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Abstract

Background: Polycyclic aromatic hydrocarbons (PAHs) are known carcinogens and suspected endocrine disruptors. Prenatal exposure to PAHs has been associated with obesity in early childhood.

Objective: We examined the association of urinary PAH metabolites with adiposity outcomes (BMI z-score, waist circumference, and rate of obesity) in children and adolescents.

Methods: We performed whole-sample analyses of 3,189 individuals 6-19 years of age who participated in the 2001-2006 National Health and Nutrition Examination Survey. We performed multivariate linear and logistic regression to analyze the association of BMI z-score, waist circumference (WC) and obesity with concentrations of single urinary PAH compounds and the sum of PAHs. Furthermore, the analyses were stratified by developmental stage [i.e., children (6-11) and adolescents (12-19)].

Results: BMI z-score, WC, and obesity were positively associated with the molecular mass sum of the PAHs and the total sum of naphthalene metabolites. Most associations increased monotonically with increasing quartiles of exposure among children 6-11 years of age, whereas dose-response trends were less consistent for adolescents (12-19 years of age). Neither total PAHs nor total naphthalene metabolites were associated with overweight in either age group, and there was little evidence of associations between the outcomes and individual PAHs.

Conclusions: Total urinary PAH metabolites and naphthalene metabolites were associated with higher body mass index, waist circumference, and obesity in children ages 6-11, with positive but less consistent associations among adolescents.

Introduction

Childhood obesity has become an increasingly prevalent problem in the United States, with the rate of obesity in children and adolescents increasing from 6.1% in 1972-1974 National Health and Nutrition Examination Survey I (NHANES I) to 18.1% in NHANES 2007-2008 (Ogden and Carroll. 2010). The causes associated with this accelerating rate are being investigated, and an emerging hypothesis is that exposure to ubiquitous environmental toxins may play a role in these childhood growth patterns (reviewed in Newbold 2010). Polycyclic aromatic hydrocarbons (PAHs) are a family of chemicals that are created through the incomplete combustion of organic materials (ATSDR 1995, 2005). They are pervasive in our environment and distributed widely in the atmosphere. Nearly 100% of urinary samples collected through NHANES contain metabolites of naphthalene, fluorene, phenanthrene, and pyrene (Huang et al. 2006; Li et al. 2008). Humans can be exposed to them through inhalation of cigarette smoke, vehicle exhaust, and processed fossil fuels; or through ingestion of grilled and charred meats, contaminated flour and bread products, processed and pickled foods, and contaminated water and cow's milk (ATSDR 1995, 2005). Contact with air, water, or soil near hazardous waste sites also poses a threat for exposure; nursing infants whose mothers live near these sites are an especially susceptible population to exposure through their mothers' milk. PAHs consist of two or more fused aromatic rings. Light molecular weight PAHs (LMW PAHs) that have two or three aromatic rings are emitted in the gaseous phase, while high molecular weight PAHs (HMW PAHs), with five or more rings, are emitted in the particulate phase (ATSDR 1995, 2005).

PAHs are known carcinogens and suspected endocrine disruptors. Hydroxylated-PAHs, the main metabolic product of PAHs, are structurally similar to estrogen and have been shown to have

estrogenic activities (Schultz and Sinks 2002; Wenger et al. 2009). There is evidence that PAHs may act either antiestrogenically or estrogenically through disrupting estrogen-mediated pathways (Gozgit et al. 2004; Sievers et al. 2013). Some PAHs, such as phenanthrene and to a lesser extent fluorantene, show antiandrogenic effects (Chang and Liao 1987; Vingaard et al. 2000). Sun et al. (2008) showed that 1-naphthol and 2-naphthol may act as thyroid hormone receptor antagonists. Additionally, PAHs are transported into all tissues of the human body containing fat and have strong lipophilic properties. They can be stored in fat cells, the liver, and the kidneys and can accumulate by repeated and long-term exposures (Laher et al. 1984; Shu and Nichols 1979). Furthermore, experiments done in mice have shown that benzo[a]pyrene, a high molecular weight PAH, impairs adipose tissue lipolysis and leads to increased weight gain, increased fat mass, and changes in food intake (Irigaray et al. 2006).

Recently, studies have shown that prenatal exposure to PAHs is associated with reduced birth weight and birth head circumference as well as smaller birth size for gestational age among African Americans (Choi et al. 2008; Perera et al. 2003). Moreover, a study done in New York, USA, showed a positive association between maternal exposure to PAHs during pregnancy and increased rates of obesity in early childhood (Rundle et al. 2012). The objective of this study was to investigate whether low molecular weight PAHs are associated with adiposity outcomes (BMI z-score and rate of obesity) in children and adolescents (ages 6-19) using data from NHANES 2001-2006.

