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Short Communication

Exposure to polycyclic aromatic hydrocarbons and serum inflammatory markers of cardiovascular disease

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ABSTRACT

Polycyclic aromatic hydrocarbons (PAHs) are environmental and occupational carcinogens produced by the incomplete combustion of organic materials, such as coal and petroleum product combustion, tobacco smoking, and food cooking, that may be significant contributors to the burden of cardiovascular disease in human populations. The purpose of this study was to investigate associations between ten monohydroxy urinary metabolites of four PAHs and three serum biomarkers of cardiovascular disease (fibrinogen, homocysteine, and white blood cell count). Using data on 3219 participants aged 20 years and older from the National Health and Nutrition Examination Survey (NHANES) 2001–2004 dataset, the associations between PAH metabolites and serum inflammatory markers were analyzed using the Spearman correlations and multiple linear regression modeling. The PAH metabolites of naphthalene, fluorene, phenanthrene, and pyrene each showed both positive and negative correlations with homocysteine, fibrinogen, and white blood cell count (correlation coefficient range: −0.077–0.143) in nonsmoking participants. Using multiple linear regression models adjusted for age, gender, race/ethnicity, and body mass index, estimates of weighted geometric means of inflammatory marker levels were not significantly different between high and low levels (75th vs. 25th percentiles) for all PAH metabolites in nonsmoking subjects. The results of this study do not provide evidence for a relationship between PAH exposure (as measured by urinary levels of PAH metabolites) and serum biomarkers of cardiovascular disease after controlling for tobacco use.

1. Introduction

Polycyclic aromatic hydrocarbons (PAH) are environmental and occupational carcinogens that are produced by the incomplete combustion of organic materials, such as coal and petroleum product combustion, tobacco smoking, and food cooking (A.T.S.D.R., 1995; Bartle, 1991; US Department of Health and Human Services, 2005). In addition to causing cancers in different organs, exposure to high levels of PAHs has been suggested to contribute to the development of atherosclerosis and to increased rates of cardiovascular disease in humans (Burstyn et al., 2005; Tuchsen et al., 1996). Considering the contribution of tobacco smoke exposure, ambient air pollution, and occupational hazards to cardiovascular morbidity and mortality, PAHs may be significant contributors to the burden of cardiovascular disease in human populations.

Evidence from both basic science and public health research has suggested associations between PAH exposure and cardiovascular disease. Animal studies in various species have demonstrated that injections of PAHs significantly increase aortic plaque volumes in a dose dependent relationship, and that chronic PAH exposure significantly increases the number of inflammatory cells in atherosclerotic plaques (Albert et al., 1977; Curfs et al., 2005; Penn and Snyder, 1988). Studies investigating the public health impact of exposure to tobacco smoke and to fine particulate matter air pollution, both of which are known to be sources of PAHs in human populations, have shown both exposures to be associated with adverse cardiovascular events (Dominici et al., 2006; Mensah et al., 2005; Peel et al., 2007; Taylor et al., 1992; Walker et al., 2008). Additionally, employees in occupations with known exposures to high levels of PAHs have been reported to have an increased risk of ischemic heart disease and cardiovascular

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mortality due to cardiovascular disease (Burstyn et al., 2005; Evanoff et al., 1993; Hansen and Hansen, 1983; Ronneberg and Ronneberg, 1995; Tuchsen et al., 1996).

