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## Urinary polycyclic aromatic hydrocarbon biomarkers and diabetes mellitus

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### Abstract

**Objective**—The aim of the current study is to investigate the association of polycyclic aromatic hydrocarbons (PAHs), a group of environmental pollutants, with diabetes mellitus. Animal studies link PAHs to inflammation and subsequent development of diabetes mellitus. In addition, occupational studies suggest that exposure to other aromatic hydrocarbons such as dioxins may be associated with diabetes risk in humans.

**Design**—We examined participants from the merged National Health and Nutrition Examination Survey 2001–2002, 2003–2004 and 2005–2006. Exposures of interest were eight urinary monohydroxy-PAHs. Our outcome was diabetes mellitus defined as a glycohemoglobin level (HbA1c)  $\geq$  6.5%, a self-reported physician diagnosis of diabetes or use of oral hypoglycaemic medication or insulin. Analyses were adjusted for age, sex, body mass index, race, alcohol consumption, poverty–income ratio, total cholesterol and serum cotinine.

**Results**—We observed a positive association between urinary biomarkers of 1 and 2-hydroxynaphthol, 2-hydroxyphenanthrene and summed low molecular weight (LMW) PAH biomarkers, and diabetes mellitus. Compared with participants with summed LMW PAH

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biomarkers in the lowest quartile, the multivariable-adjusted OR of diabetes mellitus among those in the highest quartile was 3.1 (95% CI 1.6 to 5.8).

**Conclusions**—Urinary biomarkers of 1 and 2-hydroxynaphthol, 2-hydroxyphenanthrene and summed LMW PAH biomarkers are associated with diabetes mellitus in US adults 20–65 years of age. The association of a one-time biomarker of PAH exposure has limitations commonly associated with cross-sectional studies, yet is consistent with experimental animal data and is worthy of additional consideration.

## INTRODUCTION

Recent studies have suggested that common environmental exposures affecting large sections of the population may be a determinant of diabetes mellitus risk.<sup>12</sup> Polycyclic aromatic hydrocarbons (PAHs) are a group of environmental pollutants that feature aromatic rings.<sup>3–5</sup> Major sources of PAHs include energy generation from biomass or fossil fuels, cigarette smoking and ingestion of grilled/smoked food.<sup>6–9</sup>

*In vitro* and animal studies have reported a positive association between exposure to PAHs and inflammation, with subsequent development of diabetes mellitus.<sup>10</sup> Occupational studies have also suggested that exposure to halogenated aromatic hydrocarbons such as dioxins is associated with diabetes mellitus in humans.<sup>11</sup> However, we are not aware of studies investigating PAH exposure in the general population and diabetes mellitus independent of smoking, a major source of PAHs.<sup>8</sup> With advantages of recent nationally representative sample surveys and standardised data collection approaches, the objective of the current study has been to examine the association of eight urinary monohydroxy-PAH (OH-PAH) and diabetes mellitus in adults after adjusting for age, gender, race/ethnicity, body mass index (BMI), serum cotinine, self-reported smoking status and other potential confounders. We posit that exposure to PAHs prompts chronic inflammation and the subsequent development of insulin resistance and diabetes mellitus in humans.

Low molecular weight (LMW) PAHs (eg, naphthalene, fluorene and phenanthrene) are found in gaseous form in the ambient air where they are usually absorbed by inhalation. Higher molecular weight PAHs (eg, pyrene) are found in particulate form where they can be ingested, inhaled or absorbed through the skin.<sup>12,13</sup> Because metabolism and health effects of exposure to PAHs mixtures were found to be different from that of exposure to individual PAHs,<sup>14</sup> we created a summed LMW PAH biomarker variable, indicating a graduating level of exposure to multiple LMW PAHs simultaneously.

## RESEARCH DESIGN AND METHODS

### Study population

The present study is based on merged data from the 2001–2002, 2003–2004 and 2005–2006 National Health and Nutrition Examination Survey (NHANES). NHANES surveys were designed to be nationally representative of the non-institutionalised US civilian population by using a complex stratified multistage probability sample.<sup>15</sup> Selection was based on counties, blocks, households and individuals within households, and included oversampling of certain groups in order to provide stable estimates of these groups. Data were collected

from interviews, questionnaire, examinations and laboratory tests of biological samples. The data have been released for public use in 2-year increments since 1999.