Methods

Study population

The NHANES studies from 2001–2006, conducted by the U.S. National Center for Health Statistics (NCHS; Centers for Disease Control and Prevention, CDC, Atlanta, GA) with biomonitoring data evaluated by the National Center for Environmental Health (NCEH), are cross-sectional, multi-stage, nationally representative surveys of the non-institutionalized civilian population of the United States (NCHS 2008a). NCHS maintains that Institutional Review Board (IRB) approval and informed consent was obtained from all participants in these surveys. The grouping we used consisted of 3 cycles (2001–2002, 2003–2004 and 2005–2006) that were combined using NCHS recommendations (NCHS 2008b). Interviews were conducted in participants' homes and extensive physical examinations, which included blood and urine collection, were conducted at mobile exam centers (MEC).

Measure of adiposity: BMI Z-score, waist circumference and obesity

Body Mass Index (BMI) is calculated by the weight divided by height squared (kg/m^2). However, since the relation between BMI and body weight in children depends on age and gender, it is more appropriate to calculate the BMI z-score. The BMI z-score is the number of standard deviation (SD) by which a child differs from the mean BMI of children of the same age and gender. Thus, the BMI z-score allows comparison of children of different ages and gender. The age and sex independent BMI z-scores were calculated using the methodology provided by the Centers for Disease Control and Prevention (http://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm).

Individuals were classified as overweight and obese as BMI z-score between the 85th -94th percentile and $\geq$ 95th percentile for age and sex.

Waist circumference (WC) was measured by trained technicians to the nearest 0.1 cm using standardized protocol.

Covariates

We controlled for the following a priori confounders of the association between PAHs and BMI z-score and obesity: age, race/ethnicity, gender, urinary creatinine, poverty income ratio (PIR), serum cotinine, serum c-reactive protein, calorie intake, and television, videogame and computer usage. PIR is a measure of socioeconomic status and represents the calculated ratio of household income to the poverty threshold after accounting for inflation and family size.

Caloric intake was categorized as "normal" and "excessive" based on the US Department of Agriculture calorie intake guidelines by age and sex (http://health.gov/dietaryguidelines/dga2010/DietaryGuidelines2010.pdf). The individual cut-off caloric need was the highest value for the range by age and gender assuming a moderate physical activity level. Information on daily hours of television, video or computer use was obtained by questionnaire and the covariate was categorized with a cut point of $\geq$ 2 h/d.

Laboratory analysis

PAH metabolites were measured in spot urine samples obtained from a random subsample of one third of subjects aged 6 years and older. The 8 monohydroxy-PAHs (OH-PAH) we investigated were measured using gas chromatography combined with high-resolution mass spectrometry as detailed in Romanoff et al. (2006). Additionally, we created three other variables: the sum of the

individually-calculated molar mass of all PAH metabolites (∑molPAHs), the sum of the naphthalene metabolites (∑NAPHT), and the sum of the metabolites of the PAHs with 3 (fluorene and phenanthrene) or 4 (pyrene) benzene rings (∑mol3-4PAHs). To account for variation in dilution in spot urinary samples, urinary creatinine was entered in the analyses as an independent variable as suggested by previous studies (Barr et al, 2005; Ikeda et al. 2003). Urinary creatinine was determined using a Jaffé rate reaction measured with a CX3 analyzer (NCHS 2007).

C-reactive protein (CRP) is a marker of inflammation and has been associated with obesity (Dowd et al. 2010). Serum CRP was measured by a high-sensitivity assay using latex-enhanced nephelometry, with a lower limit of detection of the assay of 0.1 mg/L. CRP was categorized in weighted tertiles. Serum cotinine, a marker of exposure to environmental tobacco smoke, was categorized by weighted quartiles.

Statistical methods

Sample weights were used for analyses to account for the complex sampling design and non-response of NHANES and were calculated according to NHANES guidelines (NCHS 2008c). We estimated sampling errors using the Taylor series linearized method. We used separate linear regression models to estimate associations between BMI z-scores and WC (as dependent variables) and individual or grouped PAHs categorized according to quartiles (based on the weighted distributions in the study population.) We used multinomial logistic regression models to simultaneously estimate adjusted odds ratios (ORs) for obesity and overweight status as distinct outcomes (compared with normal/underweight) in association with categorical PAH

exposures In addition to estimating associations for all observations combined, we performed separate analyses stratified by age (6–11 years and 12–19 years).

SAS 9.2 (SAS Institute, Cary, NC) was used for all statistical analyses and SAS-Callable SUDAAN 10 (Research Triangle Institute, Research Triangle Park, NC) was used to account for the NHANES complex sample design. P-values from Satterthwaite statistics were presented at the significance level ≤ 0.05.

