Involuntary Tobacco Smoke Exposure and Urinary Levels of Polycyclic Aromatic Hydrocarbons in the United States, 1999 to 2002

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Abstract

Evidence supports active smoking as a major source of exposure to polycyclic aromatic hydrocarbons (PAH), compounds that are mutagenic and carcinogenic in humans. The influence of involuntary exposure to tobacco smoke on PAH exposure levels among nonsmokers, however, is unknown. This study evaluated the association between both active and involuntary tobacco smoke and biomarkers of PAH exposure in the general U.S. population. A cross-sectional analysis of 5,060 participants ≥6 years of age was done using data from the 1999-2002 National Health and Nutrition Examination Survey (NHANES). PAH exposure was measured by urinary concentrations of 23 monohydroxylated metabolites of nine PAH compounds. Tobacco smoke exposure was defined as no exposure, involuntary exposure, and active exposure by combining serum cotinine levels, smoking status, and presence of household smokers. PAH metabolite levels ranged from 33.9 ng/L for 9-hydroxyphenanthrene to 2,465.4 ng/L for 2-hydroxynaphthalene. After adjustment for age, sex, race/ethnicity, education, household income, and broiled/grilled food consumption, participants involuntarily and actively exposed to tobacco smoke had urinary metabolite concentrations that were increased by a factor of 1.1 to 1.4 and 1.5 to 6.9, respectively, compared with unexposed participants. Associations for involuntary smoking were stronger and statistically significant for 1-hydroxypyrene, 2-hydroxyfluorene, 3-hydroxyfluorene, 9-hydroxyfluorene, 1-hydroxyphenanthrene, 2-hydroxyphenanthrene, and 3-hydroxyphenanthrene compared with other metabolites. Involuntary exposure to tobacco smoke was associated with elevated urinary concentrations of most PAH metabolites in a representative sample of the U.S. population. Policy and educational efforts must continue to minimize PAH exposure through active and involuntary tobacco smoke exposure. (Cancer Epidemiol Biomarkers Prev 2009;18(3):884–93)

Introduction

Polycyclic aromatic hydrocarbons (PAH), a group of more than 100 different compounds, are widely distributed in the environment as a result of incomplete combustion of natural and man-made organic materials (1, 2). Listed by the United States Environmental Protection Agency as priority environmental pollutants (3), many PAHs are established human carcinogens, mutagens, and cocarcinogens (1, 4-9). Major sources of nonoccupational exposure include tobacco smoke, contaminated foods, and polluted air and water (10-13).

Tobacco smoke, a major source of indoor air pollution, contains >60 known carcinogens, including PAHs, in both mainstream and sidestream fractions (14-16). Sufficient evidence has shown higher PAH exposure levels among current smokers compared with nonsmokers (17-20). Although the health effects among nonsmokers who live with or spend time in the proximity of smokers are well established (8), few studies have evaluated the contribution of involuntary tobacco smoke exposure (also known as secondhand smoke, passive smoke, or environmental tobacco smoke) to PAH levels (21, 22).

Our objective was to investigate the association between both active and involuntary tobacco smoke exposure with PAH as measured by urinary concentrations of monohydroxylated PAH metabolites in a representative sample of the civilian noninstitutionalized U.S. population using data from the National Health and Nutrition Examination Survey (NHANES) 1999-2002 (23, 24). Twenty-three metabolite isomers of the nine parent PAH compounds (benz[*a*]anthracene, benzo[*a*]pyrene, benzo[*c*]phenanthrene, chrysene, fluoranthene, fluorene, naphthalene, phenanthrene, and pyrene) were selected for study in NHANES 1999-2002 by the National Center for Health Statistics (NCHS). We hypothesized that the levels of tobacco smoke exposure are positively associated with urinary PAH metabolite concentrations in a dose-response manner in the general population.

Materials and Methods

Study Population. NHANES is a series of cross-sectional health and nutrition surveys designed to obtain data representing the civilian noninstitutionalized U.S. population. In 1999, NHANES began measuring urinary

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Table 1. PAH metabolite concentrations (ng/L) in urine: NHANES 1999-2002

