or as part of a mixture to two other endocrine disrupting compounds (diethyl phthalate and triclosan). Interestingly, emerging studies have implicated distortion of the normal microbial balance in obesity (Shen et al. 2013; Torres-Fuentes et al. 2017). Still, studies on the role of endocrine disrupting compounds on the human microbiome and their related health effects, including obesity, are scarce. One potential explanation for the overall inverse trend observed in our study may be the possible sequestration of parabens by adipose tissue. There is emerging evidence indicating that some endocrine disrupting compounds considered to be non-persistent, including parabens, may deposit in human adipose tissue (Artacho-Cordon et al. 2017; Wang et al. 2015). Artacho-Cordon et al. recently reported that concentrations of MP were widely detected in adipose tissue, and that MP concentrations in adipose tissue were not correlated with urinary concentrations. Thus, it is plausible that individuals with greater body fat store more parabens in their adipose tissue, potentially excreting less parabens in urine. This phenomenon would lead to inverse associations of parabens with body fat and could explain our results. Paraben storage in fat would also be consistent with the more pronounced effect observed among females, as compared to males they tend to have more adipose tissue (Fuente-Martin et al. 2013; Karastergiou et al. 2012; Taylor et al. 2010). In general, our findings among adults for most parabens, including frequently detected parabens (methyl

and propyl parabens), tend to support this hypothesis with more pronounced inverse associations observed among obese adults compared to overweight adults when comparing each of these groups to normal weight adults. However, this general trend was not observed among children in our study. More in-depth studies are needed to examine this hypothesis further.

Our results should be interpreted with caution as our study has some limitations. First, we relied on measurement of parabens in a single spot urine sample to assess exposure to chemicals considered to be non-persistent as a proxy to ascertain chronic exposure (Janjua et al. 2008). If paraben concentrations only reflect recent exposures, our measures could represent recent rather than cumulative exposure to parabens. In addition, obesity is a complex and chronic multifactorial disease that developed before the exposures were measured in our study population. Thus, given the cross-sectional design of the NHANES, there is a potential for reverse-causation if individuals with higher body fat consumed or used *less* paraben-containing products. Nonetheless, we adjusted for a wide-range of sociodemographic and dietary consumption behavior variables and strong inverse associations remained.

Although we evaluated associations of paraben exposures among children and adults, the prenatal period may be another sensitive window of susceptibility for developmental programming of metabolic disorders (Heindel et al. 2015). A recent study reported a positive association between birth weight and prenatal exposure to parabens among boys (Philippat et al. 2014). Prior studies have also reported sex-specific associations of prenatal exposures to other non-persistent consumer product chemicals with childhood body size. For example, third trimester benzophenone-3 and di-(2-ethylhexyl) phthalate metabolite concentrations were associated with lower percent body fat or body mass index among girls, but not boys, in previous birth cohort studies (Buckley et al. 2016a; Buckley et al. 2016b). Future work evaluating critical windows of susceptibility, including gestation and puberty, are needed to evaluate whether effects of paraben exposures differ by life stage.

Despite these limitations, our study has several strengths. To our knowledge, this is the first epidemiologic study to thoroughly assess the association between markers of adiposity and exposure to four commonly used parabens in a large representative sample of adults and children from the U.S. general population. Thus, our results may be generalizable to U.S. children, adolescents, and adults. Also, findings were consistent among several measures of adiposity and we observed consistent evidence of inverse linear exposure-response relationships. In addition, our findings were independent of exposure to other phenolic compounds for which a few studies have reported a link with adiposity measures.

Conclusions.

