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Polycyclic Aromatic Hydrocarbons Mediate the Association between Tobacco Smoking and Alcohol Use Disorder

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Purpose: Smoking is causally related to alcohol use disorder. Although polycyclic aromatic hydrocarbons (PAHs) are major neurotoxic pollutants in tobacco smoke, evidence is lacking on the role of PAHs in the relationship between smoking and alcohol use disorder. This study investigated the types of PAHs associated with smoking and whether exposure to those PAHs mediated the effect of smoking on alcohol use disorder.

Materials and Methods: A total of 968 male firefighters were analyzed. Smoking history and cumulative pack-years were obtained using self-reported questionnaires. Alcohol use disorder was defined using the Alcohol Use Disorder Identification Test. PAH exposure was assessed by urinary metabolites. Regression analyses were performed between exposure (smoking), outcome (alcohol use disorder), and mediator (PAH metabolites) variables. A mediation analysis was performed to test the indirect effect of PAH metabolites on the association between smoking and alcohol use disorder. All analyses were repeated for 770 participants who were followed up after 2 years, while alcohol use disorder was redefined from follow-up data ensuring the temporal sequence of the variables.

Results: Both 2-naphthol [β=0.78, 95% confidence interval (CI): 0.59–0.98] and 2-hydroxyfluorene (β=0.69, 95% CI: 0.56–0.82) were associated with smoking history. Furthermore, 2-naphthol and 2-hydroxyfluorene mediated the associations of smoking history (proportion mediated: 14.2%, 23.6% respectively) or cumulative pack-years (proportion mediated: 14.4%, 25.4% respectively) with alcohol use disorder. The results were consistent in longitudinal settings.

Conclusion: Exposure to PAHs mediated the association between tobacco smoking and alcohol use disorder. PAH exposure from tobacco may increase the risk of addictive disorders.

Key Words: Polycyclic aromatic hydrocarbons, tobacco, smoking, alcohol, alcoholism

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INTRODUCTION

Alcohol use disorder is strongly affected by smoking. Longitudinal studies[1,2] and a randomized intervention trial[3] demonstrated that smoking cessation reduces alcohol consumption. A meta-analysis of 19 randomized controlled trials showed that smoking cessation facilitates abstinence from alcohol and other substances.[4] Time-series analysis supports evidence that smoking precedes alcohol use, not vice versa.[5] Animal experiments have shown that rats implanted with nicotine pellets[6] and subcutaneous nicotine injections[7] show increased alcohol intake. These findings suggest a causal relationship from smoking to alcohol use. However, existing literature focuses only on nicotine in tobacco that can lead to addictive behaviors.[8]

Tobacco smoke is a source of polycyclic aromatic hydrocarbons (PAHs), a group of neurotoxic chemicals.[9] PAHs are generated by incomplete combustion of organic materials. Tobacco smoke contains relatively higher amounts of naphthalene and fluorene,[10,11] while occupational exposure such as firefighting was associated with a variety of PAHs (e.g. phenanthrene, pyrene, naphthalene, fluorene) by study setting.[12-14] Currently, evidence on the effect of PAHs on addictive disorders is lacking, even with the consensus that PAHs are associated with a wide range of neuropsychiatric outcomes. PAHs have been shown to be associated with cognitive decline,[15] attention-deficit/hyperactivity disorder,[16] anxiety,[17] and depression.[17] The neurotoxicity of PAHs is also supported by neuroimaging studies showing atrophy in brain regions related to cognitive function and addictive behaviors, including the frontal cortex and basal ganglia.[18,19] Given the above evidence on the neurotoxicity of PAHs, it is conceivable that exposure to PAHs via smoking could also increase the risk of alcohol use disorder.

In South Korea, firefighters are targets for interventions on tobacco and alcohol use. One study reported that the cotinine-verified smoking prevalence of male firefighters was 51%,[20] while another study reported that the problematic drinking prevalence of firefighters was 60%.[21] The current study aimed to investigate which types of PAHs were associated with tobacco smoke and whether exposure to PAHs mediates the association between smoking and alcohol use disorder, using a prospective cohort of firefighters who were at high risk of exposure to PAHs.