Urinary PAH biomarkers were only measured in a subsample of NHANES participants. The number of participants in each analysis depended on the outcome and missing data. For example, there were 3326 participants, 20–65 years of age with measured levels of all the eight urinary PAH biomarkers included in the current study. We excluded participants with missing information on serum cotinine level or other variables included in the multivariable model. This resulted in 2769 participants included in the summed LMW PAH-diabetes analyses.

### **Main outcome of interest: diabetes mellitus**

Glycohemoglobin measurements for NHANES 2001–2002 and 2003–2004 were performed by the Diabetes Diagnostic Laboratory at the University of Missouri-Columbia using Primus CLC330 and Primus CLC 385 (Primus Corporation, Kansas City, Missouri, USA). Glycohemoglobin measurements for NHANES 2005–2006 were performed by the Diabetes Laboratory at the University of Minnesota using Tosoh A1c 2.2 Plus Glycohemoglobin Analyzer (Tosoh Medics, Inc., San Francisco, California, USA). Both assays use a high-performance liquid chromatography (HPLC) system. Diabetes was defined as HbA1c level  $\geq 6.5\%$  (39 mmol/mol), a self-reported physician diagnosis of diabetes or current use of oral hypoglycaemic medication or insulin.<sup>16</sup>

### **Main exposure: urinary levels of monohydroxy-PAH**

Urine specimens were processed, stored and shipped to the Division of Environmental Health Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention for analysis. The specific analytes measured in this method are monohydroxy-PAHs (OH-PAH).<sup>17</sup> The procedure involves enzymatic hydrolysis of urine, extraction, derivatisation and analysis using capillary gas chromatography combined with high-resolution mass spectrometry (GC-HRMS). This method uses isotope dilution with carbon-13 labelled internal standards. Ions from each analyte and each carbon-13 labelled internal standard are monitored, and the abundances of each ion are measured. The ratios of these ions are used as criteria for evaluating the data. By evaluating these analytes in urine, a measurement of the body burden from PAH exposure is obtained.

Eight urinary OH-PAH analytes—1-hydroxynaphthalene, 2-hydroxynaphthalene, 2-hydroxyfluorene, 3-hydroxyfluorene, 1-hydroxyphenanthrene, 2-hydroxyphenanthrene, 3-hydroxyphenanthrene and 1-hydroxypyrene—are consistently available in NHANES 2001–2006.

All analytes were measured in the same unit (ng/L). Urinary OH-PAH were corrected for creatinine concentration, a urinary marker of kidney function to adjust for urinary dilution.<sup>18</sup> Urinary levels of OH-PAH (ng/L) were divided by urinary creatinine level (mg/dL) multiplied by 0.01, that is,  $[(\text{ng/L}) \div (\text{mg/dL} * 0.01)]$ , and expressed as nanogram per gram of creatinine (ng/g creatinine).

## Exposure measurements

Information on age, gender, race/ethnicity, alcohol intake, income and cigarette smoking were obtained from a standardised questionnaire during a home interview. Income–poverty ratio was used as a measure of the socioeconomic status. The Department of Health and Human Services’ poverty guidelines were used by NHANES to calculate this ratio. Smoking status was categorised into never smokers (smoked <100 cigarettes during their lifetime), former smokers (smoked ≥100 cigarettes during their lifetime and currently not smoking) and current smokers (smoked ≥100 cigarettes during their lifetime and currently smoking). Information on anthropometric, physical and laboratory components were obtained during the medical examination centre examination.

BMI was calculated as weight in kilograms divided by height in metres-squared. Total cholesterol was measured enzymatically. Serum cotinine was measured by isotope dilution-HPLC atmospheric pressure chemical ionisation tandem mass spectrometry (ID HPLC-APCI MS/MS).