Metabolite (MW)	Sample size	Geometric mean	Maximum	LOD	Percent <LOD	Range of CV
Pyrene						
1-OHPyr (218)	5,059	60.3	24,129	2,* 3.3 †	1.6	1.5-5.7
Phenanthrene						
1-OHPhe (194)	4,987	145.3	27,672	15,* 3.5 †	2.5	1.5-4.9
2-OHPhe (194)	4,921	69.3	26,249	11.2,* 3.2 †	6.6	1.4-6.7
3-OHPhe (194)	5,040	112.9	126,202	15.3,* 3.6 †	3.1	1.6-11.7
4-OHPhe (194)	2,741	41.9 ‡	7,323	5.7 †	25.5	1.0-3.9
9-OHPhe (194)	2,741	33.9	4,410	3.1 †	16.1	1.0-4.6
Naphthalene						
1-OHNap (144)	2,748	2,047.3	297,389	6.2 †	0.0	1.4-4.3
2-OHNap (144)	2,748	2,465.4	223,087	2.4 †	0.0	0.9-3.5
Fluorene						
2-OHFle (182)	5,060	363.0	85,466	9.5,* 3.6 †	0.9	1.4-5.4
3-OHFle (182)	5,057	146.4	29,328	15.1,* 2 †	4.3	1.5-3.7
9-OHFle (182)	2,745	218.9	67,885	2.8 †	0.9	0.9-5.9
Fluoranthene						
3-OHFrt (218)	2,236	13.4 ‡	5,490	3.5*	29.4	1.2-5.9
Benzo[*a*]pyrene						
3-OHB[*a*]P (270)	2,748	17.5 ‡	12,519	10.5 †	50.5	2.4-7.9
Benz[*a*]anthracene						
1-OHB[*a*]A (244)	4,832	3.5 ‡	1,014	4.7,* 3.9 †	93.1	1.9-7.0
3-OHB[*a*]A (244)	4,900	6.3 ‡	312	5.4,* 10.4 †	86.0	0.5-2.1
Benzo[*c*]phenanthrene						
1-OHB[*c*]P (244)	4,932	4.0 ‡	5,067	5.7,* 3.4 †	78.8	1.9-10.9
2-OHB[*c*]P (244)	4,923	4.9 ‡	4,107	6.8,* 5.4 †	86.3	0.9-12.5
3-OHB[*c*]P (244)	4,920	3.8 ‡	447	4.9,* 5.4 †	93.3	0.7-4.3
Chrysene						
1-OHChr (244)	2,748	7.1 ‡	992	5 †	71.8	1.8-3.1
2-OHChr (244)	2,748	4.4 †	460	5 †	87.9	1.4-3.1
3-OHChr (244)	4,981	7.8 ‡	2,326	9.9,* 8.3 †	84.6	1.0-7.7
4-OHChr (244)	2,748	2.3 ‡	314	2.8 †	95.4	0.7-4.7
6-OHChr (244)	5,015	3.0 ‡	868	3.4,* 2.4 †	78.5	2.5-4.6

Abbreviations: MW, molecular weight; CV, coefficient of variation.
* Data are from NHANES 1999-2000.
† Data are from NHANES 2001-2002.
‡ Proportion of results below the LOD was >20% of population.

levels of monohydroxylated PAH metabolites in participants ≥6 y of age. Details of the survey design, data collection methods, and data files for NHANES are available from the NCHS Web site[1] (23, 24). The NHANES protocol was reviewed and approved by the NCHS Institutional Review Board. All participants provided written informed consent at the time of household interview and physical examination.

NHANES 1999-2002 completed a total of 19,759 household interviews and standardized physical exams at a mobile examination center (response rate, 78%). One third of those ≥6 y of age were randomly selected for urinary monohydroxylated PAH metabolite measurements (n = 5,546), and over the period of 4 y, a total of 5,108 participants had 13 PAH metabolite measurements (23, 24). The analytic sample was reduced by about half for the 3-hydroxyfluoranthene (3-OHFrt) metabolite, which was only available in NHANES 1999-2000 (n = 2,457) and for the 3-hydroxybenzo[*a*]pyrene (3-OHB[*a*]P), 1-hydroxychrysene (1-OHChr), 2-hydroxychrysene (2-OHChr), 4-hydroxychrysene (4-OHChr), 9-hydroxyfluorene (9-OHFle), 4-hydroxyphenanthrene (4-OHPhe), 9-hydroxyphenanthrene (9-OHPhe), 1-hydroxynaphthalene (1-OHNap), and 2-hydroxynaphthalene (2-OHNap) metabolites, which were only available in NHANES 2001-2002 (n = 2,748). Additionally, sample sizes varied slightly for individual PAH metabolites due to missing levels for some metabolites (Table 1).

Urinary Monohydroxylated PAH Metabolites. A 5-mL aliquot from each spot urine specimen was taken for PAH metabolite measurements. The following 23 monohydroxylated metabolites were measured at the Division of Environmental Health Laboratory Sciences of the Centers for Disease Control and Prevention: 1-hydroxybenz[*a*]anthracene (1-OHB[*a*]A), 3-hydroxybenz[*a*]anthracene (3-OHB[*a*]A), 3-OHB[*a*]P, 1-hydroxybenzo[*c*]phenanthrene (1-OHB[*c*]P), 2-hydroxybenzo[*c*]phenanthrene (2-OHB[*c*]P), 3-hydroxybenzo[*c*]phenanthrene (3-OHB[*c*]P), 1-OHChr, 2-OHChr, 3-hydroxychrysene (3-OHChr), 4-OHChr, 6-hydroxychrysene (6-OHChr), 3-OHFrt, 2-hydroxyfluorene (2-OHFle), 3-hydroxyfluorene (3-OHFle), 9-OHFle, 1-OHNap, 2-OHNap, 1-hydroxyphenanthrene (1-OHPhe), 2-hydroxyphenanthrene (2-OHPhe), 3-hydroxyphenanthrene (3-OHPhe), 4-OHPhe, 9-OHPhe, and 1-hydroxypyrene (1-OHPyr; refs. 23, 24).

The analytic procedure for measurement of monohydroxylated metabolites of PAH involved enzymatic hydrolysis of urine, solid-phase extraction, derivatization, and analysis using capillary gas chromatography combined with high-resolution mass spectrometry

[1] http://www.cdc.gov/nchs

following previously described methods (25, 26). Isotope dilution with ^{13}C-labeled standards was used for quantification. Blanks, urine pools, and internal standard samples were used in each analytic run for quality control purposes. The ranges for the interassay coefficients of variation for each metabolite are shown in Table 1. The limits of detection (LOD) varied by metabolite and survey years, ranging from 2 ng/L for 1-OHPyr to 15.3 ng/L for 3-OHPhe (Table 1). The NCHS imputed a default value of LOD divided by the square root of two for those subjects with metabolite levels below the LOD. Metabolites for which >20% of participants were below the LOD were not considered further for this study.

