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Synergistic interaction between polycyclic aromatic hydrocarbons and environmental tobacco smoke on the risk of obesity in children and adolescents: The U.S. National Health and Nutrition Examination Survey 2003–2008

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ABSTRACT

Background: Polycyclic aromatic hydrocarbons (PAHs) may be obesogens. However, the role of PAHs independent of environmental tobacco smoke (ETS) is unclear, and the interaction between PAHs and ETS remains unknown.

Methods: We performed cross-sectional analyses of urinary concentrations of PAH metabolites, body mass index (BMI), and waist circumference (WC) in 1985 people aged 6–18 years using data from the 2003–2008 U.S. National Health and Nutrition Examination Survey. ETS exposure level was measured as serum cotinine level.

Results: PAH metabolites were positively associated with BMI and WC in both the ETS-unexposed and ETS-exposed groups. The adjusted odds ratios for general obesity defined by age- and sex-specific BMI ≥ 95th percentile across the quartiles of total PAH metabolites were 1, 4.51, 2.57, and 8.09 ($P_{trend}=0.003$) in the ETS-unexposed group and 1, 2.02, 1.83, and 3.86 ($P_{trend}<0.001$) in the ETS-exposed group. However, the association of PAH metabolites with obesity became stronger as serum cotinine levels increased ($P_{interaction}<0.05$). Among those with high ETS exposure, the adjusted odds ratios for general obesity across quartiles of total PAH metabolites were 1, 2.89, 5.26, and 16.29 ($P_{trend}<0.001$). Compared to the low PAH-exposure group without exposure to ETS, the high ETS- and high PAH-exposure group had 33.85- and 17.64-fold greater risks of general and central obesity, respectively.

Conclusion: Environmental exposure to PAHs may be associated with childhood obesity irrespective of ETS. In particular, simultaneous exposure to PAHs and ETS may substantially increase the risk of obesity.

1. Introduction

The prevalence of childhood obesity is increasing rapidly worldwide, although there is some evidence that the increase has leveled off (Nguyen and El-Serag, 2010; Ogden et al., 2014). Long-term energy imbalance such as excessive caloric intake and inadequate physical exercise is a key related factor. In addition, exposure to endocrine-disrupting chemicals such as persistent organic pollutants, organotins, phthalates, and bisphenol A may contribute to the obesity epidemic (Grun and Blumberg, 2009; Thayer et al., 2012). Such chemicals are collectively referred to as "obesogens" (Grun and Blumberg, 2009). In particular, exposure to obesogens during developmental periods of life, including early childhood and puberty, is an important issue in the study of endocrine disruption because of high susceptibility and permanent effects (Diamanti-Kandarakis et al., 2009).

Polycyclic aromatic hydrocarbons (PAHs), which are formed during the incomplete combustion of organic materials, were recently suggested to be obesogens. An animal experimental study revealed that treatment with a PAH, benzo[a]pyrene, directly inhibits lipolysis in adipocytes and causes fat mass gain in mice (Irigaray et al., 2006). In addition, an epidemiologic study of American children reports an association between urinary metabolites of PAHs and obesity (Scinicariello and Buser, 2014). The main sources of PAHs in the general population are motor vehicle

Abbreviations: BMI, body mass index; ETS, environmental tobacco smoke; FLUO, fluorine; OH-PAH, monohydroxy-PAH; NAP, naphthalene; PAH, polycyclic aromatic hydrocarbons; PHEN, phenanthrene; PPAR, peroxisome proliferator-activated receptor; PYR, pyrene; WC, waist circumference

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exhaust, residential heating, industrial byproducts such as those from coke production and oil refining, charbroiled foods, and passive and active cigarette smoking (Liu et al., 2008).