In summary, urinary paraben concentrations were inversely associated with select markers of adiposity among adults and children in a representative sample of the U.S. general population and associations were more pronounced among females. Due to the cross-sectional design of our study, our findings should be interpreted with caution and replicated in future longitudinal studies. Also, because gestation is a critical period during which

exposures to environmental contaminants may alter the developmental programming of metabolism, studies examining prenatal paraben exposures are warranted. Lastly, more studies are needed to examine the role of paraben sequestration in adipose tissue and to elucidate the potential underlying mechanisms by which parabens may influence metabolism.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

aPOR	adjusted prevalence odds ratio
BMI	Body Mass Index
BP	Butyl paraben
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
EP	Ethyl paraben
GM	Geometric Mean
GSD	Geometric Standard Deviation
LOD	Limit of detection
MP	Methyl paraben
NCHS	National Center for Health Statistics
NHANES	National Health and Nutrition Examination Survey
PP	Propyl paraben
WC	Waist circumference

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Table 1.

Study population characteristics for adults 2007–2014 (20+ years) and children 2007–2012 (6–19 years).

Characteristic		Adults (n=4730)	Children (n=1324)
		N (%)	N (%)
Gender			
	Male	2306 (48.8)	684 (51.7)
	Female	2424 (51.3)	640 (48.3)
Race/ethnicity			
	Non-Hispanic White	2246 (47.5)	403 (30.4)
	Non-Hispanic Black	871 (18.4)	305 (23.0)
	Mexican	797 (16.9)	355 (26.8)
	Other	816 (17.3)	261 (19.7)
Poverty Income Ratio			
	0–1.85	1961 (41.5)	728 (55.0)
	1.85–3.49	995 (21.0)	275 (20.8)
	≥3.50	1774 (37.5)	321 (24.2)
Smoking status[a]			
	Not a current smoker	3448 (72.9)	1179 (89.1)
	Current smoker	1282 (27.1)	145 (11.0)
Physical activity level			
	Inactive	3273 (69.2)	N/A
	Moderate activity	659 (13.9)	N/A
	Vigorous activity	798 (16.9)	N/A
Healthy diet			
	Excellent	405 (8.6)	N/A
	Very good	1044 (22.1)	N/A
	Good	1944 (41.1)	N/A
	Fair	1096 (23.2)	N/A
	Poor	241 (5.1)	N/A
Body mass index (BMI) categories[b]			
	Underweight	66 (1.4)	50 (3.8)
	Normal	1273 (26.9)	760 (57.4)
	Overweight	1622 (34.3)	223 (16.8)
	Obese	1769 (37.4)	291 (22.0)
Waist circumference (cm)[c]			
	Normal	1995 (42.2)	N/A
	High	2735 (57.8)	N/A
Number of meals not home prepared in the past 7 days			
	None	1091 (23.1)	287 (21.7)
	1–2 meals	1491 (31.5)	544 (41.1)

Characteristic	Adults (n=4730)	Children (n=1324)
	N (%)	N (%)
3 or more meals	2148 (45.4)	493 (37.2)
Number of fast food meals in the past 7 days		
None	2299 (48.6)	465 (35.12)
1–2 meals	1484 (31.4)	586 (44.0)
3 or more meals	947 (20.0)	273 (20.6)
Number of ready-to-eat meals in the past 30 days		
None	3295 (69.7)	934 (70.5)
1–2 meals	693 (14.7)	184 (13.9)
3 or more meals	742 (15.7)	206 (15.6)
Number of frozen meals or pizza in the past 30 days		
None	2952 (62.4)	630 (47.6)
1–2 meals	811 (17.2)	262 (19.8)
3 or more meals	967 (20.4)	432 (32.6)
	Mean (SD)	
Age (years)	49.6 (17.4)	12.3 (4.0)
Total calories (kcal)	2033.8 (872.9)	1959.4 (707.1)
Body mass index (kg/m^2)	29.1 (6.7)	21.8 (6.0)
BMI z-score	N/A	0.6 (1.2)
Waist circumference (cm)	99.4 (16.2)	74.9 (16.4)

a. Smoking status was ascertained by serum cotinine concentrations (individuals were classified as a non/passive smoker or not current smoker if cotinine concentrations were <3.0 μg/L and as a current or active smoker if cotinine concentrations were ≥ 3.0 μg/L).