Smoking Status and Tobacco Smoke Exposure. Participants ≥20 y of age were classified as never, former, or current smokers based on the household interview items: ''Have you smoked at least 100 cigarettes in your entire life?'' and ''Do you now smoke cigarettes?'' Smoking status among participants 12 to 19 y of age was derived from audio-computer-assisted interview items: ''Have you ever tried cigarette smoking, even 1 or 2 puffs?'' and ''During the past 30 days, on how many days did you smoke cigarettes?''

Serum cotinine, a metabolite of nicotine, was determined using isotope dilution high-performance liquid chromatography/atmospheric pressure chemical ionization tandem mass spectrometry (23, 24). The LOD for serum cotinine was <0.05 ng/mL.

Similar to Weitzman et al. (27), we defined current active smoking exposure, involuntary smoking exposure, and no exposure to tobacco smoke by combining cotinine levels, living with a smoker in the household, and smoking status as follows: (*a*) active smoking exposure was defined as self-reported current smoking or cotinine levels ≥10 ng/mL (28); (*b*) involuntary exposure to tobacco smoke was defined as parental report of any smoker in the home or detectable but <10 ng/mL cotinine levels in children <12 y of age (28, 29), and as self-report of any smoker living in the home in the absence of self-reported smoking or detectable but <10 ng/mL cotinine levels in adolescents and adults; and (*c*) no exposure to tobacco smoke was defined as cotinine levels below the LOD, not living with a smoker, and not being a current smoker. Three children ages 6 to 11 y with cotinine levels ≥10 ng/mL were dropped from our analyses; thus, no active smoking exposure category existed for this age group.

Other Variables. Potential determinants of PAH metabolites evaluated in our analyses included age, sex, race/ethnicity, education, poverty income ratio (PIR), consumption of grilled/broiled meat and alcohol, body mass index (BMI), current occupation, physical activity level, and urinary creatinine. Age, sex, race/ethnicity, education, current occupation, physical activity, and alcohol consumption were obtained during the interview based on self-reported information. PIR is a ratio of self-reported family income to the family's poverty threshold values, which were standardized by family size and inflation rates based on tables published annually by the U.S. Bureau of Census (30). Self-reported grilled/broiled meat intake was obtained from the dietary interview component of NHANES and recoded as ''yes'' or ''no'' according to whether participants reported having eaten any grilled or broiled red meat in the past 24 h. Data on description of food and cooking method consumed by each participant were obtained from the U.S. Department of Agriculture food and nutrition database (31). Alcohol consumption in adults was classified as never, former, and current. The level of physical activity was computed from the total metabolic equivalent of task scores for all physical activities done in the previous 30 d.

BMI (kg/m^2) in adults was computed from measured weight and height and categorized into normal (BMI, <25 kg/m^2), overweight (BMI, 25-29 kg/m^2), and obese (BMI, ≥30 kg/m^2). BMI in children and adolescents (<20 y old) was based on the age- and sex-specific BMI growth charts (32) as normal (BMI, <85th percentile), at risk for overweight (BMI, 85-95th percentile), and overweight (BMI, ≥95th percentile; ref. 33). Urinary creatinine was measured in the same specimen as PAH metabolites by using a photometric Boehringer Mannheim/Hitachi 912 analyzer (23, 24).

Statistical Analysis. All statistical analyses were conducted with STATA version 9.2 statistical software (Stata Corp.) using appropriate sampling weights developed by NCHS for this random subsample to obtain accurate estimates representative of the noninstitutionalized U.S. population (34). The Taylor linearization method was used to obtain proper SEs of all estimates.

PAH metabolites were right skewed and $\log_{10}$ transformed for the analyses. Geometric means and interquartile ranges were computed for all metabolites. To assess determinants of PAH exposure, the ratios and 95% confidence intervals (95% CI) of the geometric mean PAH metabolite levels were estimated using linear regression models on $\log_{10}$-transformed metabolite levels by main determinants including age, sex, race/ethnicity, education, PIR, self-reported dietary grilled/broiled meat, cotinine levels, smoking status (never/former/current), and current exposure to tobacco smoke (none/involuntary/active).

To examine the association of each metabolite with current exposure to tobacco smoke, linear regression models on $\log_{10}$-transformed PAH metabolite levels were first adjusted for age, sex, race/ethnicity, education level, and PIR. We then further adjusted for self-reported dietary grilled/broiled meat, a known source of PAH exposure (2). Because urinary PAH metabolites were measured in a spot urine sample, and thus influenced by factors such as fluid intake, perspiration, and glomerular filtration rate (35), we added urinary creatinine to each final model to adjust for individual differences in urine concentration (36). We also assessed other potential confounding by current occupation, BMI, alcohol use, and levels of physical activity by adding them one at a time to multivariable models. No noticeable changes were observed (data not shown) and these additional variables were not included in our final models.

Results

PAH Metabolite Concentrations in Urine. The overall geometric means and LOD of 23 monohydroxylated metabolites of nine parent PAH compounds in this

sample of the U.S. population ≥6 years of age are presented in Table 1. PAH levels varied widely by metabolite, with geometric means ranging from 2.3 ng/L for 4-OHChr to 2,465.4 ng/L for 2-OHNap. For metabolites of phenanthrene (4-OHPhe), fluoranthene (3-OHFrt), benzo[*a*]pyrene (3-OHB[*a*]P), benz[*a*]anthracene (1-OHB[*a*]A and 3-OHB[*a*]A), benzo[*c*]phenanthrene (1-OHB[*c*]P, 2-OHB[*c*]P, and 3-OHB[*c*]P), and chrysene (1-OHChr, 2-OHChr, 3-OHChr, 4-OHChr, and 6-OHChr), the levels were below the LOD in >20% of the population. Therefore, these metabolites were not considered in further analyses. For the other 10 PAH metabolites, the proportion of detectable values ranged from 83.9% for 9-OHPhe to 100% for 2-OHNap.