## Statistical analysis

Our first step involves exploratory data analyses to shed light on the underlying distributions of the variables of interest and examine outliers. We ran linear regression models to calculate the multivariable change and 95% CI in log-transformed HbA1c (%) for each of the log-transformed urinary OH-PAH. By taking a log transformation, the distribution of the residuals was improved when compared with the residual distribution of the untransformed variables. In the next step, we ran logistic regression models to calculate the multivariable OR and 95% CI of diabetes mellitus, for each higher urinary OH-PAH quartile by using the lowest quartile as the referent. Variables were included in the model if they satisfied two conditions: first, a plausible association with the main outcome; and second, if the per cent change of the OR after adjusting for the potential confounder was over 10%. Accordingly, final models were adjusted for age (years), sex (male/female), ethnicity (non-Hispanic White, non-Hispanic Black, all others), poverty–income ratio (<1, ≥1), alcohol consumption (yes, no), BMI (normal, overweight, obese), total cholesterol (mg/dL) and serum cotinine (ng/mL).

To further ensure that the association was parallel for subgroups, we performed subgroup analyses by gender, race/ethnicity, BMI and smoking categories. Sample weights that account for the unequal probabilities of selection, oversampling and non-response in the NHANES survey were applied for all analyses. Analyses were conducted using SAS (V.9.3, SAS Institute, Cary, North Carolina, USA) software. SEs were estimated using the Taylor series linearization method.

## RESULTS

Table 1 presents the baseline characteristics of the study population. The study population was primarily non-Hispanic White (71.7%). Normal weight, overweight and obese BMI categories were equally distributed. Approximately one-half (50.2%) were never cigarette smokers. The mean value of serum cotinine level was 74.7 ng/mL. Diabetes mellitus was

reported in 7.5% of the study population. Sample sizes, weighted means and selected percentile of urinary levels of OH-PAH used in the final analysis are presented in the online supplementary table. Compared with those who were included in the final sample, participants who were excluded because of missing data were similar with respect to basic information listed in table 1, as well as the exposure and the outcome of interest.

The main estimates of the study are presented in table 2. Urinary levels of 1-hydroxynaphthalene, 2-hydroxynaphthalene, 2-hydroxyphenanthrene and summed LMW biomarkers were positively associated with diabetes mellitus in the multivariable adjusted models. Our subsequent analyses (results not shown in the table) examined the linear association between log-transformed HbA1c (%) and log-transformed urinary OH-PAH. Only levels of 2-hydroxynaphthalene ( $\beta=0.005$ ), 2-hydroxyfluorene ( $\beta=0.007$ ) and 2-hydroxyphenanthrene ( $\beta=0.007$ ) were statistically significant ( $p<0.05$ ) in the multivariable-adjusted linear regression model.

Next to examine effect modification, we performed subgroup analyses by major characteristics of the study population (table 3). Overall, higher levels of PAH biomarkers were positively associated with diabetes within the stratified subgroups; however, we found no appreciable variation among subgroups of gender, race/ethnicity, BMI or smoking.  $p$  interaction values for cross-product terms between urinary OH-PAH levels and stratifying variables were all  $>0.20$ .

## DISCUSSION

Studying PAHs and diabetes mellitus in a relatively large multi-ethnic sample of US adults, we found evidence that higher urinary levels of 1-hydroxynaphthalene, 2-hydroxynaphthalene, 2-hydroxyphenanthrene and summed LMW biomarkers were positively associated with diabetes mellitus, independent of potential confounders. In addition, urinary levels of 2-hydroxynaphthalene, 2-hydroxyfluorene and 2-hydroxyphenanthrene showed positive associations with HbA1c. Researchers have examined PAHs directly in the blood and tissues of experimental animals; however, these methods have not been widely used in humans due to the high costs and the limited clinical significance of testing. The most commonly used biomarkers of PAH exposure are urinary OH-PAH biomarkers and PAH-DNA adducts. Urinary OH-PAH biomarkers have been found to correlate well with low background levels of exposure to PAHs.<sup>19</sup>

Previous studies have reported a role of chronic exposure to PAHs in the development of oxidative stress.<sup>20</sup> Oxidative stress plays a major role in the pathogenesis of diabetes mellitus.<sup>21</sup> Studies have also reported a positive association between PAH exposure and inflammation,<sup>22–24</sup> a strong risk factor for obesity, insulin resistance and subsequent development of diabetes mellitus.<sup>25</sup> Chronic exposure to PAHs was also found to induce intestinal inflammation with subsequent increase in the risk of type 2 diabetes in animals.<sup>10</sup> Besides its suggested inflammatory effects, PAHs cause disruption of the endocrine system, with changes in plasma oestrogen concentrations in rats.<sup>26</sup> Oestrogen participates in glucose homeostasis by modulating the expression of genes that are involved in insulin sensitivity and glucose uptake.<sup>27,28</sup>