MATERIALS AND METHODS

Study cohort

The Firefighter Research on the Enhancement of Safety and Health (FRESH) cohort aimed to explore the cardiovascular and neuropsychiatric risk factors related to occupational environments and health-related behaviors among firefighters. A total of 1022 firefighters who volunteered to the study, including freshmen and trainees, fire-control workers, rescuers and paramedics, office administrators, and retirees, were recruited across South Korea through the National Fire Agency.[22] The firefighters, without exclusion, were examined at three university hospitals. Severance Hospital in Seoul examined volunteers from Seoul, Incheon, Gyeonggi-do, Chungcheongnam-do, Daejeon, and Jeollabuk-do. Severance Christian Hospital in Wonju examined volunteers from Gangwon-do and Chungcheongbuk-do. Gyeongsang National University Hospital in Jinju examined volunteers from Gyeongsangbuk-do, Gyeongsangnam-do, and Jeollanam-do. Following a standardized protocol, the participants answered self-reported questionnaires, underwent anthropometric measurements (height and weight), and took blood and urine tests at baseline (between July 2016 and October 2017), while the same measurements were done at follow-up after 2 years (between April 2018 and August 2019). From the baseline survey, female firefighters (n=44), those with invalid smoking histories (n=2), those without urine test data (n=6), and those with missing covariate information (n=2) were excluded. A total of 968 participants remained in the analytic sample, while 770 participants who completed the 2-year follow-up period were used for longitudinal analyses.

Exposure variables (tobacco smoking)

Both smoking history and cumulative pack-years were recorded using self-reported questionnaires in the baseline survey. Both exposure variables were used in all analyses to confirm the robustness of our analysis. Based on smoking history, participants were categorized into never-smokers and ever-smokers (including ex-smokers and current smokers). Ever-smokers were classified as those who had smoked more than 100 cigarettes in their lifetime. Others were classified as never-smokers. Ex-smokers were defined as ever-smokers who did not smoke during the baseline survey. Current smokers were defined as ever-smokers who actively smoked during the baseline survey. Never-smokers were used as the reference group. Information on cumulative pack-years was obtained from ever-smokers. The cumulative dose of never-smokers was considered as 0 pack-years. Associations were assessed with every 10 cumulative pack-years of smoking.

Outcome variable (alcohol use disorder)

The Alcohol Use Disorder Identification Test-Korean (AUDIT-K) was administered to define alcohol use disorder.[23] The amount and frequency of alcohol intake, dependence on alcohol, and experience of alcohol-related harm were asked. Scores of each question ranged from 0 to 4, resulting in a total score of up to 40. There is no global cutoff score for the AUDIT, since its interpretation should consider various socio-cultural contexts and differences based on sex.[24] In this study, a cutoff score ≥10 points for males was used based on validation studies in the Korean population.[23] In the main analysis, alcohol use disorder was defined from the baseline survey. For longitudinal analyses, alcohol use disorder was defined from the follow-up survey data to

ensure the temporal relationship between the exposure, mediator, and outcome variables.

Mediators (PAH metabolites)

Exposure to PAHs was assessed with urine metabolites from the baseline dataset. Four hydroxyl-polycyclic aromatic hydrocarbons (OH-PAHs) were measured: 2-naphthol (2-NAP, metabolite of naphthalene), 2-hydroxyfluorene (2-OHF, metabolite of fluorene), 1-hydroxyphenanthrene (1-OHPHE, metabolite of phenanthrene), and 1-hydroxypyrene (1-OHP, metabolite of pyrene). The selection of the four OH-PAHs were in line with previous evidence on the dominant PAHs that Asian populations are exposed to,[25] as well as with the nationally representative measurements of PAH exposure in the Korean population.[26] Quantification was done using gas chromatography (Clarus 680, PerkinElmer, Waltham, MA, USA) and mass spectroscopy (Clarus SQ8T, PerkinElmer). Values under the limit of detection (LOD) were substituted with the values of the LOD divided by $\sqrt{2}$. The LOD values were set as 0.050, 0.040, 0.047, and 0.015 μg/L for 2-NAP, 2-OHF, 1-OHPHE, and 1-OHP, respectively, in line with previous literature.[27] All OH-PAH values were corrected for urine creatinine concentrations, log-transformed, and finally expressed as log (urine OH-PAH g/g creatinine).