Sociodemographic Determinants of Urinary PAH Concentrations. Men had higher levels for all metabolites (Fig. 1). Urinary PAH concentrations for almost all metabolites varied somewhat by age, with the highest geometric means found in persons 20 to 39 years old. By race/ethnicity, non-Hispanic Black participants had higher levels of PAH exposure than non-Hispanic White and Mexican American participants for most metabolites. The geometric means of most PAH metabolites were lower in participants with higher education level and with higher PIRs (higher adjusted income).

After multivariable adjustment, urinary concentrations of most PAH metabolites were comparable in men and women, although 1-OHPhe and 2-OHNap concentrations were significantly higher in women (Table 2). The adjusted ratios of geometric means for most metabolites were lower in participants 12 to 39 years of age with respect to the youngest age group (6-11 years of age) for most metabolites, except 2-OHPhe. Except for 1-OHNap, 3-OHFle, 1-OHPhe, 3-OHPhe, and 9-OHPhe, which were significantly lower in Mexican Americans, and 1-OHPhe and 9-OHPhe, which were lower in non-Hispanic Blacks compared with non-Hispanic Whites, no major racial/ethnic differences were observed. Inverse associations between income (as measured by PIR) and education levels with PAH metabolite concentrations remained present for most isomers.

Grilled/Broiled Meat and Urinary PAH Concentrations. After multivariable adjustment, self-reported grilled/broiled meat consumption was associated with increased concentrations of most PAH metabolites (Table 2). For 3-OHPhe, 9-OHPhe, 1-OHNap, and 2-OHNap, the adjusted ratios of the geometric means were statistically significant and increased by 18% to 37% compared with participants who did not report eating grilled/broiled meat.

Exposure to Tobacco Smoke and Urinary PAH Concentrations. Current smokers had higher urinary PAH metabolite concentrations compared with nonsmokers for all metabolites (Fig. 1), but no substantial differences were observed between nonsmokers and former smokers. Urinary concentrations of PAH metabolites also increased with increasing serum cotinine levels. Levels of all isomers were highest in the active tobacco smoke exposure group and lowest in participants not exposed to tobacco smoke. Participants involuntarily exposed to tobacco smoke had intermediate concentrations (Fig. 1).

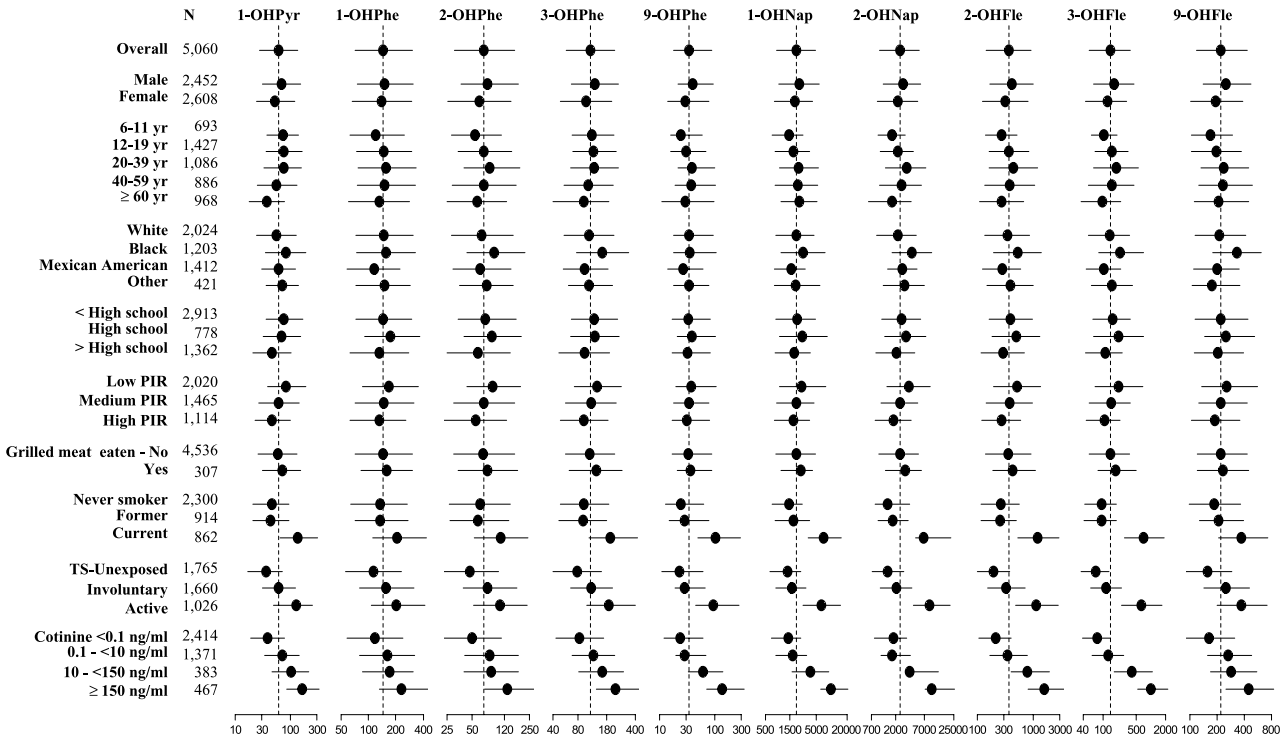

Figure 1. PAH metabolite concentrations in urine (ng/L) by participant characteristics in the 1999-2002 NHANES sample.