One mechanism by which PAHs may play a role in the development of atherosclerosis and cardiovascular disease is through inflammation. A number of inflammatory factors are important predictors and possible promoters of atherosclerosis (Wilson, 2004). Serum biomarkers of cardiovascular disease (such as white blood cell count, homocysteine, fibrinogen, and c-reactive protein) have been investigated in human populations as possible proximate mechanisms of adverse vascular outcomes and cardiovascular disease. Studies have shown that an elevated white blood cell count and serum c-reactive protein are associated with the development of cardiovascular disease (Bassuk et al., 2004; Danesh et al., 1998; Ridker et al., 2003). Elevated levels of homocysteine are associated with increased risk of cardiovascular disease; while the mechanism is not yet completely elucidated, increased levels of homocysteine have been associated with impaired fibrinolysis (Tofler et al., 2002). A large body of evidence has established fibrinogen as an independent risk factor for cardiovascular disease, and as an important mediator through which traditional risk factors, such as low-density lipoprotein, exert their effects (Kannel and Kannel, 2005). C-reactive protein has since been found to be associated with high levels of urinary monohydroxy PAH metabolites, suggesting that PAH exposure may play a role in the progression of atherosclerosis through inflammation (Everett et al., 2010).

The purpose of this study was to determine if associations existed between the serum biomarkers of cardiovascular disease fibrinogen, homocysteine, and white blood cell count and ten urinary metabolites of four PAHs using data from a study involving a nationwide probability sample representative of the non-instituitonalized US population.

2. Materials and methods

Using data from the National Health and Nutrition Examination Surveys (NHANES) 2001–2004, this study investigated associations between the urinary metabolites of PAHs and serum biomarkers of cardiovascular disease in a representative sample of the US civilian population. Conducted by the National Center for Health Statistics, the 2001–2004 NHANES used a complex sampling strategy to obtain a representative sample of the non-institutionalized US civilian population aged two months or older from 15 US communities per survey cycle (N.H.A.N.E.S., 2008). Participants completed detailed questionnaires, received physical examinations, and received laboratory analysis of biological samples.

Measurements of urinary metabolites of PAHs were assessed in participants aged 6 years and over on a one-third sample of all NHANES participants. Within the database of NHANES participants from the 2001–2002 and 2003–2004 survey cycles, some participants did not have complete demographic data to allow for sampling weight calculation needed for analyses to be representative of the US population. Therefore, for this study, a subsample of participants were identified who had (a) valid sampling weights for use in analyses adjusting for the complex sampling design of the study and (b) were age 20 years or older since children are believed to have different PAH exposure and metabolism compared to adults (Cohen Hubal et al., 2000).

White blood cell counts were performed on samples using the Beckman Coulter MAXM instrument in the Mobile Examination Centers. Homocysteine was measured using fluorescence polarization immunoassay on the Abbott IMX analyzer. Fibrinogen was measured by the clot detection technique to determine sample values. All variables (except for fibrinogen) were available for analysis in all two 2-year survey cycles; fibrinogen was available only for analysis for the first NHANES cycle (2001–2002).

At the time of this study, data on ten monohydroxy PAH metabolites were available from the 2001–2004 NHANES survey cycles for analysis. Urinary concentrations of PAH metabolites were measured by means of capillary gas chromatography combined with high-resolution mass spectroscopy methods that have been described previously (NHANES, 2001). Urinary concentrations of PAH metabolites were adjusted for urinary creatinine concentration as was done in the Center for Disease Control's Third National Report on Human Exposure to Environmental Chemicals (C.D.C., 2005).

Additional variables shown to be associated with urinary PAH metabolite levels in past studies were investigated for inclusion in adjusted linear regression models. These included age, gender, race/ethnicity, body mass index (BMI) (equal to the weight in pounds divided by the square of the height in inches), and tobacco smoke exposure (either being a current smoker or having either home or workplace exposure to secondhand smoke) (Suwan-ampai et al., 2009). Age, gender, and race were attained by self-report. Race/ethnicity was classified as Non-Hispanic White, Non-Hispanic Black, Hispanic, and other/mixed race. BMI was calculated using measured weight and height attained by physical examination.