Covariates

Age, educational level, self-reported physical and psychological health status (related to psychiatric, metabolic, cardiovascular, and cerebrovascular health), and occupational factors (duty type and on-call duty) were selected as covariates. The covariates were selected based on the assumptions of mediation analyses requiring no confounding between exposure-mediator, exposure-outcome, and mediator-outcome associations. Age and occupational factors were used since they could be common causes of the exposure, mediator, and outcome, while educational level and health status were used as potential common causes of the exposure and outcome.

Educational level was categorized into four levels: under high school, high school, university, and graduate school. Health status included psychiatric (personal and family history of any psychiatric illness), metabolic [measured body mass index (BMI), and history of hypertension and diabetes], cardiovascular (history of cardiovascular diseases), and cerebrovascular (history of stroke or transient ischemic attack) health. Health status variables were coded binary, except for BMI which was coded as a continuous variable. Duty type was categorized into the following five types: freshmen and trainees, fire-control workers, rescuers and paramedics, office administrators, and retirees. On-call duty was assessed based on whether the participants were currently engaged in on-call duty or not.

Statistical analysis

Characteristics between ever- and never-smokers were compared using the t-test (for age and BMI), Wilcoxon rank-sum test (for OH-PAHs), Fisher's exact test (for family history of psychiatric disorders, and cerebrovascular disease), and the chi-square test (for other categorical variables). Prior to conducting the mediation analyses, individual regression analyses were performed to examine the associations between exposure variables (tobacco smoking), mediators (OH-PAHs), and outcomes (alcohol use disorder). First, logistic regression was performed to evaluate the association between smoking and alcohol use disorder (exposure to outcome). In this regression analysis, ever-smokers were further categorized into ex-smokers and current smokers to observe whether they showed any heterogeneity in the association between smoking and alcohol use disorder. Second, logistic regression analysis was conducted to estimate the association between individual OH-PAHs and alcohol use disorder (mediator to outcome). Finally, to compare the types of PAHs that smokers were exposed to, a linear regression analysis was performed to examine the effect of smoking on individual OH-PAHs (exposure to mediators). This regression analysis also further categorized ever-smokers into ex-smokers and current smokers to observe whether current smokers had higher OH-PAH levels compared to ex-smokers. The models were adjusted for 1) age, and 2) age, education levels, physical and psychological health status, and occupational factors.

Based on previous evidence on the causal effect of smoking on alcohol use, mediation analyses were performed using PROC CAUSALMED to assess whether individual OH-PAHs mediated the association between smoking and alcohol use disorder. Based on the counterfactual framework, the total/direct/indirect effects are estimated by contrasting counterfactual outcomes when the exposure and mediators are present or absent, which also allows the analysis of binary outcomes. Four types of mediators (i.e. 2-NAP, 2-OHF, 1-OHPHE, and 1-OHP) were tested. Based on *a priori* knowledge that naphthalene and fluorene were more specific to tobacco smoke[10,11] compared to occupational exposure to PAH from firefighting,[12-14] 2-NAP and 2-OHF were the metabolites of interest while 1-OHPHE and 1-OHP were regarded as negative control metabolites in the mediation analysis. To confirm the robustness of our analysis, both types of tobacco smoke exposures (i.e. smoking history and 10 cumulative pack-years) was used to test whether the results were consistent by varying exposure variable settings. Mediation models included the above-mentioned covariates. Bootstrapping with 10000 simulations was performed for each analysis instead of using Wald confidence intervals, due to non-normality of the effects being estimated.[28] The direct, indirect, and total effects were expressed as odds ratios (ORs) with the corresponding bias-corrected bootstrap confidence intervals (CIs). The mediated proportion was calculated as 100× (natural indirect effect/total effect) on the risk difference scale. All statistical analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC, USA).

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Longitudinal analysis

All analyses were repeated with 770 participants who completed follow-up after 2 years. Alcohol use disorder was defined based on the 2-year follow-up data, while other variables were defined from the baseline survey. This was done to repeat the original analyses in a longitudinal setting, ensuring the temporal sequence between the exposure (tobacco smoking), mediator (PAH metabolites), and outcome (alcohol use disorder) variables.

Research ethics

Informed consent was obtained from all participants. All procedures followed the ethical guidelines of the Declaration of Helsinki and relevant national and institutional committees on human experimentation. This study received Institutional Review Board exemptions from the Yonsei University Health System (4-2022-1248).