Table 2. Ratio (95% CI) of the geometric means of PAH metabolite concentrations in urine in the U.S. population: NHANES 1999-2002

Characteristics	%*	1-OHPyr	1-OHPhe	2-OHPhe	3-OHPhe	9-OHPhe
Sex						
Male	48	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Female	52	1.00 (0.91-1.10)	1.17 (1.09-1.25)†	1.03 (0.94-1.13)	0.99 (0.92-1.06)	1.08 (0.97-1.20)
Age group (y)						
6-11	10	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
12-19	13	0.61 (0.55-0.68)†	0.85 (0.74-0.99)‡	0.85 (0.71-1.03)	0.67 (0.59-0.75)†	0.57 (0.47-0.68)†
20-39	31	0.65 (0.58-0.72)†	0.93 (0.84-1.03)	1.10 (0.97-1.24)	0.71 (0.63-0.81)†	0.68 (0.58-0.81)‡
40-59	29	0.67 (0.58-0.77)†	1.13 (1.00-1.28)	1.27 (1.08-1.48)§	0.79 (0.69-0.89)†	0.94 (0.76-1.17)
≥60	17	0.55 (0.49-0.62)†	1.12 (0.99-1.28)	1.22 (1.06-1.40)§	0.82 (0.69-0.97)‡	0.94 (0.74-1.19)
Race/ethnicity						
White	69	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Black	11	0.87 (0.74-1.02)	0.73 (0.60-0.89)§	0.84 (0.68-1.04)	0.95 (0.79-1.14)	0.65 (0.55-0.77)†
Mexican American	8	0.96 (0.82-1.13)	0.78 (0.65-0.92)§	0.85 (0.68-1.05)	0.82 (0.71-0.95)‡	0.78 (0.68-0.89)§
Other	11	1.06 (0.88-1.28)	0.85 (0.65-1.12)	0.88 (0.64-1.22)	0.82 (0.65-1.02)	0.85 (0.64-1.14)
Education						
<High school	37	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
High school	21	0.95 (0.84-1.06)	1.08 (0.96-1.22)	1.02 (0.90-1.16)	0.98 (0.87-1.11)	0.87 (0.72-1.05)
>High school	42	0.84 (0.75-0.93)§	0.91 (0.80-1.03)	0.83 (0.71-0.97)‡	0.90 (0.81-1.01)	0.99 (0.81-1.22)
PIR						
Low (0 to <1.7)	32	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Medium (1.7 to <3.9)	33	0.86 (0.75-0.98)‡	0.90 (0.78-1.04)	0.83 (0.72-0.97)‡	0.93 (0.81-1.06)	0.98 (0.86-1.11)
High (3.9 to 5)	35	0.82 (0.69-0.96)‡	0.86 (0.73-1.00)	0.75 (0.64-0.87)†	0.84 (0.73-0.97)‡	0.92 (0.76-1.12)
Grilled/broiled meat eaten						
No	93	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Yes	7	1.19 (0.97-1.45)	1.13 (0.94-1.37)	1.09 (0.90-1.32)	1.25 (1.06-1.48)‡	1.18 (1.06-1.33)§
Tobacco smoke exposure‖						
Unexposed	39	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Involuntary	34	1.43 (1.27-1.62)†	1.25 (1.09-1.42)§	1.40 (1.17-1.67)†	1.30 (1.17-1.46)†	1.09 (0.95-1.24)
Active	27	2.86 (2.45-3.35)†	1.51 (1.32-1.73)†	1.80 (1.49-2.17)†	2.08 (1.77-2.44)†	3.25 (2.81-3.76)†

Characteristics	1-OHNap	2-OHNap	2-OHFle	3-OHFle	9-OHFle
Sex					
Male	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Female	1.06 (0.99-1.14)	1.16 (1.04-1.28)‡	1.05 (0.98-1.12)	1.01 (0.94-1.09)	0.99 (0.90-1.09)
Age group (y)					
6-11	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
12-19	0.66 (0.55-0.80)†	0.66 (0.56-0.79)†	0.72 (0.62-0.83)†	0.69 (0.61-0.79)†	0.73 (0.64-0.84)†
20-39	0.76 (0.61-0.93)‡	0.86 (0.75-0.99)‡	0.86 (0.75-0.98)‡	0.79 (0.70-0.90)†	0.86 (0.70-1.05)
40-59	0.98 (0.73-1.32)	1.09 (0.97-1.23)	1.07 (0.95-1.21)	0.96 (0.84-1.10)	1.14 (0.90-1.44)
≥60	1.39 (1.05-1.85)‡	0.92 (0.78-1.10)	0.98 (0.85-1.13)	0.81 (0.71-0.92)§	1.22 (1.00-1.49)
Race/ethnicity					
White	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Black	0.97 (0.75-1.25)	1.13 (0.96-1.32)	0.94 (0.71-1.24)	1.00 (0.78-1.28)	1.07 (0.93-1.22)
Mexican American	0.85 (0.72-0.99)‡	1.14 (0.96-1.35)	0.78 (0.61-1.00)	0.73 (0.58-0.92)‡	0.93 (0.75-1.16)
Other	0.88 (0.71-1.08)	1.25 (0.95-1.64)	0.93 (0.67-1.29)	0.97 (0.74-1.27)	0.79 (0.59-1.06)
Education					
<High school	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
High school	1.00 (0.76-1.31)	0.96 (0.86-1.06)	1.07 (0.91-1.25)	1.11 (0.95-1.29)	0.98 (0.83-1.15)
>High school	0.92 (0.81-1.06)	0.94 (0.80-1.12)	0.84 (0.74-0.95)‡	0.84 (0.74-0.96)‡	1.01 (0.82-1.23)
PIR					
Low (0 to <1.7)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Medium (1.7 to <3.9)	0.85 (0.75-0.96)‡	0.82 (0.76-0.89)†	0.85 (0.74-0.97)‡	0.85 (0.74-0.97)‡	0.94 (0.84-1.05)
High (3.9 to 5)	0.85 (0.72-0.99)‡	0.72 (0.67-0.78)†	0.75 (0.65-0.86)†	0.77 (0.68-0.87)†	0.83 (0.69-1.00)
Grilled/broiled meat eaten					
No	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Yes	1.33 (1.12-1.58)§	1.37 (1.12-1.68)§	1.16 (0.96-1.40)	1.21 (0.99-1.47)	1.15 (0.96-1.38)
Tobacco smoke exposure‖					
Unexposed	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Involuntary	1.12 (0.96-1.30)	1.17 (0.98-1.40)	1.38 (1.16-1.65)†	1.36 (1.16-1.60)†	1.38 (1.17-1.63)§
Active	3.94 (3.53-4.38)†	4.50 (3.83-5.28)†	4.57 (3.84-5.43)†	6.87 (5.83-8.09)†	1.92 (1.62-2.29)†