Results

Table 1 illustrates the weighted characteristics and geometric mean concentrations (SE) of urinary PAH metabolites among participants aged 6-19 years from NHANES 2001-2006 included in this study (n = 3189). The geometric mean age of the participants was 11.8 years and 51.3% were male. Non-Hispanic whites (NHW) accounted for 62.2% of the total study group; 14.7% were non-Hispanic blacks, and 11.8% were Mexican-American. Approximately 22.2% of the participants were from families with income at or below the poverty level (PIR $\leq$ 1). The mean (SE) BMI z-score was 0.77 (0.02); 15.5% of the individuals were classified as obese and16.7% as overweight. Approximately 14.2% of children aged 6-11 were obese, whereas the percentage of obese individuals among adolescents (12-19 years) was 16.5%. Estimated mean values for BMI z-score and WC increased monotonically with increasing quartiles of the molecular mass sum of the PAHs ($\sum$molPAHs) in the population as a whole, and among children ages 6–11 years (Table 2). Positive associations were also estimated for the older age group, though adjusted mean values were similar for all exposure quartiles above the reference exposure group, without a consistent increasing trend. BMI z-score and WC also increased monotonically with increasing quartiles of the total sum of naphthalene metabolites ($\sum$NAPHT) among children

ages 6-11, whereas associations in adolescents and the overall population were positive but not monotonic (Table 2).

Odds ratios from adjusted multinomial logistic regression models indicated positive associations with obesity for ∑molPAHs and ∑NAPHT in the population as a whole and in both age groups, though monotonic increases with exposure were estimated for ∑molPAHs in children ages 6-11 years only (Table 3). Neither exposure was associated with overweight in the population as a whole or in either age group.

Associations with individual PAH metabolites and with the sum of the 3 (fluorene and phenanthrene) and 4 (pyrene) benzene ring PAHs (∑mol3-4 PAHs) were less precise than those estimated for ∑molPAHs and ∑NAPHT, but 2-naphthol was positively associated with BMI z-score, WC, and obesity (overall and in both age groups), and 1-phenanthrene and 2-phenanthrene were positively associated with BMI z-score and WC (overall and in both age groups) (Supplemental Material, Tables S1 and S2).

Discussion

To our knowledge, this is the first reporting of an association of environmental PAH exposures with childhood obesity using a nationally representative sample.

In the present study, we found that ∑NAPHT and ∑molPAHs were positively and significantly associated with BMI z-score, WC, and obesity. These associations were evident in the children age group, but not in the older age group. It is worthwhile to note that the main source of exposure for naphthalene is through inhalation (mostly ambient pollution) compared to the larger PAHs (fluorene, phenantrene, and pyrene) main source of exposure being dietary (Li et al. 2008).

Our results are in agreement with previous studies done both in animals and in humans. Irigary et al. (2006) reported that PAH exposure impaired adipose tissue lipolysis and led to increased weight gain and fat mass in mice.

Recently, Rundle and colleagues (2012), in a longitudinal birth cohort of African-Americans and Dominican mothers (18-35 years of age) residing in New York City, investigated the effect of prenatal exposure to airborne PAHs on the child's body size at age 5 (n = 422 and 7 (n = 341) years. The authors reported that reported that exposure to ambient high molecular weight PAHs was associated with higher BMI z-scores and obesity at both 5 and 7 years of age (Rundle et al. 2012).

PAHs are suspected endocrine disruptor chemicals (EDCs) (Gozgit et al. 2004; Sievers et al. 2013). Using a *S. cerevisiae* system, Schultz and Sinks (2002), reported estrogenic gene activity of the hydroxylated metabolites of naphthalene such 1-naphthol and 2-naphthol, but not in the parent compound. Estrogenic activity was also reported for 2-fluorene and 1-pyrene (Schultz and Sinks 2002). It has been proposed that exposure to EDCs and other chemicals is an important risk factor for childhood obesity (Grun and Blumberg 2006). These chemicals can act on adipocytes by altering the metabolism or lipid homeostasis through activation of the peroxisome proliferator activated receptor (PPAR), which differentiates the pre-adipocyte cells in fat tissue (Grun and Blumberg 2006). Chemicals that have been reported to act through this mechanism in experimental models are organotins, such as tributyltin, perfluoroalkyl acids, and certain phthalates (Grun and Blumberg 2006). In an *in vitro* system, Kim et al. (2005) reported activation of both PPARα and PPARβ/δ after exposure to several PAHs. Both NAP and PHEN significantly increased PPAR expression, though more weakly than benz(a)anthracene (BaA).

Experimental animal studies show that other endocrine-disruptor chemicals, such as bisphenol A (Rubin and Soto 2010) and polybrominated diphenyl ethers ((Hoppe and Carey 2007) may promote adipogenesis through a secondary metabolic imbalance instead of through PPAR. Coplanar polychlorinated biphenyls, for example, increased adipogenesis through the binding of the aryl hydrocarbon receptor (AR) in adipocytes (Arsenescu et al. 2008).

