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Research article

Effect of polycyclic aromatic hydrocarbon exposure on amnestic mild cognitive impairment and Alzheimer's disease: A matched case-control study

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ABSTRACT

There is an emerging body of evidence concerning the neurological effect of air pollutants on cognitive function and increased risk of neurodegeneration. Although previous studies have suggested that polycyclic aromatic hydrocarbons (PAHs) are neurotoxic, the effect of PAHs exposure on neurodegeneration remains unclear. This study aimed to investigate the association between PAH exposure and the risk of developing amnestic mild cognitive impairment (aMCI) and Alzheimer's disease (AD). For this matched case-control cross-sectional study, we recruited patients aged ≥50 years diagnosed with aMCI and AD from the Samsung Medical Center, Seoul, Korea, between 2014 and 2019. For each patient, we randomly selected four cognitively healthy controls through frequency matching based on sex, age group, and education level. Urinary levels of four PAH metabolites, 1-hydroxypyrene (1-OHP), 1-hydroxyphenanthrene (1-OHPhe), 2-hydroxyfluorene (2-OHFlu), and 2-naphthol (2-NAP), were measured. A conditional logistic regression model was used to evaluate the association, adjusting for potential confounders. A total of 212 patients with aMCI with 848 matched controls, and 267 patients with AD with 1068 matched controls were included in the analyses to estimate the risk of PAH exposure. We found that elevated urinary levels of PAH metabolites (specifically, 1-OHP and 2-NAP) were significantly associated with an increased risk of aMCI and AD. An increase of one unit in log-transformed level of urinary 1-OHP was associated with a 1.15- and 1.16-times higher risk of aMCI and AD, respectively. An increase of one unit in log-transformed level of urinary 2-NAP was associated with a 1.11- and 1.13-times higher risk of aMCI and AD, respectively. These findings indicate that PAH exposure may increase the risk of aMCI and AD, especially for the elderly

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population. Considering the widespread distribution of PAHs in the environment, reducing PAH exposure may be an effective strategy for the prevention of neurodegenerative diseases.

1. Introduction

Neurodegenerative diseases cause progressive cognitive, social, and physical deterioration in older adults, imposing a substantial socioeconomic burden [1]. Alzheimer's disease (AD) is a predominant neurodegenerative disorder among the elderly; in 2019, it affected 52 million people, resulting in 25 million disability-adjusted life-years worldwide [2]. Mild cognitive impairment (MCI) is a prodromal phase of AD, with 15 % of patients progressing to AD within 1 year [3]. Amnestic MCI (aMCI), characterized by memory loss, exhibits a stronger association with AD progression than non-aMCI [3]. Therefore, identifying modifiable risk factors is crucial for mitigating the increasing burden of AD in elderly adults and ageing societies.

Air pollution is one of the leading environmental risk factors potentially contributing to the onset of MCI and AD. Epidemiological cohort studies have demonstrated that exposure to particulate matter increases the risk of aMCI and AD [4,5]. Additionally, neuroimaging studies have shown an association between particulate matter exposure and brain atrophy (hippocampal atrophy) [6]. Particulate matter comprises various pollutants, including polycyclic aromatic hydrocarbons (PAHs), which are predominantly emitted into the environment through the incomplete combustion of fossil fuels, wood, petroleum products, tobacco smoke, and grilled meat [7]. The PAH contaminants are pervasive and present in both terrestrial and aquatic ecosystems, as well as in the atmosphere. Numerous studies have reported associations between exposure to PAHs and declines in neuropsychological functions such as psychomotor speed, attention, visuo-perceptual function, verbal learning and memory, and auditory memory [6,8–10]. Other studies have demonstrated that PAH exposure was associated with AD pathophysiology, including accumulation of amyloid-related protein [11,12]. A recent cross-sectional study linking PAH exposure with MCI focused on an occupational population rather than general populations, but this previous study defined MCI using a dementia screening tool and did not differentiate aMCI from non-aMCI [11]. To the best of our knowledge, no prior study has linked PAH exposure to the development of aMCI and AD. Given growing evidence on the effect of PAH exposure on AD pathophysiology and cognitive decline, it is crucial to investigate whether PAH exposure increases the risk of developing aMCI (prodromal AD) and AD.

Hence, the aim of this study was to investigate the effect of PAH exposure on the risk of aMCI and AD by employing hospital-based cases and community-based matched controls.