NOTE: Final model was adjusted by age, sex, race/ethnicity, education, PIR, tobacco smoke exposure, self-reported dietary grilled/broiled meat, and urinary creatinine. The model was fit based on linear regression with complex survey design weight using $\log_{10}$-transformed urinary PAH metabolite concentrations. Ratios were reported as detransformed β.

*Weighted percentage.

† $P \leq 0.001$.

‡ $P \leq 0.05$.

§ $P \leq 0.01$.

‖Unexposed defined as not being a current smoker, having cotinine level <0.05 ng/mL, and no report of living with any smoker in the home; involuntary defined as not being a current smoker, having cotinine level 0.05 to <10 ng/mL, or report of living with any smoker in the home; active defined as being a current smoker or having cotinine level ≥10 ng/mL.

After multivariable adjustment, tobacco smoke exposure status remained strongly associated with urinary concentrations of most isomers, showing a dose-response trend (Table 2). For example, the ratios of geometric means for 1-OHPyr in participants involuntarily and actively exposed to tobacco smoke were 1.43-fold (95% CI, 1.27-1.62) and 2.86-fold (95% CI, 2.45-3.35) greater, respectively, compared with the unexposed group. Ratios were similar for other isomers (Table 2; Fig. 1). Adjusted R^2 of full models accounted for 24% to 53% of the observed variability of most PAH metabolite concentrations. The addition of tobacco smoke exposure status to the final models explained approximately 3% to 24% of the outcome variability, supporting the hypothesis that tobacco smoke exposure was an important predictor of PAH metabolite concentrations in urine.

Exposure to Tobacco Smoke and Urinary PAH Concentrations by Sociodemographic Characteristics. Increasing levels of exposure to tobacco smoke remained consistently and strongly associated with increased urine 1-OHPyr concentrations among children >6 years, adolescents, and adults (Table 3). For most subgroups, the adjusted ratios of geometric means of 1-OHPyr among participants involuntarily exposed to tobacco smoke were ~1.5 times higher compared with unexposed groups. The corresponding adjusted ratios for active smokers compared with unexposed were 2.4 to 3 times higher. Similar patterns were observed in subgroups defined by sex, race/ethnicity, education, poverty level, and self-reported dietary grilled/broiled meat. Similar findings by sociodemographic characteristics were observed for the association of tobacco smoke with other PAH metabolites (data not shown).

Discussion

Summary of Findings. In a representative sample of the U.S. population, children and adults involuntarily and actively exposed to tobacco smoke had higher concentrations of PAH metabolites in urine compared with those not exposed. The association persisted after adjustment for other determinants of PAH exposure, including age, sex, race/ethnicity, education, income, and broiled/grilled meat consumption. A consistent dose-response relationship was observed between recent levels of tobacco smoke exposure (active/involuntary/unexposed) and by cotinine levels with almost every metabolite. No differences in PAH levels were observed between never and former smokers, supporting the view that urinary PAH metabolites reflect recent and ongoing exposure to tobacco smoke, including involuntary exposure, but not past or cumulative exposure.

PAH Exposure—Comparison with Other Countries. Urinary monohydroxylated PAH metabolite concentrations obtained in our study were similar to those previously reported for the 1999-2000 NHANES population (37) but generally lower than concentrations in selected nonoccupationally exposed populations in Canada (38), Germany (39), Sweden (40), and the Netherlands (11). Urinary PAH concentrations in this

Table 3. Ratio of geometric means (95% CI) of 1-OHPyrFS concentration in urine (ng/L) related to tobacco smoke exposure status by participant characteristics, NHANES 1999-2002