b. BMI (kg/m^2) was used to classify adults as underweight (BMI <18.5), normal weight (18.5 ≤BMI <25.0 kg/cm2), overweight (25.0 ≤BMI <30.0 kg/cm2), or obese (BMI ≥ 30.0 kg/cm2); For children, we used age- and sex-standardized BMI percentiles based on BMI z-scores to classify each child as underweight (<5th BMI percentile), normal weight (5th ≤ BMI percentile < 85th), overweight (85th < BMI percentile ≤ 95th) or obese (≥95th BMI percentile).

c. Waist circumference (wc) categories: Normal refers to males with wc ≤102 cm and females with wc ≤ 88 cm; High refers to males with wc>102 cm and females with wc >88 cm based on guidelines from NHLBI. Similar guidelines are not available for children and are thus not reported. Abbreviations: N/A- Not available; SD- standard deviation

Table 2.

Summary statistics for urinary paraben concentrations among adults (NHANES 2007–14) and children (NHANES 2007–12) in μg/L (μg/g Creatinine).[a,b]

Adults (N=4730)	DF (%)	GM	GSD	Min	p25	p50	p75	Max
BP	38.8	n/a	n/a	<LOD	<LOD	<LOD	0.6(0.7)	860(887)
EP	51.9	n/a	n/a	<LOD	<LOD	1.1(1.6)	6.7(6.6)	2100(1591)
MP	99.6	5.8(5.9)	0.10(0.11)	<LOD	18.0(16.7)	68.4(74.6)	245.9(253.8)	12500(8373)
PP	95.0	2.4(2.4)	0.05(0.05)	<LOD	1.2(1.2)	8.3(8.8)	50.9(54.5)	4490(3276)
Molar Sum	--	7.0 (7.1)	0.16 (0.12)	1.7 (1.4)	25.9 (24.7)	106.2 (114.3)	378.7 (406.5)	19299 (11851)
Children (N=1324)								
BP	40.0	n/a	n/a	<LOD	<LOD	<LOD	0.4(0.5)	493(197)
EP	39.2	n/a	n/a	<LOD	<LOD	<LOD	2.3(2.4)	1760(1044)
MP	99.4	5.4(5.2)	0.18(0.17)	<LOD	15.7(16.9)	52.4(50.1)	194(178.8)	13200(8250)
PP	95.4	2.1(2.1)	0.08(0.08)	<LOD	1.2(1.2)	5.5(5.2)	28.9(27.2)	2650(1766)
Molar Sum	--	6.4 (6.2)	0.24 (0.20)	1.9 (1.6)	23.2 (24.8)	73.7 (74.8)	291.7 (266.8)	18555 (11597)

a. Select summary statistics are not reported for butyl and ethyl paraben given their low detection frequencies; these statistics are denoted as "n/a". Creatinine-adjusted concentrations (μg/gCre) are presented in parentheses.

b. Molar sum reflects the molar sum (Σ μmol/L) of butyl- (MW=194), ethyl- (MW-166), methyl- (MW=152), and propyl- (MW=180) parabens in units of g/mol. Molar sum was expressed as propyl paraben in μg/L by multiplying by its MW (Σ μmol/L*180 = Σ μg/L). Abbreviations: DF: detection frequency; GM: geometric mean; GSD: geometric standard deviation; LOD: limit of detection (LODs for parabens in μg/L: butyl paraben=0.2; ethyl paraben=1.0; methyl paraben=1.0; propyl paraben=0.2).

Table 3.

Associations between urinary paraben concentrations and adiposity measures for ADULTS.[a]