Chang and Liao (1987) studied the effect of phenanthrene in castrated rats. They found that the compound bound weakly to the AR of rat prostate but did not bind to the estrogen receptor or the glucorticoid receptor. Higher activity was reported for the phenanthrene metabolite. Also, both phenanthrene and its metabolite reduced the androgen-dependent growth of the ventral prostate, seminal vescical and coagulating gland (Chang and Liao 1987).

A slight antiandrogenic effect of phenanthrene was similarly reported by Vinggard and colleagues (2000) in an *in vitro* system. The authors also reported antiandrogenic effect of fluorantene (Vingaard et al. 2000).

EDCs may also influence adipogenesis through effects on thyroid hormone. Thyroid hormone inhibits lipogenesis (Viguerie et al. 2002) and stimulates lipolysis in adipocytes (Smith et al. 1991; Van Inwegen et al. 1975), possibly through crosstalk with the PPARs (reviewed in Lu and Cheng 2010). In animal models, thyroid hormone receptor (TR) agonists induced fat loss and decreased plasma cholesterol and triglyceride levels (Baxter et al. 2004; Grover et al. 2003). There is evidence that 1-NAP and 2-NAP act as EDC through thyroid hormone receptor antagonist activity (Sun et al. 2008). Using an *in vitro* system based on the thyroid hormone receptor (TR)-luciferase reporter gene, Sun and colleagues (2008) tested carbaryl, 1-NAP, and 2-NAP for their TR activities. 1-NAP, 2 NAP, and carbaryl showed TR antagonist activities,

indicating that they could disrupt the normal function of the thyroid hormones. Whereas 2-NAP is an important metabolite of naphthalene, 1-NAP is a metabolite of both carbaryl and naphthalene. Therefore, it may be possible that 1-NAP and 2-NAP may increase adipocyte lipid accumulation through TR antagonism and by reducing circulation levels of thyroid hormones in children.

Li and colleagues (2008), using NHANES 2001-2002 survey, reported that the eight PAH metabolites correlate to each other to some degree (r = 0.4-0.8), which in some cases, suggests a common source of exposure. Naphthalene metabolites, as a group, correlate better with the fluorene group than with the phenantrene and pyrene. This may be explained by the difference in exposure source: naphthalene exposure through inhalation and by diet for the larger PAHs (fluorene, phenantrene, and pyrene. Although these metabolites have a good correlation with each other, our analyses show a difference in association between individual PAH metabolites and obesity and body weight outcomes. Our finding may be explained, for example, by the different action on the estrogen-responsive genes by the different PAHs as shown by Gozgit et al. (2004).

The temporal relations between exposures and outcomes cannot be determined given the cross-sectional study design. Although we controlled for several factors associated with obesity, exposure to other chemicals such as bisphenol A (Trasande et al. 2012) and phthalates (Teitelbaum et al. 2012; Trasande et al. 2013) might have confounded associations Another important limitation is that PAHs have a short half-life and exposure values are based on single-spot urine analyses Low molecular weight PAHs are ubiquitous in the environment, so it may be reasonable to assume that exposure is continuous. If so, urinary PAHs may be a good proxy for

typical PAH exposures. While there are no studies linking short-term PAHs exposure to long-term exposure, there are examples of other lipophilic chemicals, such as phthalates, where single urine sample may represent exposure over the previous 3 months (Hauser et al. 2004). We do not know whether this would apply to the PAHs, however, our results merit further investigation.

Conclusion

We found that the total molar sum of the PAHs was associated with higher body mass index, waist circumference, and obesity in children, ages 6-11. However, this association was less consistent amongst adolescents in the same survey. We found that urinary naphthalene was associated with higher BMI z-score, WC, and obesity in both children and adolescents.

References

Arsenescu V, Arsenescu RI, King V, Swanson H, Cassis LA. 2008. Polychlorinated biphenyl-77 induces adipocyte differentiation and proinflammatory adipokines and promotes obesity and atherosclerosis. Environ Health Perspect 116:761–768.

ATSDR. Agency for Toxic Substances and Disease Registry, 1995. Toxicological Profile for Polycyclic Aromatic Hydrocarbons (PAHs) Atlanta, GA: US Department of Health and Human Services, Public Health Service.

ATSDR. Agency for Toxic Substances and Disease Registry. 2005. Toxicological Profile for Naphthalene, 1-Methylnaphthalene, and 2-MethylnaphthaleneAtlanta, GA: US Department of Health and Human Services, Public Health Service.

Barr DB, Wilder LC, Caudill SP, Gonzalez AJ, Needham LL, Pirkle JL. 2005. Urinary creatinine concentrations in the U.S. population: implications for urinary biologic monitoring measurements. Environ Health Perspect 113:192-200.

Baxter JD, Webb P, Grover G, Scanlan TS. 2004. Selective activation of thyroid hormone signaling pathways by GC-1: a new approach to controlling cholesterol and body weight. Trends Endocrinol Metab 15:154-7.

Chang CS, Liao SS. 1987. Topographic recognition of cyclic hydrocarbons and related compounds by receptors for androgens, estrogens, and glucocorticoids. J Steroid Biochem 27:123-31.