All statistical analyses were conducted with SAS version 9.2 (SAS institute, Inc., Cary, NC) using survey procedures that adjusted for the complex survey design and included appropriate sampling weights developed by the National Center for Health Statistics for this random subsample to obtain accurate estimates representative of the non-institutionalized civilian US population (C.D.C., 2005). Relationships between demographic characteristics and inflammatory markers were performed to identify covariates to be used in later analyses. Due to urinary PAH metabolites having a detection limit, analyses using ranks and percentiles were performed to properly handle left-censored PAH data. Spearman correlations were performed to investigate associations between levels of urinary PAH metabolites and inflammatory markers for current smokers and nonsmokers. Lastly, associations between urinary PAH metabolites and serum biomarkers of cardiovascular disease were analyzed using simple linear regression with adjustment for sampling weights. To investigate possible relationships between PAH metabolite and serum cardiovascular disease biomarkers in nonsmoking participants, geometric mean differences were calculated for inflammatory markers by the interquartile range (75th vs. 25th percentile) of each urinary PAH metabolite in nonsmoking subjects a multiple linear regression models adjusting the variables previously shown to be associated with PAH metabolites (age, gender, race, and BMI).

3. Results

Data on 21,161 NHANES participants were available from the 2001–2004 survey cycles. A random one-sixth subsample of NHANES participants received laboratory examination of urine samples for PAHs, for a total of 5598 subjects. A total of 3219 participants (57.5% of PAH subjects; 15.2% of all NHANES subjects) with PAH measurements were age 20 years or older and had valid sampling weights for inclusion in this analysis. Fibrinogen measurements were only available for subjects aged 40 years and older and in the 2001–2002 survey cycle, for a total of 1008 participants. Sample size and weighted percentages for demographic characteristics of the NHANES 2001–2004 sample population included in this analysis are shown in Table 1.

To investigate associations between demographic covariables and serum inflammatory markers, weighted geometric mean differences of individual inflammatory markers were calculated by covariate category (Table 2). Mean homocysteine levels were significantly increased for participants aged 40–59 or 60+ years compared to age 20–39 years; mean fibrinogen level was significantly increased for age being 60+ years compared to those aged 20–39 years; mean white blood cell count was significantly decreased for age being 40–50 and 60+ years. Female gender was found to be associated with significantly decreased levels of homocysteine and significantly increased levels of fibrinogen and white blood cell count. Significant differences in mean levels of all inflammatory markers were seen in at least one racial category compared to White non-Hispanic subjects. Self-report of being a current smoker was significantly associated with increased levels of all inflammatory markers. Lastly, having a BMI defined as either overweight or obese was associated with significantly increased mean levels of fibrinogen and white blood cell count compared to normal and underweight subjects.

Spearman correlations of urinary metabolites of naphthalene, fluorene, phenanthrene, and pyrene with serum cardiovascular disease biomarkers were performed with stratification by smoking status (see online appendix, Table A). For homocysteine, current smokers were found to have weakly yet positive correlations with all urinary PAH metabolites (range: 0.133–0.259), while nonsmokers were found to have both positive and negative

Table 1
Demographic characteristics of sample populations from NHANES 2001–2004.

	n[a]	Weighted (%)	95% Confidence interval (%)		
Age (years)					
20–39	1172	39.90	37.10	–	42.69
40–59	989	38.56	36.10	–	41.01
60+	1058	21.55	19.66	–	23.44
Gender					
Male	1547	47.87	45.85	–	49.89
Female	1672	52.13	50.11	–	54.15
Race/ethnicity					
White, non-Hispanic	1701	72.42	68.16	–	76.68
Black, non-Hispanic	632	11.21	8.87	–	13.56
Mexican American	662	7.48	5.18	–	9.77
Other Hispanic	118	4.82	2.52	–	7.12
Other	106	4.07	2.92	–	5.22
Tobacco smoke exposure[b]					
Secondhand smoke unexposed nonsmoker	2122	63.10	60.06	–	66.15
Secondhand smoke exposed nonsmoker	363	12.11	10.55	–	13.67
Current smoker	731	24.79	22.33	–	27.25
Body mass index					
Normal/Underweight	1004	34.35	31.80	–	36.91
Overweight	1111	33.54	31.40	–	35.68
Obese	1000	32.10	29.43	–	34.77