	Adults: Obese vs. Normal (N=3009)												
							Male (N=1354)			Female (N=1655)			
	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
BP (<LOD vs. ≥ LOD)	0.68	(0.57, 0.82)	<0.01	0.78	(0.64, 0.94)	<0.01	0.76	(0.54, 1.08)	0.13	0.84	(0.63, 1.11)	0.22	0.70
EP (<LOD vs. ≥ LOD)	0.51	(0.43, 0.61)	<0.01	0.52	(0.41, 0.66)	<0.01	0.46	(0.35, 0.60)	<0.01	0.60	(0.45, 0.82)	<0.01	0.10
MP (log10)	0.72	(0.63, 0.83)	<0.01	0.64	(0.55, 0.73)	<0.01	0.82	(0.67, 1.01)	0.06	0.51	(0.42, 0.61)	<0.01	<0.01
PP (log10)	0.79	(0.71, 0.87)	<0.01	0.74	(0.67, 0.83)	<0.01	0.91	(0.78, 1.06)	0.23	0.64	(0.55, 0.75)	<0.01	<0.01
Molar sum (log10)	0.70	(0.61, 0.81)	<0.01	0.62	(0.54, 0.71)	<0.01	0.80	(0.66, 0.98)	0.03	0.50	(0.41, 0.60)	<0.01	<0.01
	Adults: Overweight vs. Normal (N=2862)												
							Male (N=1473)			Female (N=1389)			
	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
BP (<LOD vs. ≥ LOD)	0.59	(0.50, 0.70)	<0.01	0.75	(0.61, 0.92)	0.01	0.81	(0.59, 1.10)	0.18	0.75	(0.58, 0.97)	0.03	0.69
EP (<LOD vs. ≥ LOD)	0.66	(0.53, 0.82)	<0.01	0.79	(0.63, 0.98)	0.03	0.72	(0.54, 0.95)	0.02	0.89	(0.66, 1.20)	0.44	0.28
MP (log10)	0.78	(0.69, 0.89)	<0.01	0.89	(0.77, 1.02)	0.09	0.96	(0.78, 1.19)	0.72	0.83	(0.68, 1.01)	0.06	0.33
PP (log10)	0.85	(0.77, 0.93)	<0.01	0.98	(0.88, 1.08)	0.66	1.03	(0.91, 1.17)	0.64	0.95	(0.83, 1.10)	0.50	0.37
Molar sum (log10)	0.78	(0.69, 0.88)	<0.01	0.89	(0.78, 1.02)	0.08	0.96	(0.78, 1.18)	0.68	0.84	(0.69, 1.02)	0.07	0.40
	Adults: BMI (kg/m^2) (N=4730)												
							Male (N=2306)			Female (N=2424)			
	All Adults Crude β	95% CI	p-value	All Adults β	95% CI	p-value	β	95% CI	p-value	β	95% CI	p-value	EMM p-value

	Adults: Obese vs. Normal (N=3009)												
							Male (N=1354)			Female (N=1655)			
	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
BP (<LOD vs. ≥ LOD)	−1.04	(−1.53, −0.56)	<0.01	−1.10	(−1.59, −0.60)	<0.01	−1.07	(−1.63, −0.51)	<0.01	−0.95	(−1.70, −0.21)	0.01	0.81
EP (<LOD vs. ≥ LOD)	−1.46	(−1.85, −1.06)	<0.01	−1.40	(−1.89, −0.92)	<0.01	−1.60	(−2.10, −1.10)	<0.01	−1.04	(−1.80, −0.27)	<0.01	0.21
MP (log10)	−0.83	(−1.22, −0.45)	<0.01	−1.21	(−1.58, −0.85)	<0.01	−0.51	(−0.94, −0.08)	0.02	−1.58	(−2.15, −1.01)	<0.01	<0.01
PP (log10)	−0.57	(−0.83, −0.31)	<0.01	−0.82	(−1.07, −0.57)	<0.01	−0.32	(−0.63, −0.00)	0.05	−1.08	(−1.46, −0.69)	<0.01	<0.01
Molar sum (log10)	−0.89	(−1.26, −0.52)	<0.01	−1.28	(−1.63, −0.93)	<0.01	−0.57	(−1.00, −0.14)	0.01	−1.64	(−2.19, −1.08)	<0.01	<0.01
	Adults: High vs. Normal Waist Circumference[b] (N=4730)												
							Male (N=2306)			Female (N=2424)			
	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
BP (<LOD vs. ≥ LOD)	1.05	(0.92, 1.21)	0.46	0.80	(0.67, 0.95)	0.01	0.77	(0.60, 0.98)	0.04	0.86	(0.68, 1.10)	0.23	0.51
EP (<LOD vs. ≥ LOD)	0.80	(0.70, 0.92)	<0.01	0.64	(0.54, 0.76)	<0.01	0.61	(0.49, 0.77)	<0.01	0.71	(0.56, 0.90)	<0.01	0.37
MP (log10)	1.00	(0.92, 1.10)	0.95	0.70	(0.63, 0.78)	<0.01	0.84	(0.71, 0.99)	0.04	0.59	(0.51, 0.68)	<0.01	0.01
PP (log10)	1.04	(0.97, 1.11)	0.31	0.81	(0.75, 0.88)	<0.01	0.93	(0.83, 1.04)	0.22	0.72	(0.64, 0.81)	<0.01	0.01
Molar sum (log10)	1.00	(0.92, 1.09)	0.99	0.69	(0.63, 0.77)	<0.01	0.83	(0.70, 0.98)	0.03	0.59	(0.51, 0.68)	<0.01	0.01