Choi H, Rauh V, Garfinkel R, Tu Y, Perera FP. 2008. Prenatal exposure to airborne polycyclic aromatic hydrocarbons and risk of intrauterine growth restriction. Environ Health Perspect 116:658-65.

Dowd JB, Zajacova A, Aiello AE. 2010. Predictors of inflammation in U.S. Children aged 3-16 years. Am J Prev Med 39:314-320.

Gozgit JM, Nestor KM, Fasco MJ, Pentecost BT, Acaro KF. 2004. Differential action of polycyclic aromatic hydrocarbons on endogenous estrogen-responsive genes and on a transfected estrogen-responsive reporter in MCF-7 cells. Toxicol App Pharmacol 196:58-67.

Grover GJ, Mellström K, Ye L, Malm J, Li YL, Bladh LG, et al. 2003. Selective thyroid hormone receptor-beta activation: a strategy for reduction of weight, cholesterol, and lipoprotein (a) with reduced cardiovascular liability. Proc Natl Acad Sci U S A 100:10067-72.

Grun F, Blumberg B. 2006. Environmental obesogens: organotins and endocrine disruption via nuclear receptor signaling. Endocrinology 147:S50–S55.

Hauser R, Meeker JD, Park S, Silva MJ, Calafat AM. 2004. Temporal variability of urinary phthalate metabolite levels in men of reproductive age. Environ Health Perspect 112:1734-1740.

Hoppe AA, Carey GB. 2007. Polybrominated diphenyl ethers as endocrine disruptors of adipocyte metabolism. Obesity 15:2942-50.

Huang E, Caudill SP, Grainger J, Needham LL, Patterson Jr DG. 2006. Levels of 1-hydroxypyrene and other monohydroxy polycylic aromatic hydrocarbons in children: A study based on US reference range values. Toxicol Lett 163:10-19.

Ikeda M, Ezaki T, Tsukahara T, Moriguchi J, Furuki K, Fukui Y, et al. 2003. Bias induced by the use of creatinine-corrected values in evaluation of beta2-microgloblin levels. Toxicol Lett 145:197-207.

Irigaray P, Ogier V, Jacquenet S, Notet V, Sibille P, Mejean L, et al. 2006. Benzo[a]pyrene impairs beta-adrenergic stimulation of adipose tissue lipolysis and causes weight gain in mice. A novel molecular mechanism of toxicity for a common food pollutant. FECS J. 273:1362-1372.

Kim JH, Yamaguchi K, Lee SH, Tithof PK, Sayler GS, Yoon JH, et al.2005. Evaluation of polycyclic aromatic hydrocarbons in the activation of early growth response-1 and peroxisome proliferator activated receptors. Toxicol Sci 85:585-593.

Laher JM, Rigler MW, Vetter RD, Barrowman JA, Patton JS. 1984. Similar bioavailability and lymphatic transport of benzo[a]pyrene when administered to rats in different mounts of dietary fat. J Lipid Res 25:1337-1342.

Li Z, Sandau CD, Romanoff LC, Caudill SP, Sjodin A, Needham LL, et al. 2008. Concentration and profile of 22 urinary polycyclic aromatic hydrocarbon metabolites in the US population. Environ Res 107:320-31.

Lu C, Cheng SY. 2010. Thyroid hormone receptors regulate adipogenesis and carcinogenesis via crosstalk signaling with peroxisome proliferator-activated receptors. J Mol Endocrinol 44:143-54.

NCHS. National Center for Health Statistics. 2007. National Health and Nutrition Examination Survey 2005–2006. Laboratory Procedure Manuals. Atlanta, GA: Centers for Disease Control and Prevention, National Center for Health Statistics. [Accessed March 2012].

NCHS. National Center for Health Statistics. 2008a. National Health and Nutrition Examination Survey Home Page. Atlanta, GA: Centers for Disease Control and Prevention, National Center for Health Statistics. http://www.cdc.gov/nchs/nhanes.htm. [Accessed March 2013].

NCHS. National Center for Health Statistics. 2008b. National Health and Nutrition Examination.Survey analytic guidelines. Atlanta, GA: Centers for Disease Control and Prevention, National Center for Health Statistics. [Accessed March 2013].

NCHS. National Center for Health Statistics. 2008c. Continuous National Health and Nutrition Examination Survey (NHANES) Web Tutorial. Constructing Weights for Combined NHANES Survey Cycles. Atlanta, GA: Centers for Disease Control and Prevention, National Center for Health Statistics. http://www.cdc.gov/nchs/tutorials/nhanes/SurveyDesign/Weighting/intro.htm [Accessed March 2013].

Newbold RR. 2010. Impact of environmental endocrine disrupting chemicals on the development of obesity. Hormones 9:206-217.