[a] Sample size varies due to item non-response.
[b] Self-reported exposure to secondhand smoke in either the home or the workplace.

weak correlations with PAH metabolites (range: −0.077–0.143). For fibrinogen, current smokers and nonsmokers were found to have both positive and negative weak correlations with urinary PAH metabolites (smokers: −0.034–0.144, nonsmokers: −0.061–0.023). For white blood cell count, current smokers were found to have weak yet positive correlations with all urinary PAH metabolites (range: 0.024–0.118), while nonsmokers were found to have both positive and negative weak correlations with PAH metabolites (range: −0.036–0.076).

Table 3 shows associations between estimates of adjusted, weighted geometric mean levels of inflammatory markers by the interquartile range (75th vs. 25th percentile) of monohydroxy PAH metabolites and serum biomarkers of cardiovascular disease in nonsmokers using age-adjusted and multiple linear regression models after adjusting demographic characteristics. For both homocysteine and white blood cell count, elevated levels of all urinary PAH metabolites were associated with small increases on inflammatory marker levels that were not statistically significant in nonsmoking subjects in both age-adjusted and multiple linear regression models (homocysteine range: 0.00 to 0.08, white blood cell count range: 0.00–0.06). For fibrinogen, elevated levels of urinary PAH metabolites were associated with small increases and decreases in inflammatory marker levels that were not statistically significant in nonsmoking subjects in both age-adjusted and multiple linear regression models (range: −0.45–2.88).

4. Discussion

The results of this study do not provide evidence for a relationship between PAH exposure (as measured by urinary levels of PAH metabolites) and serum biomarkers of cardiovascular disease after controlling for tobacco use. While current smokers were found to have consistently small yet positive correlations between urinary PAH metabolites with levels of homocysteine and white blood cell count, this trend in correlations was not seen in nonsmokers. In the case of fibrinogen, no consistent trend was seen, with both small positive and negative correlations with urinary PAH metabolites for both smokers and nonsmokers. In our analysis of nonsmoking subjects using multiple linear regression models, no statistically significant differences existed in the estimated mean levels of inflammatory markers between high and low levels (75th vs. 25th percentiles) of each PAH metabolite. Thus, the results of our analyses do not support the tentative hypothesis that PAH exposure contributes to cardiovascular disease development.

The results of this study also do not support the hypothesis that environmental exposure to PAHs, such as with exposure to secondhand tobacco smoke and/or environmental air pollution, are a significant contributor to the burden of cardiovascular disease via inflammation in the US population. Past research has shown that exposure to tobacco smoke, which contains mixtures of PAHs, is associated with elevated levels of serum biomarkers of cardiovascular disease (Bazzano et al., 2003; Wilkinson et al., 2007). Similarly, past studies have found that people exposed to high levels of ambient air particulate matter, which also contains mixtures of PAHs, may have increased levels of c-reactive protein, fibrinogen, and white blood cells (Ruckerl et al., 2007; Ruckerl et al., 2006; Schwartz, 2001). While a recent study that used data from the NHANES 2003–2004 found associations between urinary PAH metabolites and c-reactive protein, believed to be the most reliable of the inflammatory biomarkers, the results of this study do not provide additional evidence of such an association (Everett et al., 2010; Pearson et al., 2003). The lack of associations between urinary metabolites of the PAHs naphthalene, fluorene, phenanthrene, and pyrene with serum biomarkers of inflammation, however, suggests that PAH exposure may not be a significant contributor to the development of cardiovascular disease through an inflammatory mechanism in the US population.

One important strength of this study is that our analysis incorporated 4 years of collected data (2001–2004) with more than 3000 adult subjects of a nationally representative sample of the entire US civilian population whose PAH metabolites were assessed under controlled conditions. In addition, this study used 3 biomarkers of inflammation as surrogate measures of inflammation involved in cardiovascular disease development. However, the cross-sectional nature of NHANES limits the conclusions that can be made based on the results of this analysis. Additionally,

Table 2
Weighted geometric mean differences and 95% confidence intervals of inflammatory markers by demographic characteristics.