On the other hand, cigarette smoke comprises several chemicals with endocrine-disrupting properties. Environmental tobacco smoke (ETS) is another potential risk factor of obesity (Weitzman et al., 2005; Xie et al., 2010). ETS plays an important role in the relationship between PAHs and childhood obesity, because cigarette smoke itself is one of main sources of exposure to PAHs (Ding et al., 2005). A previous epidemiologic study on PAHs and childhood obesity adjusted for serum cotinine as a potential confounder (Scinicariello and Buser, 2014). However, this may be an overadjustment, considering the strong correlation between PAHs and plasma cotinine (St Helen et al., 2012). Meanwhile, not adjusting for ETS exposure could result in the overestimation of the strength of association between PAHs and childhood obesity. Therefore, the independent effects of PAHs on childhood obesity could be most accurately evaluated in children without ETS exposure.

Furthermore, despite the fact that humans are simultaneously exposed to numerous chemicals originating from the environment, most experimental and epidemiologic studies of obesogens focus on single chemicals. As endocrine-disrupting chemicals tend to exhibit non-monotonic dose–response relationships with various biological outcomes such as weight gain (Vandenberg et al., 2012) and the biologic effects of one endocrine-disrupting chemical can vary greatly depending on the presence others (Makita et al., 2004), the associations among these chemicals may be complicated. Therefore, determining if the associations between PAHs and obesity differ according to ETS levels would be interesting.

Accordingly, this study aimed to (1) confirm the independent role of PAHs as obesogens by evaluating the association between PAHs and obesity in children and adolescence without ETS exposure, which was assessed according to serum cotinine level, and (2) evaluate the possible interaction between PAHs and ETS on the risk of obesity.

2. Materials and methods

2.1. Data collection and study population

The present study is based on merged data from the 2003–2004, 2005–2006, and 2007–2008 National Health and Nutrition Examination Survey (NHANES). The NHANES is a continuous, 2-year-cycle program administrated by the National Centers for Health Statics (NCHS) of the Centers for Disease Control and Prevention (CDC). The surveys focus on various health and nutrition measurements, including bio-monitoring for environmental chemicals. The NHANES involves a stratified multistage probability sample representative of the civilian non-institutionalized US population. Detailed descriptions of the NHANES study design can be found elsewhere (Centers for Disease Control and Prevention (CDC), 2013).

The present analysis used data from the questionnaire including diet, laboratory, and physical examination of the NHANES. One-third of NHANES participants aged 6 years or older were randomly selected to measure urinary monohydroxy-PAH (OH-PAH) levels. The study sample consisted of 2667 children aged 6–18 years with valid measurements of OH-PAHs. Those without information on body mass index (BMI), waist circumference (WC) ($n=57$), and serum cotinine level ($n=289$) were excluded. In addition, participants whose serum cotinine level was ≥ 10 ng/mL ($n=169$), which is equivalent to active smoking (Pirkle et al., 2006), were excluded; this is because current light or moderate smokers tend to have lower body weight than never smokers (Chiolero et al., 2007). Finally, we excluded participants with overly diluted or concentrated urine samples (urine creatinine concentration: >300 or <30 mg/dL) to ensure valid results ($n=167$) (World Health Organization, 1996). Therefore, a total of 1985 subjects were analyzed. Even though the 2001–2002 NHANES data included information on PAHs, they were not included in the analyses, because the kinds of measured PAH metabolites and analytic methods were slightly different from those of the 2003–2008 datasets (Li et al., 2006).

Written informed consent and child assent when appropriate were obtained from parents/guardians and/or participants. This study was approved by the NCHS Research Ethics Review Board.

2.2. Anthropometric measurements

In the NHANES, trained health technicians performed body measurements (i.e., BMI and WC) following standardized procedures (Lohman et al. 1998). BMI (kg/m^2) was calculated by using height (cm) and weight (kg). Because BMI and WC vary widely by age and sex, we defined general and central obesity in children and adolescents as age- and sex-specific BMI $\geq$ 95th percentile (Barlow and Expert, 2007) and WC $\geq$ 90th percentile (Fernandez et al., 2004; Lee et al., 2009), respectively. BMI percentiles were calculated on the basis of the 2000 CDC growth curves.