a. All crude models were adjusted for log10-creatinine concentrations and for adjusted models we controlled for age, gender, race/ethnicity, poverty income ratio, cycle year, total calories, physical activity, serum cotinine, log-10 creatinine, healthy diet, number of meals not home prepared, number of fast food meals, number of ready-to-eat meals, number of frozen meals or pizza, and, for overall models, sex.

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

Table 4.

Associations between urinary paraben concentrations and adiposity measures for CHILDREN.[a]

	All Children Crude POR	95% CI	p-value	All Children aPOR	95% CI	p-value	Male (N=554) aPOR	Male (N=554) 95% CI	Male (N=554) p-value	Female (N=497) aPOR	Female (N=497) 95% CI	Female (N=497) p-value	EMM p-value
Children: Obese vs. Normal (N=1051)													
BP (<LOD vs. ≥ LOD)	0.87	(0.61, 1.25)	0.45	0.98	(0.64, 1.49)	0.92	1.27	(0.77, 2.11)	0.35	0.75	(0.47, 1.19)	0.22	0.05
EP (<LOD vs. ≥ LOD)	0.74	(0.53, 1.02)	0.06	0.83	(0.61, 1.12)	0.21	1.14	(0.68, 1.89)	0.63	0.69	(0.31, 1.55)	0.37	0.40
MP (log10)	0.75	(0.60, 0.95)	0.02	0.71	(0.52, 0.95)	0.02	0.81	(0.56, 1.18)	0.27	0.65	(0.41, 1.01)	0.06	0.42
PP (log10)	0.87	(0.71, 1.05)	0.14	0.89	(0.72, 1.10)	0.27	1.02	(0.76, 1.37)	0.91	0.79	(0.53, 1.18)	0.25	0.36
Molar sum (log10)	0.75	(0.59, 0.96)	0.02	0.72	(0.53, 0.96)	0.03	0.83	(0.56, 1.21)	0.32	0.67	(0.41, 1.09)	0.11	0.51
Children: Overweight vs. Normal (N=983)													
BP (<LOD vs. ≥ LOD)	1.17	(0.69,1.98)	0.56	1.16	(0.64, 2.09)	0.63	1.08	(0.53, 2.21)	0.84	1.52	(0.66, 3.46)	0.32	0.50
EP (<LOD vs. ≥ LOD)	0.97	(0.65, 1.43)	0.86	0.95	(0.64, 1.42)	0.82	1.30	(0.65, 2.57)	0.45	0.89	(0.55, 1.45)	0.65	0.41
MP (log10)	0.81	(0.59, 1.11)	0.19	0.67	(0.45, 0.99)	0.05	0.80	(0.41, 1.56)	0.51	0.52	(0.32, 0.85)	0.01	0.31
PP (log10)	0.86	(0.65, 1.13)	0.26	0.75	(0.55, 1.02)	0.07	0.77	(0.50, 1.18)	0.23	0.70	(0.49, 1.01)	0.06	0.71
Molar sum (log10)	0.81	(0.57, 1.13)	0.22	0.70	(0.48, 1.02)	0.07	0.79	(0.41, 1.54)	0.49	0.54	(0.33, 0.90)	0.02	0.34
Children: BMI z-score (N=1324)													
	All Children Crude β	95% CI	p-value	All Children β	95% CI	p-value	Male (N=684) β	Male (N=684) 95% CI	Male (N=684) p-value	Female (N=640) β	Female (N=640) 95% CI	Female (N=640) p-value	EMM p-value