	Tobacco smoke exposure status		
	Unexposed*	Involuntary†	Active‡
Age group (y)			
Children (6-11)	1.00 (reference)	1.58 (1.25-1.99)	N/A
Adolescents (12-19)	1.00 (reference)	1.56 (1.18-2.08)	2.35 (1.95-2.83)
Adults (20-85)	1.00 (reference)	1.38 (1.19-1.60)	2.95 (2.46-3.54)
Sex			
Male	1.00 (reference)	1.51 (1.26-1.80)	2.73 (2.32-3.22)
Female	1.00 (reference)	1.35 (1.18-1.55)	2.83 (2.30-3.49)
Race/ethnicity			
White	1.00 (reference)	1.50 (1.28-1.75)	2.98 (2.41-3.68)
Black	1.00 (reference)	1.20 (0.90-1.62)	2.69 (1.87-3.86)
Mexican American	1.00 (reference)	1.42 (1.17-1.73)	1.95 (1.57-2.42)
Other	1.00 (reference)	1.25 (0.91-1.70)	2.04 (1.49-2.80)
Education level			
<High school	1.00 (reference)	1.47 (1.30-1.65)	2.79 (2.44-3.18)
High school	1.00 (reference)	1.44 (1.16-1.78)	3.15 (2.34-4.25)
>High school	1.00 (reference)	1.45 (1.19-1.78)	2.67 (2.16-3.31)
Poverty level (PIR)			
Low	1.00 (reference)	1.38 (1.11-1.72)	2.99 (2.35-3.81)
Medium	1.00 (reference)	1.47 (1.19-1.81)	2.80 (2.21-3.52)
High	1.00 (reference)	1.47 (1.24-1.74)	2.41 (2.03-2.87)
Grilled/broiled meat			
No	1.00 (reference)	1.46 (1.29-1.66)	2.83 (2.39-3.35)
Yes	1.00 (reference)	1.10 (0.82-1.48)	2.16 (1.47-3.18)

NOTE: Model was adjusted by age, sex, race/ethnicity, education, PIR, self-reported dietary grilled/broiled meat, and urinary creatinine. The model was fit based on linear regression with complex survey design weighting using $\log_{10}$-transformed urinary PAH metabolite concentrations. Ratios were reported as detransformed β. A ratio of 1.58, for instance, indicates a 58% increased level with respect to the reference category.

*Unexposed defined as not being a current smoker, having cotinine level <0.05 ng/mL, and no report of living with any smoker in the home.

† Involuntary defined as not being a current smoker, having cotinine level 0.05 to <10 ng/mL, or report of living with any smoker in the home.

‡ Active defined as being a current smoker or having cotinine level ≥10 ng/mL.

U.S. sample were also much lower than in populations in China, where the average ambient air levels of PAH in urban areas are much higher (116 ng/m^3; ref. 41) compared with average PAH levels in ambient air in urban and rural areas of the United States (0.15-19.3 ng/m^3 and 0.02-1.2 ng/m^3, respectively; refs. 42, 43).

Differences in target populations and in the methodology used in different studies, including differences in analytic techniques, make comparisons across studies difficult (37). Whereas most studies have measured PAHs in selective occupationally exposed individuals or in individuals living in areas with significant environmental sources of PAH, NHANES is a nationally representative sample of the U.S. general population. In the United States, levels of PAH concentrations in the ambient air are generally low and food and tobacco smoke are likely to be the most significant sources of PAH exposure. Given important recent reductions in active smoking (44) and in involuntary exposure to tobacco smoke at home and in public places in the United States (45), it is possible that lower PAH metabolite concentrations in the U.S. population also reflect lower exposure to tobacco smoke compared with other countries. Because this was the first time that PAH metabolites were measured in the general U.S. population, however, it is not possible to compare our findings with previous times.

Tobacco Smoke Exposure. Urinary excretion of PAH metabolites was increased in participants with involuntary and active tobacco smoke exposure by a factor of 1.1 to 1.4 and 1.5 to 6.9, respectively, compared with unexposed participants. The contribution of active cigarette smoking to PAH exposure is well established. Multiple studies have consistently reported 1-OHPyr concentrations in urine to be 1.5 to 3 times higher among current smokers compared with nonsmokers (18, 20, 39, 46, 47). Although less frequently studied, similar trends have been observed for other monohydroxylated PAH metabolites, such as 2-OHFle (48), 1-OHPhe, 2-OHPhe, 3-OHPhe, 4-OHPhe, and 9-OHPhe (39, 49), 3-OHB[*a*]P (20), and 1-OHNap and 2-OHNap (48, 50).

A limited number of studies have evaluated the effect of involuntary tobacco smoke exposure on PAH biomarkers (11, 22, 49, 50), with some detecting a positive association with urinary 1-OHPyr (52, 53) and with PAH-albumin adducts (22). Merlo et al. (52) estimated that the contribution of involuntary tobacco smoke exposure to 1-OHPyr urinary excretion would be similar to exposure among police officers working in a traffic setting. In addition, consistent with our findings in children, Tsai et al. (53) reported an average 9.6% increase in urinary 1-OHPyr in preschool children per one cigarette smoked by the child's father. The higher concentrations of urinary PAH metabolites in nonsmokers who are involuntary exposed to tobacco smoke compared with unexposed can be related to high PAH levels in the sidestream fraction of tobacco smoke, the main fraction to which nonsmokers are exposed (54-56).

In a controlled atmosphere experiment, high concentrations of several PAH compounds were measured in aged and diluted sidestream tobacco smoke particles (57). Increased levels of multiple PAH compounds have also been reported in field studies comparing smoking with control environments (58). In the present study, the statistically significant differences in PAH metabolites between involuntarily exposed and unexposed participants were observed for 1-OHPyr, 2-OHFle, 3-OHFle, 9-OHFle, 1-OHPhe, 2-OHPhe, and 3-OHPhe, but not for 9-OHPhe or 1-OHNap and 2-OHNap isomers, suggesting that involuntary tobacco smoke exposure could be a relevant source for these PAH metabolites. Overall, the higher concentrations of PAH metabolites in the urine of nonsmokers involuntarily exposed to tobacco smoke compared with the urine of unexposed nonsmokers suggest that inhalation of tobacco smoke–contaminated air contributes significantly to PAH excretions in urine.