	Homocysteine (mg/dL)				Fibrinogen (mg/dL)				White blood cell count (SI)			
	N[a]	Weighted geometric mean	Weighted geometric mean difference	95% Confidence interval	*N*[b]	Weighted geometric mean	Weighted geometric mean difference	95% Confidence interval	*N*[a]	Weighted geometric mean	Weighted geometric mean difference	95% Confidence interval
Age (years)												
20–39	1110	7.35	Reference		–				1117	7.18	Reference	
40–59	954	8.42	1.07	0.85–1.30	508	355.18	Reference		957	6.94	−0.25	−0.41 to −0.09
60+	1022	10.21	2.86	2.55–3.17	500	395.92	40.74	32.12–49.55	1025	6.74	−0.44	−0.60 to −0.29
Gender												
Male	1481	9.16	Reference		515	352.18	Reference		1483	6.89	Reference	
Female	1605	7.61	−1.55	−1.74 to −1.36	493	376.14	23.96	10.95–37.43	1616	7.08	0.19	0.04–0.35
Race/ethnicity												
White, non-Hispanic	1651	8.48	Reference		572	364.13	Reference		1657	7.06	Reference	
Black, non-Hispanic	584	8.42	−0.06	−0.26–0.15	193	389.61	25.48	12.10–39.35	588	6.30	−0.76	−0.99 to −0.52
Mexican American	635	7.12	−1.36	−1.52 to −1.19	174	351.63	−12.50	−27.91–3.62	638	7.17	0.11	−0.12–0.35
Other Hispanic	116	8.03	−0.45	−0.81 to −0.07	25	349.03	−15.10	−36.45–7.64	116	7.57	0.51	0.15–0.88
Other	100	8.01	−0.46	−1.07–0.20	44	350.33	−13.80	−43.14–18.24	100	6.69	−0.37	−0.69 to −0.02
Tobacco smoke exposure												
Secondhand smoke unexposed nonsmoker	2027	8.12	Reference		712	362.10	Reference		2039	6.75	Reference	
Secondhand smoke exposed nonsmoker	357	8.19	0.07	−0.33–0.48	104	355.09	−7.02	−34.88–23.23	357	6.67	−0.08	−0.34–0.19
Current Smoker	699	8.92	0.80	0.45–1.16	191	378.47	16.37	2.48–30.78	700	7.80	1.04	0.84–1.25
Body mass index												
Normal/ underweight	966	8.19	Reference		266	340.21	Reference		969	6.69	Reference	
Overweight	1073	8.40	0.21	0.00–0.44	367	355.53	15.32	1.32–29.90	1076	6.91	0.22	0.07–0.38
Obese	958	8.35	0.16	−0.06–0.38	325	391.65	51.44	39.55–63.71	965	7.39	0.70	0.49–0.93

[a] Sample size due to inflammatory marker availability for subjects aged 20 years and older from NHANES 2001–2004.
[b] Sample size due to inflammatory marker availability from subjects aged 40 years and older from NHANES 2001–2002.

Table 3
Estimates of weighted, adjusted geometric mean differences of inflammatory markers by the interquartile range (75th vs. 25th percentile) of urinary polycyclic aromatic hydrocarbon metabolite levels in nonsmoking subjects of NHANES 2001–2004 using multiple linear regression models.