The strengths of this study include the relatively large multi-ethnic sample of US adults, the high quality of NHANES laboratory and data collection methods and the ability to adjust for confounders. In addition, we believe this is the first study to investigate the association between PAHs and diabetes in the general US population, adjusting for potential confounders including serum cotinine, an objective measure of cigarette smoke exposure. Serum cotinine is considered a more precise measure of exposure to cigarette smoking compared with self-reported smoking status<sup>29,30</sup> and is also considered a useful biomarker of secondhand smoke exposure.<sup>31</sup>

The study has several limitations. The cross-sectional nature of NHANES does not allow us to draw temporal or causal inferences regarding the relationship between PAHs and diabetes mellitus. Urinary PAH measurements reflect recent exposure if there are great differences between the current exposure sources and the past exposure sources for each subject. However, these biases are likely to be non-differential biases,<sup>32</sup> which would bias the association towards the null. In addition, because NHANES does not collect information to identify the type of diabetes, we cannot distinguish type 1 and type 2 diabetes. However, based on the population distribution of the two diabetes mellitus phenotypes, we believe that the majority of diabetes subjects in our sample have type 2 diabetes mellitus. It is also possible that diabetes mellitus causes higher PAH concentrations retained in the body due to subnormal kidney functions, a reverse causation that we address but that cannot be ruled out in prevalence data.

In conclusion, urinary biomarker levels of LMW PAHs were found to be positively associated with diabetes mellitus, independent of potential confounders and consistent with emerging toxicology data. Both PAH exposure and diabetes mellitus are highly prevalent in the USA. Considering the limitations of our study, further prospective studies are necessary to determine the causal relationship.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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**What this paper adds**

- ▶ Occupational and animal studies link polycyclic aromatic hydrocarbons (PAHs) to inflammation and subsequent development of diabetes mellitus.
- ▶ It is not clear whether exposure to PAHs in the general population is associated with diabetes mellitus risk in humans independent of cigarette smoking.
- ▶ We report a positive association between urinary biomarkers of 1 and 2-hydroxynaphthol, 2-hydroxyphenanthrene and summed low molecular weight PAH biomarkers, and diabetes mellitus in US adults 20–65 years of age.
- ▶ Considering the limitations of our study, further prospective studies are necessary to determine the causal relationship.

**Table 1**

Baseline characteristics of the study population with measured urinary levels of OH-PAH (n=2769)

Characteristics	Mean values±SE of mean or sample size (weighted percentages)*
Female (%)	1418 (49.8)
Age (years)	41.0±0.3
Race/ethnicity (%)	
Non-Hispanic Whites	1374 (71.7)
Non-Hispanic Blacks	584 (10.9)
Others	811 (17.4)
Education categories (%)	
Less than high school	667 (14.5)
High school	650 (24.9)
Above high school	1452 (60.6)
Below poverty level (%)	493 (12.9)
Smoking categories (%)	
Never	1443 (50.2)
Former smokers	584 (21.6)
Current smokers	741 (28.2)
Alcohol drinking (%)	
Yes	1993 (76.2)
Body mass index (%)	
Normal weight (<25.0 kg/m <sup>2</sup> )	861 (34.3)
Overweight (25.0–29.9 kg/m <sup>2</sup> )	925 (31.6)
Obese (>30.0 kg/m <sup>2</sup> )	983 (34.1)
Serum cotinine (ng/mL)	74.7±4.0
Total cholesterol (mg/dL)	201.2±1.3
Diabetes (%)	257 (7.5)

\* Data for the USA based on the National Health and Human Examination Survey, 2001–2006.

OH-PAH, monohydroxy polycyclic aromatic hydrocarbon.