RESULTS

Characteristics of study participants

The mean age of the participants was 42.0 years (Table 1). The prevalence of alcohol use disorder was higher in ever-smokers (48.7%) than in never-smokers (31.9%). Ever-smokers were more likely to have a history of psychiatric disorders (2.7%) than never-smokers (0.6%). The concentrations of 2-NAP, 2-OHF, and 1-OHP were significantly higher in ever-smokers than in never-smokers.

Associations between smoking, PAHs, and alcohol use disorder

In the fully-adjusted model, ever-smokers had higher odds of alcohol use disorder (OR: 2.27, 95% CI: 1.69–3.04) compared to never-smokers (Table 2). After further stratification, ex-smokers (OR: 2.27, 95% CI: 1.68–3.07) and current smokers (OR: 2.28, 95% CI: 1.42–3.66) showed similar strengths of associations with alcohol use disorder. Every 10 cumulative pack-years of smoking was also associated with alcohol use disorder (OR: 1.42, 95% CI: 1.23–1.65). All PAH metabolites measured (i.e. 2-NAP, 2-OHF, 1-OHPHE, and 1-OHP) were significantly associated with alcohol use disorder (Table 2). Compared with never-smokers, ever-smokers had significantly higher concentrations of 2-NAP (β=0.78, 95% CI: 0.59–0.98) and 2-OHF (β=0.69, 95% CI: 0.56–0.82), but not 1-OHPHE and 1-OHP (Table 3). Current smokers had even higher concentrations of 2-NAP (β=1.55, 95% CI: 1.23–1.87) and 2-OHF (β=1.40, 95% CI: 1.19–1.61). Similarly, every 10 cumulative pack-years of smoking was significantly associated with increased concentrations of 2-NAP (β=0.37, 95% CI: 0.27–0.47) and 2-OHF (β=0.35, 95% CI: 0.28–0.41). Cumulative pack-years was significantly associated with 1-OHPHE and 1-OHP, but the strength of the associations were approximately 7 times weaker than that of 2-NAP and 2-OHF (Table 3).

Mediation analysis

The association between ever-smoking (vs. never-smoking) and alcohol use disorder was significantly mediated by 2-NAP (proportion mediated: 14.2%, indirect effect OR: 1.09, 95% CI: 1.01–1.18) and 2-OHF (proportion mediated: 23.6%, indirect effect OR: 1.15, 95% CI: 1.04–1.28) concentrations (Fig. 1). However, mediation of the negative controls (i.e. 1-OHPHE, 1-OHP) were not significant. The association between cumulative smoking dose (10 cumulative pack-years) and alcohol use disorder was significantly mediated by 2-NAP (proportion mediated: 14.4%, indirect effect OR: 1.04, 95% CI: 1.01–1.10) and 2-OHF (proportion mediated: 25.4%, indirect OR: 1.08, 95% CI: 1.03–1.15) concentrations (Fig. 1). The indirect effect of 1-OHPHE and 1-OHP were statistically significant, but substantially weaker than that of 2-NAP and 2-OHF.

Longitudinal analysis

All analyses were repeated with participants who completed the 2-year follow-up, while alcohol use disorder was defined from the follow-up data to ensure alcohol use disorder was measured after tobacco smoking and PAH metabolites. Results of bivariate analyses comparing characteristics (Supplementary Table 1, only online), regression analyses (Supplementary Table 2 and 3, only online), and mediation analyses (Fig. 2) were similar to those of original analyses. The association between ever-smoking (vs. never-smoking) and alcohol use disorder was only significantly mediated by 2-NAP (proportion mediated: 18.2%, indirect effect OR: 1.08, 95% CI: 1.00–1.18) and 2-OHF (proportion mediated: 28.1%, indirect effect OR: 1.13, 95% CI: 1.02–1.26), but not by the negative control metabolites. Similarly, the association between cumulative smoking dose (10 cumulative pack-years) and alcohol use disorder was only significantly mediated by 2-NAP (proportion mediated: 14.2%, indirect effect OR: 1.04, 95% CI: 1.00–1.09) and 2-OHF (proportion mediated: 23.1%, indirect effect OR: 1.06, 95% CI: 1.01–1.12), but not by 1-OHPHE and 1-OHP.