Grilled/Broiled Meat Consumption. Diets that are rich in PAHs are recognized as one of the most important sources of PAH exposure for nonoccupationally exposed nonsmokers (17, 59). Several studies have reported elevated urinary PAH biomarkers, particularly 1-OHPyr, with consumption of foods that are rich in PAH, such as those cooked by open-flame methods. In a controlled experimental study of 21 nonoccupationally PAH-exposed volunteers, urinary levels of 1-OHPyr increased after consuming 170 g/d barbecued hamburgers for 5 days compared with baseline (17). Similarly, urinary excretion of 1-OHPyr glucuronide increased 10- to 80-fold following the ingestion of broiled beef (60). Compared with a control group, exposure to dietary PAH from charcoal-grilled meat resulted in a 4- to 12-fold increase of 1-OHPyr level in urine (61). However, few studies have evaluated the effect of dietary PAH exposure on other monohydroxylated metabolites, although Hoepfner et al. (49) did observe a 2-fold increase in urinary excretion of OHPhe in subjects with a PAH-rich diet.

In the present study, we found only a weak association between reported consumption of grilled/broiled meat in the past 24 hours and 1-OHPyr levels in urine, possibly related to incomplete assessment of all relevant food items and cooking methods. It is important to note that grilled/broiled meats contribute less than half the PAHs consumed through dietary sources (12). The associations, however, were stronger for 3-OHPhe, 9-OHPhe, 1-OHNap, and 2-OHNap, even after adjusting for smoking and other confounding factors, suggesting that these metabolites, rather than 1-OHPyr, may be relevant biomarkers for monitoring low-level PAH exposure related to intake of PAHs from foods.

The observed variability in the relationship of grilled/broiled meat consumption across individual PAH metabolites in urine may be explained by interindividual variation in doses and bioavailability of ingested PAHs, and possibly by interindividual variation in genetic polymorphisms that encode enzymes involved in PAH biotransformation as suggested by Rihs et al. (60, 62-65). Alternatively, the induction of metabolizing enzymes through chronic exposure could lead to differential metabolism of individual PAHs. Active smokers may metabolize ingested PAHs differently from unexposed individuals (66).

Other Sociodemographic Determinants. In our study, age and household income level, and to a lesser extent race/ethnicity and education attainment, were significant determinants of urinary excretion of PAH

metabolites. The influence of age and race/ethnicity on PAH metabolite levels has not been extensively studied. The inverse association between low income and education levels with urinary excretion for most PAH metabolites after adjustment for tobacco exposure may reflect additional sources of PAH exposure, either inside or outside the home.

Strengths and Limitations. Important strengths add to the relevance of the study findings. First, this is a large study, multiethnic, and representative of the general U.S. population ≥6 years old. Second, we were able to evaluate multiple PAH metabolites in urine. Urine PAH levels integrate several sources of exposure and are considered validated markers, even at low levels. Third, involuntary exposure to tobacco smoke was defined by combining serum cotinine levels and self-reported measures of smoking status, thus reducing the likelihood of smoking status misclassification. Other strengths of this study include the ability to control for several relevant covariates, including dietary factors, the consistency of the findings by participant characteristics, and the high quality measures and procedures used by NHANES.

Several limitations must be considered. First, although we used a commonly used cutoff for cotinine (≥10 ng/mL; refs. 28, 45) to classify active versus involuntary smoke exposure, it is possible that some infrequent smokers who denied smoking remained classified as involuntarily exposed. Conducting sensitivity analyses using 5 ng/mL as a cutoff, however, did not substantially affect the study findings. Second, although PAH concentrations in food can vary depending on type of meat, method of preparation, cooking temperature, and fuel sources (67), NHANES dietary data were limited, thus restricting our ability to estimate and control for those aspects related to PAH content in food items. This might have affected our analysis of the association between grilled or broiled meat and PAH levels. It is unlikely to have confounded the relationship between tobacco exposure and PAH metabolites, however, because our findings were consistent according to participant characteristics such as differences in gender, ethnicity, education level, and age, including young children. Third, the possibility of reporting bias with regard to smoking status could not be ruled out. Current smokers who had not recently smoked a cigarette may have been classified as a nonsmoker if they incorrectly reported their smoking history. Similarly, nonsmokers with extreme levels of environmental tobacco exposure and consequent high levels of cotinine, such as those working in smoky environments, may have been classified as smokers. Although our study included subjects as young as 6 years, infants and preschool children were not evaluated because PAH measures were not available in NHANES data for children <6 years of age. Thus, we were unable to address the implications of involuntary smoke exposure for this important group. Other potential limitations include the cross-sectional design of NHANES, uncontrolled confounding, and potential biases resulting from nonparticipation and response error.

Conclusions. This study supports the hypothesis that involuntary and active tobacco smoke exposure is associated with urinary levels of several PAH metabolites. The clear dose-response relationship between levels of tobacco smoke exposure and elevated urinary concentrations of 1-OHPyr, 2-OHFle, 3-OHFle, 9-OHFle, 1-OHPhe, 2-OHPhe, and 3-OHPhe suggests that environmental tobacco smoke is a source of PAH exposure. The finding of involuntary exposure to tobacco smoke as a relevant source of mutagenic and carcinogenic PAH compounds underscores the public health relevance of this study and the need for public health and medical professionals to continue policy and educational efforts to minimize active and involuntary tobacco smoke exposure.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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