Ogden C and Carroll M. 2010. Prevalence of Obesity Among Children and Adolescents: United States, Trends 1963–1965 Through 2007–2008. NCHS Health E-Stat (http://www.cdc.gov/nchs/data/hestat/obesity_child_07_08/obesity_child_07_08.pdf)

Perera FP, Rauh V, Tsai WY, Kinney P, Camann D, Barr D, et al. 2003. Effects of transplacental exposure to environmental pollutants on birth outcomes in a multiethnic population. Environ Health Perspect 111:201-205.

Romanoff LC, Li Z, Young KJ, Blakely NC 3rd, Patterson DG Jr, Sandau CD. 2006. Automated solid-phase extraction method for measuring urinary polycyclic aromatic hydrocarbon metabolites in human biomonitoring using isotope-dilution gas chromatography high-resolution mass spectrometry. J Chromatogr B Analyt Technol Biomed Life Sci 835:47-54.

Rundle A, Hoepner L, Hassoun A, Oberfield S, Freyer G, Holmes D, et al. 2012. Association of childhood obesity with maternal exposure to ambient air polycyclic aromatic hydrocarbons during pregnancy. Am J Epidemiol 175:1163-1172.

Schultz TW, Sinks GD. 2002. Xenoestrogenic gene expression: structural features of active polycyclic aromatic hydrocarbons. Environ Toxicol Chem 21:783-6.

Shu HP, Nichols AV. 1979. Benzo[a]pyrene uptake by human plasma lipoproteins in vitro. Cancer Res 39:1224-1230.

Sievers CK, Shanle EK, Bradfield CA, Xu W. 2013. Differential action of monohydroxylated polycyclic aromatic hydrocarbons with estrogen receptors α and β. Toxicol Sci 132:359-367.

Smith CJ, Vasta V, Degerman E, Belfrage P, Manganiello VC. 1991. Hormone-sensitive cyclic GMP-inhibited cyclic AMP phosphodiesterase in rat adipocytes. Regulation of insulin- and cAMP-dependent activation by phosphorylation. J Biol Chem 266:13385–13390.

Sun H, Shen OX, Xu XL, Song L, Wang XR. 2008. Carbaryl, 1-naphthol and 2-naphtholinhibit the beta-1 thyroid hormone receptor-mediated transcription in vitro. Toxicology 249:238-42.

Teitelbaum SL, Mervish N, Moshier EL, Vangeepuram N, Galvez MP, Calafat AM, et al. 2012. Associations between phthalate metabolite urinary concentrations and body size measures in New York City children. Environ Res.112:186-93.

Trasande L, Attina TM, Blustein J. 2012. Association between urinary bisphenol A concentration and obesity prevalence in children and adolescents. JAMA 308:1113-21.

Trasande L, Attina TM, Sathyanarayana S, Spanier AJ, Blustein J. 2013. Race/Ethnicity-specific associations of urinary phthalates with childhood body mass in a nationally representative sample. Environ Health Perspect. 121:501-6.

Van Inwegen RG, Robison GA, Thompson WJ. 1975. Cyclic nucleotide phosphodiesterases and thyroid hormones. J Biol Chem 250:2452–2456.

Viguerie N, Millet L, Avizou S, Vidal H, Larrouy D, Langin D. 2002. Regulation of human adipocyte gene expression by thyroid hormone. J Clin Endocrinol Metab 87:630–634.

Vinggaard AM, Hnida C, Larsen JC. 2000. Environmental polycyclic aromatic hydrocarbons affect androgen receptor activation in vitro. Toxicology 145:173-83.

Wenger D, Gerecke AC, Heeb NV, Schmid P, Hueglin C, Naegeli H, et al. 2009. In vitro estrogenicity of ambient particulate matter: contribution of hydroxylated polycyclic aromatic hydrocarbons. J Appl Toxicol 29:223-232.

Table 1. Weighted characteristics of NHANES 2001-2006 participants aged 6-19.