DISCUSSION

This study investigated the types of PAHs exposed from smoking and whether exposure to those PAHs mediated the association between smoking and alcohol use disorder in a cohort of firefighters. Smoking was associated with higher concentrations of 2-NAP and 2-OHF. Those metabolites also significantly mediated the association between smoking and alcohol use disorder. Both 2-NAP (14.2%) and 2-OHF (23.6%) significantly contributed to the association between ever-smoking history and alcohol use disorder. Similarly, 2-NAP (14.4%) and 2-OHF (25.4%) showed significant mediating effects on the association between 10 cumulative pack-years of smoking and al-

cohol use disorder. The results were robust when tested in a longitudinal setting, where 2-NAP and 2-OHF mediated the association between smoking at baseline and alcohol use disorder at follow-up.

The neurotoxicity of PAHs has been suggested in several studies. A meta-analysis showed that PAH exposure was asso-

Table 1. Characteristics of the Study Population

	Total (n=968)	Never-smokers (n=335)	Ever-smokers (n=633)	*p* value*
Alcohol use disorder				<0.001
Absent (AUDIT-K<10)	553 (57.13)	228 (68.06)	325 (58.77)	
Present (AUDIT-K≥10)	415 (42.87)	107 (31.94)	308 (48.66)	
Age (yr), mean±SD†	41.97±10.67	39.17±10.98	43.46±10.20	<0.001
Education level				0.019
Less than high school	18 (1.86)	4 (1.19)	14 (2.21)	
High school	289 (29.86)	81 (24.18)	208 (32.86)	
College	612 (63.22)	233 (69.55)	379 (59.87)	
Graduate school	49 (5.06)	17 (5.07)	32 (5.06)	
Psychiatric family history				0.757
Absent	957 (98.86)	332 (99.10)	625 (98.74)	
Present	11 (1.14)	3 (0.90)	8 (1.26)	
Psychiatric past history				0.026
Absent	949 (98.04)	333 (99.40)	616 (97.31)	
Present	19 (1.96)	2 (0.60)	17 (2.69)	
Body mass index	24.93 (2.61)	24.78 (2.70)	25.02 (2.55)	0.169
Hypertension				0.081
Absent	864 (89.26)	307 (91.64)	557 (87.99)	
Present	104 (10.74)	28 (8.36)	76 (12.01)	
Diabetes				0.433
Absent	936 (96.69)	326 (97.31)	610 (96.37)	
Present	32 (3.31)	9 (2.69)	23 (3.63)	
Cardiovascular disease				0.607
Absent	934 (96.49)	328 (97.91)	606 (95.73)	
Present	34 (3.51)	7 (2.09)	27 (4.27)	
Cerebrovascular disease				0.721
Absent	960 (99.17)	333 (99.40)	627 (99.05)	
Present	8 (0.83)	2 (0.60)	6 (0.95)	
Duty types				0.260
Freshmen & trainees	95 (9.81)	41 (12.24)	54 (8.53)	
Fire-control workers	435 (44.94)	146 (43.58)	289 (45.66)	
Rescuers & paramedics	188 (19.42)	70 (20.90)	118 (18.64)	
Office administrators	174 (17.98)	53 (15.82)	121 (19.12)	
Retirees	76 (7.85)	25 (7.46)	51 (8.06)	
On-call duty				0.128
Absent	723 (74.69)	260 (77.61)	463 (73.14)	
Present	245 (25.31)	75 (22.39)	170 (26.86)	
Urinary metabolites of PAHs (μg/L), median (IQR)				
2-Naphthol	2.67 (5.96)	1.83 (2.88)	3.73 (8.58)	<0.001
2-Hydroxyfluorene	0.19 (0.26)	0.15 (0.12)	0.22 (0.45)	<0.001
1-Hydroxyphenanthrene	0.19 (0.13)	0.19 (0.12)	0.19 (0.13)	0.972
1-Hydroxypyrene	0.20 (0.08)	0.20 (0.06)	0.20 (0.08)	0.044

AUDIT-K, Alcohol Use Disorder Identification Test (Korean); PAH, polycyclic aromatic hydrocarbon; IQR, interquartile range.
All values were expressed as number (%), unless otherwise specified. Alcohol use disorder was measured at the follow-up survey.
*Significance of difference between ever-smokers and never-smokers; calculated using Fisher's exact tests (for psychiatric family history), chi-squared tests (for other categorical variables), Wilcoxon rank-sum tests (for urinary metabolites of PAHs), and t-test (for age and body mass index); †Age range was 23–64 years for never-smokers and 21–65 years for ever-smokers.