2.3. Measurements of urinary PAH metabolites

The following 9 urinary PAH metabolites, commonly available in 3 data cycles of NHANES, were analyzed: 2 naphthalene (NAP) metabolites (i.e., 1-OH NAP, 2-OH NAP), 3 fluorene (FLUO) metabolites (i.e., 2-OH FLUO, 3-OH FLUO, 9-OH FLUO), 3 phenanthrene (PHEN) metabolites (i.e., 1-OH PHEN, 2-OH PHEN, 3-OH PHEN), and a pyrene (PYR) metabolite (i.e., 1-OH PYR). To reflect environmental exposure to the parent compound, we combined the concentrations of metabolites arising from the same parent compound. In addition, total PAH metabolites were calculated as the sum of all urinary PAH metabolites and used as a measure of cumulative exposure to multiple PAHs.

PAH metabolites were collected and measured in one spot urine sample using capillary gas chromatography combined with high-resolution mass spectrometry as described previously (Romanoff et al., 2006). Analytes below the detection limit were assigned a value equal to the detection limit divided by the square root of 2 ($<3\%$ for 2-OH PHEN, $<1\%$ for other OH-PAHs). To control urine dilution in spot urine samples, urinary creatinine was included as a covariate in the analyses as recommended previously (Barr et al., 2005).

2.4. Statistical analysis

Participants were categorized in quartiles of urinary concentration of combined PAH metabolites. The cutoffs of individual PAH metabolites are shown in Supplementary Table 1. ETS was classified into 4 groups on the basis of serum cotinine levels (detection limit: 0.015 ng/mL) (Benowitz, 1996): non-exposed to ETS (at or below the detection limit), low ETS (detection limit to 0.1 ng/mL), medium ETS (0.1–1.0 ng/mL), and high ETS (1.0–10.0 ng/mL).

The associations of PAH metabolites with adiposity measures (i.e., BMI percentile and WC) and the prevalences of general and central obesity were evaluated using multiple linear or logistic regression analysis where appropriate. All covariates were selected on the basis of evidence from the literature and availability in the datasets; they included age (continuous), sex (male or female), race (non-Hispanic white, non-Hispanic black, Hispanic, or other), urinary creatinine (continuous), parent/caregiver education ($<$ high school, high school, or $>$ high school), ETS, poverty income ratio (<1 or ≥ 1), television watching hours (<1, 1, 2, 3, 4, or ≥ 5 h/day), and calorie intake (continuous). Height (continuous) was also included in the models with the outcomes of waist circumference and central obesity. The poverty income ratio was used as an indicator of socioeconomic status; it was calculated by dividing family income by the poverty threshold adjusted for family size and inflation. Daily hours of television watching was used as a proxy of physical activity. Calorie intake was assessed according to the ratio of 24-h calorie intake to age- and sex-specific calorie needs according to the U.S. Department of Agriculture guideline (US Department of Agriculture, Dietary Guideline for Americans, 2010). To maximize the sample size in the multivariate analysis, missing covariate values were substituted with the median values of each variable. Among all subjects, 20.7% had missing values for television watching hours and $<5\%$ had missing values for any other covariate. Excluding individuals with missing values from the analysis did not change any conclusions.

First, we present the results of all participants and those without or with ETS exposure. When subjects with ETS exposure were included, models adjusted and unadjusted for serum cotinine are shown. Next, we evaluated if there were statistically significant interactions between PAH (quartiles) and ETS (low, medium, or high ETS) among those with ETS exposure by including multiplicative interaction terms in the models. In addition, we conducted stratified analyses according to serum cotinine levels. Appropriate sample weights reflecting the NHANES complex survey sampling design were applied to all analyses using Stata 12.0. All tests were 2 sided, and the level of significance was set at $P<0.05$.

3. Results

The geometric mean concentrations of urinary PAH metabolites were mostly higher in individuals with a lower poverty income ratio, lower parent/caregiver education, and higher ETS exposure. Ethnicity exhibited different patterns with respect to different PAH metabolites. Television watching and calorie