	Homocysteine (mg/dL)			Fibrinogen (mg/dL)			White blood cell count (SI)		
Urinary PAH metabolite	***N***	**Age-adjusted weighted geometric mean difference**	**95% Confidence intervals**	***N***	**Age-adjusted weighted geometric mean difference**	**95% Confidence intervals**	***N***	**Age-adjusted weighted geometric mean difference**	**95% Confidence interval**
1-Hydroxynaphthalene	2272	0.02	−0.14–0.18	767	0.44	−13.09–14.48	2284	0.01	−0.08–0.10
2-Hydroxynaphthalene	2261	0.07	−0.08–0.23	767	2.88	−9.89–16.11	2273	0.06	−0.03–0.14
2-Hydroxyfluorene	2230	0.06	−0.10–0.23	767	0.18	−13.26–14.14	2242	0.02	−0.07–0.11
3-Hydroxyfluorene	2223	0.11	−0.05–0.27	767	0.44	−13.01–14.40	2295	0.03	−0.06–0.12
9-Hydroxyfluorene[a]	1051	0.07	−0.13–0.27		–[b]	–[b]	1055	0.05	−0.11–0.20
1-Hydroxyphenanthrene	2227	0.03	−0.13–0.20	765	0.04	−13.33–13.92	2239	0.02	−0.07–0.12
2-Hydroxyphenanthrene	2221	0.03	−0.14–0.19	766	0.29	−13.03–14.12	2233	0.03	−0.06–0.12
3-Hydroxyphenanthrene	2186	0.00	−0.16–0.17	765	0.26	−13.06–14.07	2198	0.00	−0.09–0.09
4-Hydroxyphenanthrene[a]	1027	0.08	−0.13–0.29		–[b]	–[b]	1091	0.05	−0.09–0.19
1-Hydroxypyrene	2231	0.07	−0.09–0.23	767	0.62	−12.49–14.22	2243	0.02	−0.07–0.12
Urinary PAH metabolite	***N***	**Multivariable djusted weighted geometric mean difference[c]**	**95% Confidence interval**	***N***	**Multivariable adjusted weighted geometric mean difference[d]**	**95% Confidence interval**	***N***	**Multivariable adjusted weighted geometric mean difference [d]**	**95% Confidence interval**
1-Hydroxynaphthalene	2272	0.03	−0.14–0.20	767	0.45	−11.10–12.02	2284	0.01	−0.08–0.08
2-Hydroxynaphthalene	2261	0.02	−0.14–0.19	767	1.51	−9.50–13.12	2273	0.06	−0.04–0.13
2-Hydroxyfluorene	2230	0.02	−0.13–0.17	767	0.01	−11.01–11.37	2242	0.03	−0.04–0.11
3-Hydroxyfluorene	2223	0.02	−0.14–0.18	767	0.45	−10.51–10.79	2295	0.05	−0.02–0.12
9-Hydroxyfluorene[a]	1051	0.03	−0.21–0.28		–[b]	–[b]	1055	0.06	−0.04–0.14
1-Hydroxyphenanthrene	2227	0.02	−0.15–0.20	765	−0.25	−11.45–10.77	2239	0.02	−0.08–0.11
2-Hydroxyphenanthrene	2221	0.02	−0.17–0.20	766	−0.05	−11.02–11.29	2233	0.02	−0.08–0.13
3-Hydroxyphenanthrene	2186	0.01	−0.14–0.16	765	0.25	−10.11–11.82	2198	0.01	−0.07–0.08
4-Hydroxyphenanthrene[a]	1027	0.03	−0.19–0.25		–[b]	–[b]	1091	0.04	−0.04–0.14
1-Hydroxypyrene	2231	0.01	−0.16–0.18	767	−0.45	−11.06–9.98	2243	0.04	−0.04–0.11

[a] PAH metabolites were not available for the 2001–2002 survey cycle.
[b] Sample size due to inflammatory marker availability for subjects aged 20 years and older from NHANES 2001–2004.
[c] Adjusting for age, gender, race and body mass index.
[d] Adjusting for age, gender, race, and body mass index.

many statistical tests were performed in our analysis, which may result in some statistically significant results that may not accurately represent the true state of tested relationships.

5. Conclusions

In conclusion, the results of this study do not provide evidence for a relationship between PAH exposure (as measured by urinary monohydroxy PAH metabolites) and serum biomarkers of cardiovascular disease independent of tobacco smoke exposure.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.envres.2012.04.012.

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