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ciated with attention-deficit/hyperactivity disorder in the early development phase in childhood.[16] Also, prenatal exposure to PAHs was associated with depression and anxiety,[17] as well as disturbance in cognitive development in children.[29] An association between PAHs and depression was also reported in young and middle-aged populations.[30] Studies including older populations have shown that exposure to PAHs was associated with decreased cognitive function,[15] functional disability,[31] and a decline in verbal learning and memory function.[18] The current study is the first to report the effect of PAHs on the risk of alcohol use disorder, the most common addictive disorder.[32] Whereas nicotine exposure via tobacco smoking is known to induce addictive behaviors,[8] this study adds novel evidence that PAH exposure via tobacco smoking may increase the risk of addictive behaviors.

Table 2. Associations between Smoking History or Urine OH-PAH Concentrations and Alcohol Use Disorder

	Age-adjusted model	Fully adjusted model*
	OR (95% CI)	OR (95% CI)
Ever- versus never-smokers		
Never-smokers (n=335)	Reference	Reference
Ever-smokers (n=633)	2.17 (1.63–2.88)	2.27 (1.69–3.04)
Ex- and current smokers versus never smokers		
Never-smokers (n=335)	Reference	Reference
Ex-smokers (n=530)	2.17 (1.62–2.91)	2.27 (1.68–3.07)
Current smokers (n=103)	2.17 (1.38–3.40)	2.28 (1.42–3.66)
Cumulative smoking dose		
Per 10 pack-years	1.42 (1.23–1.64)	1.42 (1.23–1.65)
Log-transformed urine OH-PAHs†		
2-Naphthol	1.16 (1.06–1.27)	1.18 (1.07–1.29)
2-Hydroxyfluorene	1.32 (1.16–1.50)	1.35 (1.19–1.54)
1-Hydroxyphenanthrene	1.29 (1.07–1.54)	1.33 (1.10–1.61)
1-Hydroxypyrene	1.23 (1.04–1.46)	1.24 (1.04–1.48)

OH-PAH, hydroxy-polycyclic aromatic hydrocarbons; OR, odds ratio; CI, confidence interval.
OH-PAHs were corrected for urine creatinine and log-transformed.
*Adjusted for age, education levels, physical and psychological health status (body mass index, psychiatric past or family history, hypertension, diabetes mellitus, history of cardiovascular and cerebrovascular diseases), and occupational factors (duty type and on-call duty); †Median (interquartile range) for OH-PAH μg/L: 2-naphthol, 2.67 (5.96); 2-hydroxyfluorene 0.19 (0.26); 1-hydroxyphenanthrene 0.19 (0.13); 1-hydroxypyrene 0.20 (0.08).

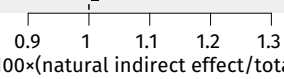
The significant indirect effect of PAHs on alcohol use disorder is consistent with neuroimaging studies that have shown an association between exposure to PAHs and brain atrophy in extensive areas including the frontal lobe and basal ganglia.[18,19,33,34] These brain regions are involved in the mesolimbic dopaminergic pathway, the major reward circuit. One study found that postnatal exposure to PAHs was associated with decreased prefrontal white matter volume in children.[33] Another study showed that exposure to PAHs during childhood was associated with decreased volume of the caudate.[34] Studies including adults have demonstrated that exposure to PAHs is associated with decreased cortical thickness in the frontal lobe.[18,19] A previous analysis of a neuroimaging subsample of the FRESH cohort found that exposure to PAHs was associated with reduced volumes of the nucleus accumbens, putamen, caudate, and thalamus.[19] This potential effect of PAHs on the mesolimbic dopaminergic pathway is also supported by animal studies, showing that exposure to PAHs changes the level of dopamine, the key neurotransmitter related to addictive behaviors, in different brain regions.[35-37] Specifically, animal studies have suggested that changes in dopamine levels in the nucleus accumbens reinforce drug-seeking behaviors.[38,39] Further research is required to better understand how PAH neurotoxicity leads to the devel-