Characteristics	6-19 years	6-11 years	12-19 years
Number	3189	1081	2108
1-naphthol (ng/L), GM (SE)	1604.55 (48.24)	1370.51 (59.58)	1804.98 (77.10)
2-naphthol (ng/L), GM (SE)	2530.30 (81.94)	2032.47 (74.13)	2979.43 (131.06)
2-fluorene (ng/L), GM (SE)	249.89 (7.25)	212.32 (6.92)	282.95 (10.35)
3-fluorene (ng/L), GM (SE)	105.58 (3.45)	89.35 (3.16)	119.97 (4.90)
1-phenanthrene (ng/L), GM (SE)	135.48 (3.75)	122.68 (3.82)	145.95 (4.90)
2-phenanthrene (ng/L), GM (SE)	50.10 (1.55)	42.74 (1.42)	56.49 (2.35)
3-phenanthrene (ng/L , GM (SE)	106.54 (3.46)	101.92 (4.00)	110.15 (4.17)
1-pyrene (ng/L), GM (SE)	98.91 (3.36)	95.58 (3.85)	101.49 (4.16)
∑PAHs (ng/L), GM (SE)	5704.66 (167.69)	4891.34 (189.24)	6417.88 (262.67)
Age, GM (SE)	11.81 (0.14)	8.37 (0.07)	15.23 (0.08)
BMI Z score, GM (SE)	0.77 (0.02)	0.74 (0.04)	0.79 (0.03)
C-reactive protein, (mg/dL,)GM (SE)	0.05 (0.00)	0.04 (0.00)	0.05 (0.00)
Blood cotinine , (ng/mL), GM (SE)	0.16 (0.02)	0.09 (0.01)	0.24 (0.03)
BMI	20.50 (0.13)	17.92 (0.14)	22.64 (0.16)
Urinary creatinine (mg/dL), GM (SE)	113.72 (2.46)	91.73 (2.07)	133.51 (3.11)
Sex			
Male, % (SE)	51.34 (1.25)	51.14 (2.13)	51.49 (1.48)
Female, % (SE)	48.66 (1.25)	48.86 (2.13)	48.51 (1.48)
Race/ethnicity			
White (non-Hispanic) , % (SE)	62.18 (2.28)	60.06 (2.71)	64.74 (2.53)
Non-Hispanic Black, % (SE)	14.71 (1.48)	15.00 (1.68)	14.49 (1.52)
Mexican-American, % (SE)	11.79 (1.19)	13.21 (1.30)	10.75 (1.31)
Other Hispanic, % (SE)	5.22 (0.81)	4.59 (1.27)	5.68 (0.97)
Other, % (SE)	6.11 (0.75)	7.14 (1.32)	5.34 (0.82)

Characteristics	6-19 years	6-11 years	12-19 years
Weight			
Obese, *N* (%, SE)	608 (15.53%, 0.98)	204 (14.17%, 1.44)	404 (16.54%, 1.14)
Overweight, *N* (%, SE)	510 (16.69%, 0.89)	169 (16.60%, 1.43)	341 (16.76%, 1.53)
Normal and underweight, *N* (%, SE)	2071 (67.78%, 1.23)	708 (69.23%, 1.99)	1363 (66.70%, 1.66)
Poverty income ratio (PIR)			
PIR $\leq$ 1, % (SE)	22.22 (1.43)	22.55 (1.76)	21.96 (1.87)
PIR > 1% (SE)	77.78 (1.43)	77.45 (1.76)	78.04 (1.87)
TV and video games use			
$\leq$ 2 hours, % (SE)	48.61 (1.63)	52.46 (2.38)	45.70 (1.89)
> 2, % (SE)	51.39 (1.63)	47.54 (2.38)	54.30 (1.89)
Caloric intake			
Normal intake, % (SE)	53.95 (1.20)	50.10 (1.91)	56.78 (1.75)
Excessive intake, % (SE)	46.05 (1.20)	49.90 (1.91)	43.22 (1.75)
c-Reactive protein			
c-RP Tertile 1, $\leq$ 0.01 mg/dL; % (SE)	28.76 (1.07)	34.68 (1.89)	24.69 (1.56)
c-RP Tertile 2,> 0.01 – 0.07 mg/dL; % (SE)	38.26 (1.10)	35.91 (2.03)	39.88 (1.39)
c-RP Tertile 3, > 0.07 mg/dL; % (SE)	32.98 (1.00)	29.41 (1.99)	35.43 (1.53)

Table 2. Multivariate linear regression Beta coefficient (95% CI)* association between BMI z-score, waist circumference and quartile** of ∑molPAHs, or ∑NAPHT.