**Table 2**  
Logistic regression: association of urinary OH-PAH (ng/g creatinine) and diabetes mellitus

Chemicals	Sample size	Multivariable OR (95% CI)*			
		Quartile 1	Quartile 2	Quartile 3	Quartile 4
1-Hydroxynaphthalene	2900	1 (Referent)	1.3 (0.8 to 2.3)	1.7 (1.1 to 2.8)	3.0 (1.5 to 5.9)
2-Hydroxynaphthalene	2916	1 (Referent)	2.6 (1.6 to 4.4)	1.8 (1.0 to 3.0)	3.3 (1.9 to 6.0)
2-Hydroxyfluorene	2892	1 (Referent)	0.8 (0.5 to 1.3)	1.2 (0.7 to 2.0)	1.4 (0.8 to 2.6)
3-Hydroxyfluorene	2875	1 (Referent)	0.8 (0.5 to 1.3)	1.3 (0.8 to 2.1)	1.5 (0.8 to 2.9)
1-Hydroxyphenanthrene	2897	1 (Referent)	1.5 (0.9 to 2.6)	1.3 (0.7 to 2.3)	1.4 (0.9 to 2.4)
2-Hydroxyphenanthrene	2872	1 (Referent)	1.0 (0.5 to 1.1)	1.4 (0.9 to 2.1)	1.9 (1.2 to 3.1)
3-Hydroxyphenanthrene	2866	1 (Referent)	1.1 (0.7 to 1.8)	1.4 (0.8 to 2.2)	1.4 (0.9 to 2.2)
1-Hydroxypyrene	2887	1 (Referent)	1.6 (0.9 to 2.8)	1.8 (1.0 to 3.5)	1.8 (1.0 to 3.0)
Summed LMW PAH biomarkers	2769	1 (Referent)	1.7 (1.0 to 2.8)	2.0 (1.3 to 3.2)	3.1 (1.6 to 5.8)

Data for the USA based on the National Health and Human Examination Survey, 2001–2006.

\* Adjusted for age (years), sex (male, female), BMI (normal weight, overweight, obese), race (non-Hispanic White, non-Hispanic Black, all others), alcohol drinking (yes, no), poverty-income ratio (<1, 1 or more), total cholesterol (mg/dL) and serum cotinine (ng/mL).

BMI, body mass index; LMW, low molecular weight; OH-PAH, monohydroxy polycyclic aromatic hydrocarbon.

**Table 3**

Logistic regression: association of urinary OH-PAH (ng/g creatinine)\* and diabetes mellitus by sociodemographic characteristics

Subgroups	Multivariable OR of diabetes mellitus (95% CI)	
	Summed urinary levels LMW PAH biomarkers	1-Hydroxypyrene
Gender <sup>†</sup>		
Female	1.2 (0.9 to 1.8)	1.0 (0.8 to 1.3)
Males	1.5 (1.1 to 1.9)	1.2 (1.0 to 1.5)
Race/ethnicity <sup>†</sup>		
Non-Hispanic White	1.4 (1.1 to 1.8)	1.1 (0.9 to 1.4)
Non-Hispanic Black	1.1 (0.8 to 1.4)	1.0 (0.7 to 1.4)
All others	1.5 (0.9 to 2.6)	1.4 (1.0 to 1.9)
Body mass index <sup>‡</sup>		
<30 kg/m <sup>2</sup>	1.2 (0.9 to 1.7)	1.2 (0.9 to 1.4)
≥30 kg/m <sup>2</sup>	1.4 (1.1 to 1.9)	1.1 (0.8 to 1.4)
Smoking <sup>†</sup>		
Never smokers	1.3 (1.0 to 1.7)	1.1 (0.8 to 1.4)
Former smokers	1.4 (1.0 to 2.1)	1.2 (0.9 to 1.6)
Current smokers	2.2 (1.1 to 4.5)	1.3 (0.9 to 1.9)

Data for the USA based on the National Health and Human Examination Survey, 2001–2006.

\* Urinary OH-PAH values used were log-transformed.

<sup>†</sup> Adjusted for age (years), sex (male, female), ethnicity (non-Hispanic White, non-Hispanic Black, all others), poverty–income ratio (<1, ≥1), alcohol drinking (yes, no), BMI (normal, overweight, obese), total cholesterol (mg/dL) and serum cotinine (ng/mL), except for stratified variables.

<sup>‡</sup> Adjusted for age (years), sex (male, female), ethnicity (non-Hispanic White, non-Hispanic Black, all others), poverty–income ratio (<1, ≥1), alcohol drinking (yes, no), BMI (kg/m<sup>2</sup>), total cholesterol (mg/dL) and serum cotinine (ng/mL), except for stratified variables.

BMI, body mass index; LMW, low molecular weight; OH-PAH, monohydroxy polycyclic aromatic hydrocarbon.