	Children: Obese vs. Normal (N=1051)												
							Male (N=554)			Female (N=497)			
	All Children Crude POR	95% CI	p-value	All Children aPOR	95% CI	p-value	aPOR	95% CI	p-value	aPOR	95% CI	p-value	EMM p-value
BP (<LOD vs. ≥ LOD)	−0.04	(−0.19, 0.11)	0.63	−0.06	(−0.23, 0.11)	0.46	−0.04	(−0.29, 0.22)	0.78	−0.09	(−0.30, 0.11)	0.37	0.74
EP (<LOD vs. ≥ LOD)	−0.09	(−0.25, 0.07)	0.28	−0.08	(−0.24, 0.08) (	0.31	0.10	(−0.18, 0.38)	0.50	−0.24	(−0.43, −0.04)	0.02	0.06
MP (log10)	−0.06	(−0.16, 0.05)	0.27	−0.13	(−0.25, 0.00)	0.05	−0.07	(−0.28, 0.13)	0.48	−0.19	(−0.33, −0.06)	<0.00	0.31
PP (log10)	−0.03	(−0.12, 0.06)	0.49	−0.07	(−0.15, 0.01)	0.09	−0.03	(−0.16, 0.09)	0.62	−0.11	(−0.22, 0.01)	0.07	0.41
Molar sum (log10)	−0.06	(−0.17, 0.05)	0.31	−0.13	(−0.25, 0.00)	0.05	−0.06	(−0.26, 0.14)	0.58	−0.20	(−0.34, −0.06)	0.01	0.21
	>Children: Waist Circumference (cm) (N=1324)												
							Male (N=684)			Female (N=640)			
	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
BP (<LOD vs. ≥ LOD)	−1.17	(−2.91, 0.57)	0.19	−1.29	(−3.17, 0.60)	0.18	−0.30	(−3.18, 2.57)	0.84	−1.78	(−4.07, 0.51)	0.13	0.43
EP (<LOD vs. ≥ LOD)	−0.98	(−2.95, 1.00)	0.33	−1.26	(−3.15, 0.63)	0.19	0.75	(−2.18, 3.67)	0.62	−2.45	(−5.31, 0.41)	0.09	0.14
MP (log10)	−1.41	(−2.70, −0.12)	0.03	−2.36	(−3.91, −0.82)	<0.01	−1.28	(−3.36, 0.80)	0.23	−2.92	(−4.89, −0.95)	<0.01	0.22
PP (log10)	0.08	(−0.96, 1.11)	0.88	−1.15	(−2.31, 0.00)	0.05	−0.08	(−1.58, 1.42)	0.92	−1.67	(−3.31, −0.02)	0.05	0.15
Molar sum (log10)	−1.00	(−2.29, 0.30)	0.13	−2.23	(−3.82, −0.64)	0.01	−0.98	(−3.07, 1.11)	0.36	−2.83	(−4.92, −0.73)	0.01	0.19

a. All crude models were adjusted for log10-creatinine concentrations and for adjusted models we controlled for age, gender, race, poverty income ratio, cycle year, total calories, serum cotinine, log-10 creatinine, number of meals not home prepared, number of fast food meals, number of ready-to-eat meals, number of frozen meals or pizza, and, for overall models, sex. Abbreviations: aPOR: Adjusted prevalence odds ratio; EMM p-value: p-value for effect measure modification (EMM) by sex.