Exposure	BMI-z score	Waist circumference
ALL (6-19 years), n	3189	3189
∑molPAHs Q 1	Referent	Referent
∑molPAHs Q 2	0.18 (0.04, 0.32) p=0.01	1.37 (-0.11, 2.85) p=0.07
∑molPAHs Q 3	0.18 (0.01, 0.35) p=0.04	1.34 (-0.28, 2.96) p=0.10
∑molPAHs Q4	0.25 (0.08, 0.43) p=0.01	2.24 (0.25, 4.23) p=0.03
∑NAPHT Q1	Referent	Referent
∑NAPHT Q2	0.22 (0.06, 0.39) p=0.01	1.79 (0.15, 3.43) p=0.03
∑NAPHT Q3	0.24 (0.08, 0.40) p<0.01	1.78 (0.24, 3.32) p=0.02
∑NAPHT Q4	0.31 (0.15,0.50) p<0.01	2.68 (0.88, 4.49) p<0.01
Children (6-11 years), n	1081	1081
∑molPAHs Q1	Referent	Referent
∑molPAHs Q2	0.20 (-0.04, 0.44) p=0.09	1.08 (-0.85, 3.00) p=0.27
∑molPAHs Q3	0.24 (-0.02, 0.49) p=0.07	1.36 (-0.83, 3.56) p=0.22
∑molPAHs Q4	0.41 (0.04, 0.77) p=0.03	3.30 (0.24, 6.35) p=0.03
∑NAPHT Q1	Referent	Referent
∑NAPHT Q2	0.25 (-0.03, 0.52) p=0.07	1.56 (-0.68, 3.80) p=0.17
∑NAPHT Q3	0.31 (0.04, 0.56) p=0.02	1.95 (-0.44, 4.34) p=0.11
∑NAPHT Q4	0.37 (0.03, 0.70) p=0.03	3.07 (0.19, 5.96) p=0.04
Adolescents (12-19 years), n	2108	2108
∑molPAHs Q1	Referent	Referent
∑molPAHs Q2	0.20 (0.01, 0.39) p=0.04	2.37 (-0.07, 4.82) p=0.06
∑molPAHs Q3	0.12 (-0.14, 0.38) p=0.35	2.01 (-1.16, 5.17) p=0.21
∑molPAHs Q4	0.18 (-0.06, 0.43) p=0.13	2.65 (-0.16, 5.45) p=0.06
∑NAPHT Q1	Referent	Referent
∑NAPHT Q2	0.24 (0.04, 0.45) p=0.02	2.83 (0.35, 5.31) p=0.03
∑NAPHT Q3	0.21 (-0.01, 0.45) p=0.08	2.53 (-0.07, 5.12) p=0.06
∑NAPHT Q4	0.32 (0.07, 0.59) p=0.02	3.66 (1.15, 6.17) p=0.01

*Adjusted for age, race/ethnicity, gender, urinary creatinine, poverty income ratio (PIR), serum cotinine, serum c-reactive protein, calorie intake, and television, videogame and computer usage

Quartiles ∑molPAHs **(nmol/L**): Q1:** ≤ 19.90; **Q2:** 19.91 – 34.89; **Q3:** 34.90 – 64.48; **Q4:** >64.48. **Quartiles** ∑NAPHT (ng/L)**: Q1:** ≤ 2404.34; **Q2:** 2404.35 – 4259.03; **Q3:** 4259.04 – 8256.64; **Q4:** >8256.04.

Table 3. OR (95% CI)* from multinomial logistic regression models of association between urinary quartile** PAHs and obesity and overweight versus normal/underweight.

Exposure	6-19 years Obese vs. Normal	6-19 years Overweight vs. Normal	6-11 years Obese vs. Normal	6-11 years Overweight vs. Normal	12-19 years Obese vs. Normal	12-19 years Overweight vs. Normal
∑molPAHs Q1	1.00	1.00	1.00	1.00	1.00	1.00
∑molPAHs Q2	2.08 (1.21, 3.56)	1.12 (0.75, 1.67)	1.99 (0.83, 4.75)	1.45 (0.73, 2.89)	2.37 (1.18, 4.77)	0.95 (0.58, 1.56)
∑molPAHs Q3	1.74 (1.00, 3.05)	0.96 (0.61, 1.52)	1.78 (0.81, 3.90)	1.30 (0.60, 2.81)	1.76(0.71, 4.35)	0.70 (0.37, 1.33)
∑molPAHs Q4	2.56 (1.40, 4.69)	0.87 (0.53, 1.41)	4.42 (1.57, 12.42)	1.12 (0.43, 2.92)	2.16 (0.94, 4.98)	0.67 (0.33, 1.35)
∑NAPHT Q1	1.00	1.00	1.00	1.00	1.00	1.00
∑NAPHT Q2	1.99 (1.12, 3.53)	1.47 (0.94, 2.31)	1.52 (0.61, 3.79)	1.96 (0.96, 4.00)	2.58 (1.24, 5.40)	1.24 (0.72, 2.14)
∑NAPHT Q3	1.70 (1.02, 2.81)	1.00 (0.66, 1.50)	1.77 (0.77, 4.06)	1.27 (0.55, 2.90)	1.83 (0.79, 4.23)	0.80(0.48, 1.35)
∑NAPHT Q4	2.53 (1.40, 4.56)	0.89 (0.59, 1.39)	3.24 (1.27, 8.28)	0.78 (0.28, 2.12)	2.54 (1.14, 5.68)	0.88 (0.47, 1.67)

*Adjusted for age, race/ethnicity, gender, urinary creatinine, poverty income ratio (PIR), serum cotinine, serum c-reactive protein, calorie intake, and television, videogame and computer usage.

Quartiles ∑molPAHs (nmol/L): Q1: ≤ 19.90; **Q2: 19.91 – 34.89; **Q3:** 34.90 – 64.48; **Q4:** > 64.48.

Quartiles ∑NAPHT (ng/L): Q1: ≤ 2404.34; **Q2:** 2404.35 – 4259.03; **Q3:** 4259.04 – 8256.64; **Q4:** > 8256.04.