Table 3. Associations between Smoking History and Urine OH-PAH Concentrations

	2-Naphthol	2-Hydroxyfluorene	1-Hydroxyphenanthrene	1-Hydroxyphenanthrene
	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
Ever- versus never-smokers*				
Age-adjusted model	0.79 (0.60–0.99)	0.68 (0.55–0.81)	0.01 (-0.09–0.11)	0.08 (-0.02–0.19)
Fully adjusted model†	0.78 (0.59–0.98)	0.69 (0.56–0.82)	0.02 (-0.07–0.11)	0.09 (-0.01–0.19)
Ex- and current smokers versus never smokers*				
Ex-smokers, age-adjusted	0.65 (0.45–0.85)	0.56 (0.43–0.69)	0.05 (-0.05–0.15)	0.10 (-0.01–0.20)
Ex-smokers, fully adjusted†	0.63 (0.43–0.82)	0.55 (0.42–0.68)	0.04 (-0.06–0.14)	0.09 (-0.01–0.19)
Current smokers, age-adjusted	1.49 (1.18–1.80)	1.29 (1.08–1.50)	-0.20 (-0.35–-0.04)	0.09 (-0.01–0.19)
Current smokers, fully adjusted†	1.55 (1.23–1.87)	1.40 (1.19–1.61)	-0.08 (-0.24–0.07)	0.11 (-0.05–0.28)
Per 10 pack-years				
Age-adjusted model	0.37 (0.27–0.47)	0.35 (0.28–0.41)	0.05 (0.00–0.10)	0.06 (0.01–0.11)
Fully adjusted model†	0.37 (0.27–0.47)	0.35 (0.28–0.41)	0.05 (0.00–0.10)	0.06 (0.01–0.11)

OH-PAH, hydroxy-polycyclic aromatic hydrocarbon; CI, confidence interval.
OH-PAHs were corrected for urine creatinine and log-transformed.
*The number of participants was as follows: never-smokers (n=335), ever-smokers (n=633, 530 ex- and 103 current smokers); †Adjusted for age, education levels, physical and psychological health status (body mass index, psychiatric past or family history, hypertension, diabetes mellitus, history of cardiovascular and cerebrovascular diseases), and occupational factors (duty type and on-call duty).

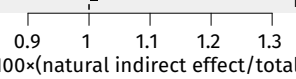
Exposure and mediator variables	Indirect effect	Direct effect	Total effect	Proportion mediated
	OR (95% CI)	OR (95% CI)	OR (95% CI)	
Ever- versus never-smokers				
2-Naphthol	1.09 (1.01–1.18)	2.09 (1.53–2.83)	2.27 (1.66–3.05)	14.16
2-Hydroxyfluorene	1.15 (1.04–1.28)	1.97 (1.43–2.69)	2.27 (1.66–3.05)	23.62
1-Hydroxyphenanthrene	1.01 (0.98–1.04)	2.27 (1.67–3.06)	2.29 (1.67–3.07)	0.98
1-Hydroxypyrene	1.02 (1.00–1.06)	2.24 (1.64–2.99)	2.28 (1.67–3.05)	3.20
Per 10 pack-years				
2-Naphthol	1.04 (1.01–1.10)	1.36 (1.14–1.62)	1.42 (1.20–1.69)	14.44
2-Hydroxyfluorene	1.08 (1.03–1.15)	1.31 (1.10–1.57)	1.42 (1.20–1.69)	25.39
1-Hydroxyphenanthrene	1.01 (1.00–1.04)	1.41 (1.18–1.68)	1.42 (1.20–1.70)	4.30
1-Hydroxypyrene	1.01 (1.00–1.03)	1.41 (1.19–1.68)	1.42 (1.20–1.70)	3.60



Footnotes. Proportion mediated=100×(natural indirect effect/total effect) on the risk difference scale.

Fig. 1. Mediation effects by PAH exposures in the association between tobacco smoking and alcohol use disorder. PAH, polycyclic aromatic hydrocarbon; OR, odds ratio; CI, confidence interval.