2. Materials and methods

2.1. Study participants

A matched case-control design was implemented in this study. Patients aged ≥50 years diagnosed with aMCI and AD were recruited from the Samsung Medical Center, Seoul, Korea, between 2014 and 2019. Diagnoses of the neurological conditions were established through detailed clinical interviews and neurological examinations. Patients with AD met the diagnostic criteria outlined by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association [13], whereas patients with aMCI fulfilled the modified Petersen's criteria for MCI [14]. Detailed information about the study protocols is provided in a previous publication [15]. The control group comprised healthy adults who were randomly selected from participants who completed a baseline survey for a community-based cohort study called the Environmental Pollution-Induced Neurological Effects (EPINEF) study [16]. The EPINEF study included adults aged ≥50 years without a history of neurological disorders (dementia, movement disorders, or stroke). To ensure normal cognitive health among the participants, those with a Mini-Mental State Examination score <24 were excluded. Among the 3422 eligible participants, four controls were frequency-matched with each case of aMCI or AD based on sex, age (<65 or ≥ 65 years), and education level (≤9 or > 9 years). Age refers to the age at diagnosis and enrollment for cases and controls, respectively. All patients with aMCI or AD and healthy participants (control group) underwent a standardized investigation protocol that comprised questionnaires, anthropometric measurements, and blood and urine collection and examination. Blood samples were obtained following a 12-h fasting and subsequently transported to a central laboratory (Seoul Clinical Laboratory Co., Ltd., Seoul, Korea) within 24 h of collection.

This study was conducted in accordance with the principles of the Declaration of Helsinki, and all procedures were approved by the Yonsei University Health System Institutional Review Board (IRB No. 4-2014-0359) and the Institutional Review Board of the Samsung Medical Center (SMC 2015-09-880). All participants provided written informed consent.

2.2. Exposure assessment

To assess PAH exposure, we measured the urinary concentrations of four PAH metabolites: 1-hydroxypyrene (1-OHP), 1-hydroxyphenanthrene (1-OHPhe), 2-hydroxyfluorene (2-OHFlu), and 2-naphthol (2-NAP) following previously described methods [6]. All samples were analyzed at a central laboratory (Green Cross Laboratories Co., Ltd., Yongin, Korea) using gas chromatography–mass spectrometry [17]. Urinary concentrations of PAH metabolites were log-transformed owing to their skewed distribution. The limit of detection (LOD) for 1-OHP, 1-OHPhe, 2-OHFlu, and 2-NAP were 0.015, 0.047, 0.040, and 0.050 μg/L, respectively. Values below the LOD were imputed using the method detection limit divided by the square root of two. All urinary PAH levels were adjusted for urinary

Table 1
Characteristics of study participants of the study.

Variables	aMCI vs. Healthy controls			AD vs. Healthy controls		
	aMCI (n = 212)	Healthy controls (n = 848)	*p*-value[a]	AD (n = 267)	Healthy controls (n = 1068)	*p*-value[a]
Age (years), mean (SD)	71.7 (8.4)	69.3 (6.3)	1.00	75.5 (9.5)	70.2 (5.8)	1.00
<65 years	45 (21.2)	180 (21.3)		36 (13.5)	144 (13.5)	
≥65 years	167 (78.8)	668 (78.8)		231 (86.5)	924 (86.5)	
Sex, n (%)			1.00			1.00
Men	89 (42.0)	356 (42.0)		85 (31.8)	340 (31.8)	
Women	123 (58.0)	492 (58.0)		182 (68.2)	728 (68.2)	
Years of education, median (IQR)	12 (9–16)	12 (9–14)	1.00	12 (9–14)	12 (9–14)	1.00
Undergraduate middle school	75 (35.4)	300 (35.4)		114 (42.7)	456 (42.7)	
Graduate, high school, and over	137 (64.6)	548 (64.6)		153 (57.3)	612 (57.3)	
Body mass index, n (%)			<0.001			<0.001
Normal	81 (38.2)	205 (24.2)		113 (42.3)	301 (28.2)	
Overweight	56 (26.4)	269 (31.7)		71 (26.6)	315 (29.5)	
Obese	75 (35.4)	374 (44.1)		83 (31.1)	452 (42.3)	
Smoking status, n (%)			<0.001			<0.001
Current smokers	55 (25.9)	46 (5.4)		42 (15.7)	45 (4.2)	
Former smokers	45 (21.2)	230 (27.1)		45 (16.9)	211 (19.8)	
Lifelong non-smokers	12 (52.8)	572 (67.5)		180 (67.4)	812 (76.0)	
Alcohol consumption, n (%)			<0.001			<0.001
Drinkers	53 (25.0)	159 (75.0)		26 (9.7)	402 (37.6)	
Non-drinkers	367 (43.3)	481 (56.7)		241 (90.3)	666 (62.4)	
History of diseases, n (%)						
Angina or myocardial infarction	15 (7.1)	85 (10.0)	0.24	16 (6.0)	95 (8.9)	0.14
Diabetes mellitus	40 (18.9)	156 (18.4)	0.87	61 (22.9)	195 (18.3)	0.09
Hypertension	100 (47.2)	392 (46.2)	0.81	135 (50.6)	494 (46.3)	0.21
Dyslipidemia	75 (35.4)	317 (37.4)	0.59	82 (30.7)	430 (40.3)	0.004

Abbreviations: aMCI, amnestic mild cognitive impairment; AD, