



# Association of Urinary Polycyclic Aromatic Hydrocarbons and Diabetes in Korean Adults: Data from the Korean National Environmental Health Survey Cycle 2 (2012–2014)

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**Purpose:** To investigate the associations between the urinary levels of polycyclic aromatic hydrocarbons (PAHs) and diabetes mellitus in Korean adults.

**Materials and Methods:** We examined the data of 6478 participants aged  $\geq 19$  years from the Korean National Environmental Health Survey (KoNEHS) cycle 2 (2012–2014). The urinary levels of 1-hydroxypyrene (1-OHP), 2-naphthol (2-NAP), 1-hydroxyphenanthrene (1-OHPhe), and 2-hydroxyfluorene (2-OHFlu) were measured by gas chromatography-mass spectrometry. Diabetes mellitus was defined as a self-report of physician-diagnosed diabetes mellitus or the use of oral hypoglycemics or insulin. Analyses were adjusted for sex, age, body mass index, household income, alcohol consumption, physical activity, urinary creatinine and cotinine, menopausal status, and quartiles of all other PAHs.

**Results:** The prevalence of diabetes was 6.5% in the study population. In men, the geometric means of the 2-NAP and 2-OHFlu levels were higher in participants with diabetes mellitus than in those without diabetes mellitus [4.11 vs 3.26  $\mu\text{g/L}$  ( $P < 0.05$ ) and 0.45 vs 0.40  $\mu\text{g/L}$  ( $P < 0.05$ ), respectively]. In women, the geometric mean of 2-NAP levels was also higher in participants with diabetes mellitus than in those without diabetes mellitus (1.81 vs 0.56  $\mu\text{g/L}$ ,  $P < 0.05$ ), but there were no significant differences in geometric means for other PAHs. A higher odds ratio (OR) of diabetes was found in participants with the highest quartiles of urinary 2-NAP [OR 1.83, 95% confidence interval (CI) 1.29–2.60] and 2-OHFlu (OR 1.81, 95% CI 1.10–2.98) than in those with the lowest quartiles.

**Conclusion:** The urinary 2-NAP and 2-OHFlu levels were associated with diabetes mellitus in Korean adults. Further studies are needed to determine a potential causal relationship between PAH exposure and diabetes mellitus and its underlying mechanism.

**Keywords:** environmental pollutant, 2-naphthol, 2-hydroxyfluorene, environmental exposure, health survey, endocrine disruptors

## Introduction

Over the last few decades, the prevalence of type 2 diabetes has significantly increased worldwide.<sup>1</sup> The prevalence of diabetes is predicted to reach 693 million individuals by 2045,<sup>2</sup> and especially in Korea, it has increased astonishingly among adults over the past 15 years.<sup>3</sup> In addition to the well-known risk factors of diabetes, including genetic predisposition and obesity,<sup>4</sup> recent reports have indicated that endocrine-disrupting chemicals (EDCs) may play a significant

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role in the development of diabetes.<sup>1</sup> Among EDCs, polycyclic aromatic hydrocarbons (PAHs) have been extensively studied recently.

PAHs are a group of environmental pollutants whose structures contain aromatic rings. They are generated by incomplete combustion of organic materials, such as coal, gasoline, and wood. The major sources of PAH exposure include inhalation of cigarette smoke, vehicle exhaust, and processed fossil fuels. It could also be derived from the ingestion of grilled and charred meats, contaminated food products, and the cooking process.<sup>5</sup>

In experimental studies, the possible mechanisms linking PAH exposure to diabetes include oxidative stress<sup>6</sup> and systemic inflammation,<sup>7,8</sup> which induce  $\beta$ -cell dysfunction<sup>9</sup> and disruption of the insulin signaling pathway.<sup>10</sup>

Previous epidemiologic studies from the USA<sup>11–14</sup> and China<sup>15–18</sup> have shown a positive association between PAH exposure determined by the urinary PAH levels and diabetes. However, no studies on this issue have been conducted using nationwide data except for the US National Health and Nutrition Examination Survey (NHANES). Severe air pollution in Korea has also become an increasing threat.<sup>19</sup> Given the rapidly increasing prevalence of diabetes in the Korean population,<sup>3</sup> epidemiologic studies are needed to elucidate the link between PAH exposure and diabetes in Korean adults.

In this study, we aimed to evaluate the associations between the urinary PAH levels and diabetes using nationally representative data from the Korean National Environmental Health Survey (KoNEHS).

## Materials and Methods

### Study Population

The KoNEHS is a cross-sectional nationwide biomonitoring survey, which aims to monitor the exposure of people to environmental chemicals. It involves a stratified multi-stage probability sample representative of the entire Korean population. The survey collects data on socioeconomic status and health conditions and conducts questionnaire-based personal interviews on environmental chemical exposure, physical examinations, and laboratory tests. A detailed description of the KoNEHS study design was provided in a previous study.<sup>20</sup>

We specifically used data from the second cycle of the KoNEHS, which was conducted between 2012 and 2014. A total of 6478 participants aged  $\geq 19$  years with data on urinary levels of 1-hydroxypyrene (1-OHP), 2-naphthol

(2-NAP), 1-hydroxyphenanthrene (1-OHPhe), and 2-hydroxyfluorene (2-OHFlu) were included for analysis. Diabetes was defined as a self-report of physician-diagnosed diabetes or the current oral hypoglycemic medication or insulin use at the time of the interview.

The KoNEHS was conducted in accordance with the Declaration of Helsinki. All participants of the KoNEHS agreed to participate the survey and signed a written informed consent. The study protocol was approved by the Institutional Review Board of Inje University Sanggye Paik Hospital (approval number: SGPAIK-2020-08-001).

### Measurement of Urinary PAHs

Random spot urine samples were collected and stored within 24 h following the standard procedures established by the National Institute of Environmental Research. The urinary levels of PAHs were analyzed by gas chromatography-mass spectrometry (Clarus 680T, PerkinElmer, Waltham, MA, USA).

For external quality control, all institutions involved in the analysis participated in the German G-EQUAS and the Special Health Quality Control program by the Occupational Safety and Health Research Institute. All institutions passed both programs. Internal quality control was conducted following the guidelines of the National Institute of Environmental Research using G-EQUAS, Bio-Rad, ClinCheck I and II, and NIST standards. The limit of detection (LOD) values for 1-OHP, 2-NAP, 1-OHPhe, and 2-OHFlu were 0.015, 0.050, 0.047, and 0.040  $\mu\text{g/L}$ , respectively. Values below the LOD were calculated as the method detection limit divided by  $\sqrt{2}$ . All urinary PAH levels were adjusted for the urinary creatinine levels.

### Study Covariates

Information on age, sex, household income, smoking, alcohol consumption, physical activity, and menopausal status (in women) was obtained using standardized questionnaires during the survey interview. Monthly household income of the participants [in US dollars (USD)] was grouped into four categories:  $< 920$ , 920–2090, 2090–3400, and  $\geq 3400$  USD. Former or current smokers were active smokers who had smoked at least 100 cigarettes in their lifetime. Former smokers were defined as those who had quit smoking at the time of the interview. The participants who had consumed at least one glass of alcohol every month over the past year were defined as

former or current drinkers. Former drinkers were defined as those who had quit drinking at the time of the interview. Regular physical activity was indicated as “yes” when the participant engaged in moderate and severe exercise on a regular basis for >30 min at a time and more than three times/week.

Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m<sup>2</sup>). The participants were classified as underweight (<18.5), normal weight (18.5–22.9), overweight (23–24.9), and obese (≥25) according to the Asian BMI classifications.<sup>21</sup>

## Statistical Analysis

Statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Sampling weights were used for the complex sampling model for all analyses. The demographic characteristics and health behaviors of participants were analyzed using the complex samples general linear model and cross-tabulation procedures. The complex samples descriptive procedure was used to calculate the geometric means (GMs) and 95% confidence intervals (95% CIs) of the PAH levels. The GMs of the urinary PAH levels were compared in terms of the demographic and behavioral factors of diabetes using the complex samples general linear model after adjusting for the log-transformed urinary creatinine and cotinine levels. The urinary PAH levels were log-transformed due to their skewed distribution. Complex samples logistic regression analyses were used to calculate the odds ratios (ORs) and 95% CIs for diabetes, according to the PAH quartiles, after adjusting the multiple covariates for sex, age, BMI, household income, alcohol consumption, physical activity, log-transformed urinary creatinine and cotinine, and menopausal status (in women). For all analyses, *P* values were two-tailed, and a *P* value <0.05 was considered statistically significant.

## Results

### General Characteristics of Participants

Table 1 presents the general characteristics of the study participants. The mean age was 46.3 ± 0.4 years, and 42.8% of participants were men. The proportions of overweight and obese participants were significantly higher in men (25.1% and 43.3%) than in women (20.9% and 32.0%). Smoking prevalence was significantly higher in men than in women (39.8% vs 3.8%, *P* <0.001). The

overall prevalence of diabetes was 6.5%, which was not significantly different by sex.

### Distributions of PAHs According to the Participant Characteristics

Table 2 summarizes the urinary PAH levels according to the participant characteristics. The proportion of participants who had a detectable level (above the LOD) of each urinary PAH was 97.1%, 98.8%, 79.0%, and 92.9% for 1-OHP, 2-NAP, 1-OHPhe, and 2-OHFlu, respectively. The GMs of the urinary levels of 1-OHP, 2-NAP, 1-OHPhe, and 2-OHFlu were 0.15, 2.23, 0.10, and 0.27 µg/L, respectively, and were significantly higher in men than in women. Moreover, the GMs of all urinary PAH levels were significantly higher in former/current smokers than in never smokers.

Table 3 shows the adjusted GMs of the urinary PAH levels in men. The GM values were significantly higher in those aged ≥40 years than in those aged <40 years (*P* < 0.05). In men, the GM of 2-OHFlu levels was significantly higher in the highest-BMI than in the normal-BMI group. There were no significant differences in other PAH levels according to the BMI status. There were also no significant differences in all PAH levels according to the household income and the alcohol consumption status. Meanwhile, the GM of the 1-OHPhe levels was significantly higher in participants who performed regular physical activity than in those who did not (*P* <0.05), but there were no significant differences with other PAHs. The GMs of the urinary 2-NAP and 2-OHFlu levels were significantly higher in participants with diabetes mellitus than in those without (4.11 vs 3.26 µg/L and 0.45 vs 0.40 µg/L, respectively; all *P* <0.05).

Table 4 presents the adjusted GMs of the urinary PAH levels in women. The GMs of the 1-OHP, 1-OHPhe, and 1-OHFlu levels were significantly higher in the lowest-BMI than in the normal-BMI group (*P* <0.05), whereas the GMs of 1-OHP and 1-OHPhe levels were significantly higher in the highest-BMI than in the normal-BMI group (*P* <0.05). No significant differences in the PAH levels were observed in women based on the household income, alcohol consumption, physical activity, and menopausal status. Women with diabetes mellitus had a higher GM of the urinary 2-NAP levels than women without (1.81 vs 0.56 µg/L, *P* <0.05). Regarding other urinary PAHs in women, no significant differences in GM values were found between those with and without diabetes mellitus.

**Table 1** General Characteristics of the Study Subjects

	Total (n=6478)			Men (n=2774)			Women (n=3704)			P-value
Age (years)	46.3	±	0.4	45.4	±	0.4	47.1	±	0.5	<0.001
Age group (n,%)										<0.001
19–29 yr	537		17.7%	263		18.5%	274		16.9%	
30–39 yr	1056		19.9%	435		20.7%	621		19.1%	
40–49 yr	1226		21.4%	504		22.0%	722		20.8%	
50–59 yr	1439		19.4%	578		19.7%	861		19.1%	
60–69 yr	1335		11.1%	597		10.8%	738		11.3%	
≥70 yr	885		10.6%	397		8.3%	488		12.8%	
BMI group (n,%)										<0.001
Underweight	154		3.0%	48		1.6%	106		4.40%	
Normal	2183		36.4%	809		29.9%	1374		42.80%	
Overweight	1600		23.0%	738		25.1%	862		20.90%	
Obese	2541		37.6%	1179		43.4%	1362		32.00%	
Household income (USD/months)										<0.001
< 920 USD	1629		17.3%	639		14.6%	990		19.9%	
920–2090 USD	1396		19.1%	615		19.0%	781		19.2%	
2090–3400 USD	1488		26.4%	660		27.5%	828		25.4%	
≥3400 USD	1965		37.2%	860		38.9%	1105		35.5%	
Smoking (n,%)										<0.001
Never	4259		62.7%	762		30.6%	3497		93.9%	
Former	1058		15.8%	990		29.6%	68		2.3%	
Current	1161		21.5%	1022		39.8%	139		3.8%	
Drinking (n,%)										<0.001
Never	2230		29.7%	447		15.30%	1783		43.6%	
Former	424		5.6%	282		7.00%	142		4.2%	
Current	3824		64.7%	2045		77.60%	1779		52.2%	
Regular physical activity (n,%)										<0.001
No	4658		72.3%	1931		69.3%	2727		75.1%	
Yes	1820		27.7%	843		30.7%	977		24.9%	
Diabetes mellitus (n,%)										0.482
No	5928		93.5%	2504		93.3%	3424		93.8%	
Yes	550		6.5%	270		6.7%	280		6.2%	

**Notes:** Mean ± SE or number (%), BMI <18.5 for underweight, 18.5–22.9 for normal weight, 23–24.9 for overweight, ≥25 for obese.

**Abbreviations:** BMI, body mass index; USD, US dollars.

## Association Between the Urinary PAH Levels and Diabetes

Adjusted ORs and 95% CIs for diabetes mellitus according to the quartiles of urinary PAHs are presented in Table 5. The participants in the highest 2-NAP quartile had a higher OR for diabetes than those in the lowest quartile (OR 1.83, 95% CI 1.29–2.60). The adjusted ORs for diabetes across quartiles of 2-NAP were 1, 1.08, 1.57, and 1.83 (*P* <0.001). Conversely, the OR for diabetes was higher in participants in the highest than in the lowest 2-OHFlu quartile (OR 1.81, 95% CI 1.10–2.98). However,

this association was not statistically significant in the subgroup analysis by sex.

## Discussion

In this study, using national representative data, we demonstrated that Korean adults with diabetes mellitus had higher urinary levels of 2-NAP in both sexes than those without. We also presented that men had higher urinary 2-OHFlu levels than women. Moreover, quartiles of urinary 2-NAP levels were positively associated with OR for diabetes in a dose-dependent manner in both sexes

**Table 2** Distributions of Urinary PAHs Metabolites Concentrations

	N	GM (95% CI)	%≥LOD	Selected Percentiles			
		Crude		25th	50th	75th	95th
1-hydroxypyrene (µg/L)							
Total	6418	0.15 (0.14–0.16)	97.1	0.09	0.14	0.25	0.60
Men <sup>a</sup>	2745	0.18 (0.17–0.19)	98.1	0.1	0.18	0.32	0.76
Women	3673	0.13 (0.12–0.14)***	96.4	0.08	0.13	0.21	0.56
Smoking status							
Never <sup>a</sup>	4226	0.12 (0.12–0.13)	96.4	0.08	0.13	0.21	0.49
Former	1046	0.15 (0.14–0.16)***	97.7	0.09	0.14	0.23	0.57
Current	1146	0.27 (0.25–0.28)***	99.2	0.16	0.28	0.44	0.9
2-naphthol (µg/L)							
Total	6410	2.23 (2.11–2.35)	98.8	0.83	1.91	5.32	19.9
Men <sup>a</sup>	2750	3.02 (2.82–3.25)	99.3	1.09	2.93	8.5	23.1
Women	3660	1.64 (1.54–1.76)***	98.4	0.71	1.46	3.53	14.3
Smoking status							
Never <sup>a</sup>	4210	1.52 (1.43–1.61)	98.5	0.68	1.39	3.23	12.6
Former	1049	1.76 (1.60–1.92)**	98.7	0.8	1.66	3.85	17.1
Current	1151	7.93 (7.39–8.52)***	100.0	4.51	8.8	14.7	30.7
1-hydroxyphenanthrene (µg/L)							
Total	6413	0.10 (0.09–0.10)	79.0	0.05	0.09	0.16	0.38
Men <sup>a</sup>	2746	0.11 (0.10–0.11)	82.9	0.06	0.11	0.19	0.45
Women	3667	0.09 (0.08–0.09)***	76.1	0.05	0.08	0.14	0.39
Smoking status							
Never <sup>a</sup>	4220	0.08 (0.08–0.09)	75.8	0.05	0.08	0.14	0.33
Former	1047	0.09 (0.09–0.10)*	78.4	0.05	0.09	0.16	0.40
Current	1146	0.14 (0.13–0.15)***	91.5	0.09	0.14	0.24	0.48
2-hydroxyfluorene (µg/L)							
Total	6397	0.27 (0.25–0.28)	92.9	0.12	0.24	0.51	1.86
Men <sup>a</sup>	2735	0.40 (0.37–0.43)	95.7	0.17	0.38	1.00	2.38
Women	3662	0.18 (0.17–0.19)***	90.8	0.09	0.19	0.35	1.00
Smoking status							
Never <sup>a</sup>	4216	0.18 (0.17–0.19)	91.1	0.10	0.19	0.33	0.80
Former	1045	0.22 (0.20–0.24)***	93.6	0.12	0.23	0.42	1.11
Current	1136	1.01 (0.93–1.09)***	99.1	0.62	1.13	1.82	3.32

**Notes:** <sup>a</sup>Reference for comparison of geometric mean in each variable. \*\*\*P<0.001, \*\*P<0.01, \*P<0.05.

**Abbreviations:** BMI, body mass index; CI, confidence interval; GM, geometric mean; LOD, limit of detection.

after considering all covariates, including other PAH levels. The positive association between the urinary 2-OHFlu levels and diabetes was weak and lost its statistical significance in the sex-specific analysis. To our knowledge, this is the first large-scale nationwide epidemiologic study showing the relationship between urinary PAHs and diabetes in the non-Western population.

We found that the urinary levels of all four PAHs in this study were significantly higher in men than in women and higher in former/current smokers than in never smokers. These findings were consistent with those of previous studies based on the US NHANES<sup>22</sup> and the Canadian Health Measure Survey.<sup>23</sup> Since PAHs are produced during the incomplete combustion of organic material, the

**Table 3** Adjusted Geometric Mean of Polycyclic Aromatic Hydrocarbons (µg/L) Stratified by Participants Characteristics in Men

Factors	Adjusted Geometric Mean (95% CI)			
	1-hydroxypyrene (µg/L)	2-naphthol (µg/L)	1-hydroxyphenanthrene (µg/L)	2-hydroxyfluorene (µg/L)
<b>Total</b>	<b>0.19 (0.17–0.21)</b>	<b>3.66 (3.26–4.12)</b>	<b>0.11 (0.10–0.12)</b>	<b>0.43 (0.39–0.47)</b>
Age group				
19–29 yr <sup>a</sup>	0.15 (0.13–0.17)	2.99 (2.45–3.65)	0.09 (0.08–0.10)	0.37 (0.32–0.43)
30–39 yr	0.15 (0.14–0.17)	3.21 (2.73–3.77)	0.10 (0.09–0.11)*	0.37 (0.33–0.43)
40–49 yr	0.20 (0.18–0.23)***	3.78 (3.26–4.39)**	0.11 (0.10–0.13)***	0.46 (0.40–0.53)**
50–59 yr	0.21 (0.19–0.24)***	3.84 (3.33–4.42)**	0.12 (0.11–0.14)***	0.50 (0.44–0.56)***
60–69 yr	0.22 (0.20–0.25)***	3.81 (3.24–4.48)*	0.12 (0.10–0.13)***	0.45 (0.39–0.51)**
≥70 yr	0.21 (0.19–0.24)***	4.55 (3.76–5.51)**	0.11 (0.10–0.13)***	0.42 (0.37–0.48)*
BMI group				
Underweight	0.21 (0.16–0.27)	4.20 (3.17–5.55)	0.10 (0.08–0.12)	0.45 (0.35–0.57)
Normal <sup>a</sup>	0.18 (0.16–0.19)	3.49 (3.07–3.97)	0.11 (0.10–0.12)	0.39 (0.35–0.43)
Overweight	0.19 (0.17–0.21)	3.48 (3.05–3.97)	0.11 (0.10–0.12)	0.43 (0.39–0.47)
Obese	0.19 (0.17–0.20)	3.52 (3.16–3.93)	0.11 (0.11–0.12)	0.44 (0.40–0.48)*
Household income (USD/month)				
< 920 USD	0.19 (0.16–0.21)	3.85 (3.25–4.55)	0.10 (0.09–0.12)	0.43 (0.38–0.48)
920–2090 USD	0.20 (0.17–0.22)	3.67 (3.17–4.24)	0.11 (0.09–0.12)	0.42 (0.37–0.48)
2090–3400 USD	0.19 (0.17–0.21)	3.70 (3.22–4.25)	0.11 (0.10–0.12)	0.43 (0.38–0.48)
≥3400 USD <sup>a</sup>	0.19 (0.17–0.22)	3.44 (3.01–3.93)	0.11 (0.10–0.12)	0.43 (0.38–0.48)
Alcohol consumption				
Never <sup>a</sup>	0.18 (0.16–0.21)	3.67 (3.17–4.25)	0.11 (0.10–0.12)	0.43 (0.38–0.48)
Former	0.19 (0.16–0.22)	3.68 (3.03–4.47)	0.11 (0.09–0.12)	0.43 (0.36–0.50)
Current	0.20 (0.18–0.22)	3.64 (3.23–4.09)	0.11 (0.10–0.12)	0.43 (0.39–0.47)
Regular physical activity				
No <sup>a</sup>	0.19 (0.17–0.21)	2.38 (2.20–2.59)	0.10 (0.09–0.11)	0.42 (0.38–0.46)
Yes	0.19 (0.17–0.22)	2.51 (2.30–2.74)	0.11 (0.10–0.12)*	0.43 (0.39–0.48)
Diabetes mellitus				
No <sup>a</sup>	0.18 (0.16–0.20)	3.26 (2.96–3.60)	0.10 (0.10–0.11)	0.40 (0.37–0.43)
Yes	0.20 (0.18–0.23)	4.11 (3.40–4.97)*	0.11 (0.10–0.13)	0.45 (0.39–0.52)*

**Notes:** BMI <18.5 for underweight, 18.5–22.9 for normal weight, 23–24.9 for overweight, ≥25 for obese. <sup>a</sup>Reference for comparison of geometric mean in each variable. Adjusted for log-transformed urine creatinine, log-transformed urine cotinine, and all variables in the table. \*\*\*P < 0.001; \*\*P < 0.01; \*P < 0.05.

**Abbreviations:** BMI, body mass index; CI, confidence interval; USD, US dollars.

major environmental sources of PAHs are tobacco smoking, urban air pollution, and occupational exposure. Many previous studies have shown significantly elevated levels of urinary PAHs among coal-handling workers or motor vehicle drivers, and the urinary 1-OHP levels are widely used as a biomarker of PAH exposure.<sup>24–26</sup> Therefore, the higher levels of PAHs in men can be attributed to their higher smoking rates and occupational exposure compared to women.<sup>27–29</sup>

Older men (≥40 years) had higher levels of all four PAHs than their younger counterparts (≤39 years). Exposure to PAHs is primarily through breathing ambient air, and PAHs

can be eliminated by bronchial clearance.<sup>30</sup> Impaired removal of contaminated particles by the mucociliary system may enhance the penetration of particles into the bronchial epithelial cells where PAHs are metabolized.<sup>30</sup> Most PAHs are excreted from the body shortly after exposure. However, small amounts are known to be retained in body fat and the liver, which may induce bioaccumulation of PAHs in the body over time.<sup>31</sup> These mechanisms may explain the higher PAH exposure in the older Korean population. As this age-related relationship has not been consistently observed in other ethnic populations,<sup>32,33</sup> further studies are needed to reveal this finding.

**Table 4** Adjusted Geometric Mean of Polycyclic Aromatic Hydrocarbons ( $\mu\text{g/L}$ ) Stratified by Participants Characteristics in Women

Factors	Adjusted Geometric Mean (95% CI)			
	1-hydroxypyrene ( $\mu\text{g/L}$ )	2-naphthol ( $\mu\text{g/L}$ )	1-hydroxyphenanthrene ( $\mu\text{g/L}$ )	2-hydroxyfluorene ( $\mu\text{g/L}$ )
<b>Total</b>	<b>0.13 (0.12–0.14)</b>	<b>1.64 (1.45–1.86)</b>	<b>0.09 (0.08–0.10)</b>	<b>0.19 (0.17–0.21)</b>
Age group				
19–29 yr <sup>a</sup>	0.12 (0.10–0.14)	1.88 (1.48–2.39)	0.08 (0.07–0.09)	0.19 (0.16–0.23)
30–39 yr	0.11 (0.10–0.13)	1.51 (1.25–1.83)*	0.08 (0.07–0.10)	0.19 (0.17–0.23)
40–49 yr	0.13 (0.11–0.14)	1.57 (1.32–1.88)	0.09 (0.08–0.10)	0.20 (0.17–0.23)
50–59 yr	0.13 (0.12–0.15)	1.70 (1.44–2.02)	0.09 (0.08–0.10)	0.19 (0.17–0.22)
60–69 yr	0.15 (0.13–0.18)	1.54 (1.26–1.90)	0.09 (0.08–0.11)	0.19 (0.17–0.22)
$\geq 70$ yr	0.14 (0.12–0.16)	1.66 (1.33–2.07)	0.09 (0.08–0.10)	0.18 (0.15–0.21)
BMI group				
Underweight	0.15 (0.12–0.18)*	1.55 (1.25–1.92)	0.10 (0.08–0.12)*	0.22 (0.18–0.26)*
Normal <sup>a</sup>	0.12 (0.11–0.13)	1.64 (1.41–1.91)	0.08 (0.07–0.09)	0.18 (0.16–0.20)
Overweight	0.12 (0.11–0.13)	1.63 (1.37–1.93)	0.08 (0.07–0.09)	0.18 (0.16–0.20)
Obese	0.13 (0.12–0.15)*	1.76 (1.54–2.00)	0.09 (0.08–0.10)**	0.19 (0.17–0.21)
Household income (USD/month)				
< 920 USD	0.13 (0.11–0.14)	1.73 (1.44–2.07)	0.09 (0.08–0.10)	0.19 (0.16–0.21)
920–2090 USD	0.14 (0.12–0.15)	1.77 (1.51–2.09)	0.09 (0.08–0.10)	0.20 (0.17–0.22)
2090–3400 USD	0.13 (0.11–0.14)	1.54 (1.30–1.82)	0.09 (0.08–0.10)	0.20 (0.18–0.22)
$\geq 3400$ USD <sup>a</sup>	0.13 (0.12–0.15)	1.54 (1.34–1.77)	0.09 (0.08–0.10)	0.18 (0.16–0.21)
Alcohol consumption				
Never <sup>a</sup>	0.13 (0.11–0.14)	1.84 (1.64–2.07)	0.09 (0.08–0.10)	0.19 (0.17–0.21)
Former	0.13 (0.11–0.15)	1.44 (1.11–1.88)	0.09 (0.07–0.11)	0.20 (0.16–0.24)
Current	0.14 (0.12–0.15)	1.66 (1.48–1.87)	0.09 (0.08–0.09)	0.18 (0.17–0.20)
Regular physical activity				
No <sup>a</sup>	0.13 (0.12–0.14)	1.59 (1.40–1.80)	0.09 (0.08–0.10)	0.19 (0.17–0.22)
Yes	0.13 (0.12–0.15)	1.70 (1.46–1.97)	0.09 (0.08–0.10)	0.19 (0.17–0.21)
Menopause				
No	0.13 (0.12–0.15)	1.61 (1.38–1.89)	0.08 (0.07–0.09)	0.18 (0.16–0.20)
Yes <sup>a</sup>	0.13 (0.11–0.14)	1.67 (1.43–1.95)	0.09 (0.08–0.10)	0.20 (0.18–0.23)
Diabetes mellitus				
No <sup>a</sup>	0.14 (0.12–0.15)	0.56 (1.43–1.70)	0.09 (0.08–0.10)	0.19 (1.04–0.17)
Yes	0.13 (0.11–0.14)	1.81 (1.54–2.12)*	0.09 (0.08–0.10)	0.20 (1.07–0.18)

**Notes:** BMI <18.5 for underweight, 18.5–22.9 for normal weight, 23–24.9 for overweight,  $\geq 25$  for obese. <sup>a</sup>Reference for comparison of geometric mean in each variable. Adjusted for log-transformed urine creatinine, log-transformed urine cotinine, and all variables in the table. \*\* $P < 0.01$ ; \* $P < 0.05$ .

**Abbreviations:** BMI, body mass index; CI, confidence interval; USD, US dollars.

Participants who performed regular physical activity had higher levels of 1-OHPhe than those who did not. 1-OHPhe is a human metabolite of phenanthrene that can be found in the urine of individuals exposed to phenanthrene.<sup>34</sup> Phenanthrene is detected in particulate emissions from burning natural gas and municipal incinerator waste and in particulates present in atmospheric air pollution near heavy vehicle traffic and manufacturing areas.<sup>35</sup> During aerobic activity, respiratory absorption of

airborne pollutants increases with increase in minute ventilation and diffusion capacity in the lungs.<sup>36</sup> Although a direct evidence showing higher PAH exposure during the exercise has not been found in human studies, previous epidemiologic studies have demonstrated that habitual exercise in highly pollutant outdoor areas or indoor environments, such as schools, may increase the amount of exposure to air pollutants.<sup>37,38</sup> Thus, increased urinary 1-OHPhe levels in individuals who performed regular

**Table 5** Adjusted Odds Ratio (95% CI) for Diabetes Mellitus According to the Quartile of Urinary Polycyclic Aromatic Hydrocarbons ( $\mu\text{g/L}$ )

	Adjusted Odds Ratio (95% CI)				P-trend
	I	II	III	IV	
1-hydroxypyrene					
Total	1.00	0.98 (0.66–1.46)	0.85 (0.55–1.31)	1.02 (0.62–1.71)	0.963
Men	1.00	1.35 (0.73–2.50)	0.91 (0.49–1.68)	1.50 (0.70–3.20)	0.455
Women	1.00	0.79 (0.49–1.29)	0.84 (0.48–1.48)	0.74 (0.38–1.43)	0.427
2-naphthol					
Total	1.00	1.08 (0.79–1.49)	1.57 (1.09–2.27)	1.83 (1.29–2.60)	<0.001
Men	1.00	0.91 (0.56–1.50)	1.27 (0.73–2.27)	2.07 (1.20–3.55)	0.013
Women	1.00	1.43 (0.89–2.29)	2.31 (1.41–3.81)	1.94 (1.18–3.18)	0.002
1-hydroxyphenanthrene					
Total	1.00	0.89 (0.59–1.36)	1.02 (0.64–1.63)	0.77 (0.47–1.25)	0.936
Men	1.00	0.81 (0.41–1.59)	0.73 (0.34–1.57)	0.78 (0.36–1.67)	0.918
Women	1.00	1.04 (0.62–1.75)	1.40 (0.82–2.40)	0.71 (0.37–1.36)	0.425
2-hydroxyfluorene					
Total	1.00	1.40 (0.95–2.05)	1.21 (0.78–1.90)	1.81 (1.10–2.98)	0.064
Men	1.00	1.59 (0.88–2.88)	1.29 (0.64–2.62)	2.19 (0.92–5.24)	0.212
Women	1.00	1.28 (0.79–2.02)	1.26 (0.69–2.29)	1.90 (0.98–3.71)	0.078

**Notes:** Odds ratios were adjusted for sex, age group, body mass index group, household income, alcohol consumption, physical activity, log-transformed urinary creatinine and cotinine, menopausal status (in women), and quartiles of all other PAHs.

**Abbreviation:** CI, confidence interval.

physical activity may reflect increased inhalation of outdoor or indoor phenanthrene during the exercise through the aforementioned manner. Further epidemiologic and experimental studies are required to disclose this finding.

In this study, Korean adults with diabetes showed higher urinary 2-NAP levels in both sexes than those without. We also found that higher urinary 2-NAP quartiles were significantly associated with an increased OR for diabetes in a dose-dependent manner. The highest quartile had a higher OR for diabetes (1.83, 95% CI 1.29–2.60) than the lowest quartile. Similarly, previous studies using the NHANES data have found elevated ORs (1.42–3.30) in adults with higher 2-NAP exposure.<sup>11,12,14</sup> Meanwhile, a study from China showed a higher likelihood of diabetes in individuals with higher 2-NAP exposure, but the difference was not statistically significant.<sup>39</sup>

We found significantly higher urinary 2-OHFlu levels in men with diabetes than in those without. Particularly, the urinary 2-OHFlu levels were positively associated with diabetes (OR 1.81, 95% CI 1.10–2.98), although the significance was lost in the sex-specific analysis. This positive association between 2-OHFlu exposure and diabetes has been reported in previous studies;<sup>11,39</sup> while other studies have found no statistically significant associations.<sup>12,14</sup>

We could not find any significant association between the 1-OHP and 1-OHPhe levels and diabetes, which is inconsistent with previous studies showing positive associations of 1-OHP<sup>12,14</sup> and 1-OHPhe<sup>39</sup> exposure with diabetes. This discrepancy might be partly due to the lower urinary levels of 1-OHP and 1-OHPhe in Korea than in other countries.<sup>11–14,16–18,39</sup>

Besides the four PAH metabolites mentioned in this study, other studies have shown a link between diabetes and other PAHs, which were not analyzed in Korea, such as 1-NAP,<sup>12,14</sup> 9-OHFlu,<sup>11,39</sup> 2-OHPhe,<sup>11,12,14,39</sup> 4-OHPhe,<sup>39</sup> and 9-OHPhe.<sup>39</sup> The KoNEHS currently examines only the four types of metabolites; therefore, analyzing the different types of PAHs and verifying their mixture effects would be necessary in further studies.

Although a causal relationship is not clear so far, several plausible mechanisms regarding the association between PAHs and diabetes are suggested. First, PAHs are known to enhance the generation of reactive oxygen species<sup>40</sup> by inducing aryl hydrocarbon receptor-dependent gene expression.<sup>41</sup> Oxidative stress plays a critical role in systemic inflammation and impairs the function of  $\beta$ -cells, resulting in insulin resistance.<sup>7,42,43</sup> Second, PAHs can disrupt peroxisome proliferator-activated receptors (PPARs),<sup>44</sup>



which are major regulators of adipogenesis and glucose metabolism. Third, PAHs influence epigenetic modification, such as defects in DNA methylation. PAHs interfere with DNA methylation during pancreatic  $\beta$ -cell development<sup>9</sup> and DNA methylation of insulin receptor substrate 2<sup>10</sup> and PPAR- $\gamma$ .<sup>45</sup> Other mechanisms include hepatic dysfunction,<sup>41</sup> skeletal muscle inflammation, and endothelial dysfunction, which reduce peripheral glucose uptake.<sup>46,47</sup> To summarize, PAHs may directly impair  $\beta$ -cell function through oxidative stress and systemic inflammation, and indirectly induce diabetes by adipose tissue dysregulation.

An important feature of this study is that we analyzed creatinine level by adjustment rather than division with the PAH level. When urinary dilution is adjusted by merely dividing the PAH levels by the creatinine levels, the study results might be greatly affected by factors involved with creatinine levels, such as kidney function, BMI, and age.<sup>48,49</sup> We also used the urinary cotinine levels as covariates to reduce the smoking effect on diabetes, as smoking is a major contributor of PAH exposure. Besides, the risk of diabetes could be affected by the endogenous estrogen status; hence, we included the menopausal status in women as a covariate. Furthermore, as PAHs showed positive correlations with diabetes, we adjusted for all other PAH levels to see the individual effects of each PAH.

Our study had some limitations. We did not assess the possible routes of exposure other than smoking. Although second-hand smoke exposure was not investigated, urine cotinine concentrations were adjusted in all statistics to overcome this limitation. Due to the relatively short half-lives of PAHs, the spot urine PAH levels may reflect only recent and not past or long-term exposure. Additionally, the diagnosis of diabetes was based only on a questionnaire survey and not on biochemical studies, such as a fasting blood glucose or glycosylated hemoglobin test. Moreover, the KoNEHS data did not differentiate the types of diabetes (ie, whether the participants have type 1 or type 2 diabetes). Finally, because of the cross-sectional nature of the study, we could not draw a causal relationship between PAHs and diabetes mellitus. Despite these limitations, this is the first study to investigate the association between PAH exposure and diabetes in a large population, with adjustment for various confounding factors, such as sex, age, BMI, household income, alcohol consumption, physical activity, urinary creatinine and cotinine, menopausal status (in women), and quartiles of all other PAHs.

## Conclusion

This study revealed that the urinary 2-NAP and 2-OHFlu levels were associated with diabetes mellitus in Korean adults. Given the ongoing rise in diabetes prevalence, our findings may have considerable implications for public health. To understand the mechanism between PAH exposure and diabetes mellitus, further longitudinal studies including analyses of exposure sources, air pollution data, and the mixture effects of environmental pollutants, are warranted.

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