Exposure and mediator variables	Indirect effect	Direct effect	Total effect	Proportion mediated
	OR (95% CI)	OR (95% CI)	OR (95% CI)	
Ever- versus never-smokers				
2-Naphthol	1.08 (1.00–1.18)	1.55 (1.10–2.18)	1.67 (1.19–2.33)	18.24
2-Hydroxyfluorene	1.13 (1.02–1.26)	1.48 (1.04–2.10)	1.67 (1.19–2.33)	28.12
1-Hydroxyphenanthrene	0.99 (0.95–1.01)	1.69 (1.21–2.37)	1.68 (1.19–2.34)	–2.39
1-Hydroxypyrene	1.01 (0.99–1.07)	1.66 (1.18–2.32)	1.68 (1.19–2.34)	3.49
Per 10 pack-years				
2-Naphthol	1.04 (1.00–1.09)	1.27 (1.06–1.54)	1.32 (1.09–1.59)	14.18
2-Hydroxyfluorene	1.06 (1.01–1.12)	1.25 (1.03–1.51)	1.32 (1.09–1.59)	23.09
1-Hydroxyphenanthrene	1.00 (1.00–1.03)	1.32 (1.08–1.59)	1.32 (1.09–1.60)	1.86
1-Hydroxypyrene	1.01 (0.99–1.03)	1.31 (1.08–1.59)	1.32 (1.09–1.60)	3.17



Footnotes. Proportion mediated=100×(natural indirect effect/total effect) on the risk difference scale.

Fig. 2. Mediation effects by PAH exposures in the association between tobacco smoking and alcohol use disorder in a longitudinal setting. PAH, polycyclic aromatic hydrocarbon; OR, odds ratio; CI, confidence interval.

opment of addictive disorders.

Notably, the effect of PAH exposure on alcohol use disorder was examined in the context of smoking in the present study. Fluorene and naphthalene are the main PAHs that smokers are exposed to,[10,11] which is also consistent with our study results. This study found that 2-OHF and 2-NAP from tobacco smoke exerted significant mediating effects on the association between smoking and alcohol use disorder. In contrast, a previous neuroimaging analysis of the FRESH cohort found that 1-OHPHE was the major PAH metabolite associated with atrophy in extensive brain areas in patients with minimal tobacco smoke exposure.[19] Taken together, exposure to phenanthrene may be attributed to occupational factors such as fire extinguishment, whereas tobacco smoke was the major source of naphthalene and fluorene exposure. This study showed that naphthalene and fluorene exposures mediated 14.2%–14.4% and 23.6%–25.4%, respectively, to the smoking-alcohol use disorder association. This suggests that multiple chemicals in tobacco mediate the development of alcohol use disorder. For example, the nicotine in tobacco has been suggested to potentiate alcohol abuse.[8] Future studies need to investigate the relative contributions of chemicals in tobacco to the development of addictive behaviors.

The study had some limitations. First, the cross-sectional analysis had limitations in interpreting causality. Although the longitudinal analysis showed similar results, data with multiple observation points could give better causal inference. Second, analysis was limited to males due to the small sample size of female firefighters. However, given that we evaluated the effect of PAHs in the context of tobacco smoking, our approach to include only male participants may be reasonable since the majority of females in the Korean population are never-smokers.[40] In addition, although the measurement of urinary OH-PAHs is a commonly used method for assessing PAH exposure, the short half-lives of OH-PAHs might have influenced our results. However, an animal study showed that PAH metabolites displayed moderate-to-good correlations with PAH-DNA adducts,[41] which have a longer half-life up to several months.[42]

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Furthermore, the detection rate for most OH-PAHs was over 99% in the general population, indicating that the measured OH-PAHs reflected the degree of baseline chronic exposure.[43] Also, although the types of occupation and the presence of on-call duties have been addressed, there may be unmeasured occupation-related confounders. One example of a potential confounder that affects the mediator is recent fire extinguishment, which is strongly related to acute exposure to PAHs. However, given that urinary OH-PAH concentrations in this firefighter cohort were similar to those in the general Korean population,[26] the urinary OH-PAH measured likely reflected chronic exposure to PAHs via habitual smoking rather than acute occupational exposure such as fire extinguishment. Still, potential confounders of the exposure-outcome association, such as occupational stress or distress in daily life, may need to be considered in further studies. Finally, since the findings of this study were based on data from three university hospitals and not all participants were followed up, the results may not be generalizable to the entire firefighter population.

In conclusion, exposure to PAHs (particularly, fluorene, and naphthalene) mediated the effect of smoking on alcohol use disorder among firefighters. PAH exposure via smoking could increase the risk of alcohol use disorder. Although firefighters are at high risk of occupational exposure to PAHs, tobacco smoke is still an important source of chronic exposure to PAHs among firefighters. Smoking cessation may be crucial for enhancing the mental health of firefighters.

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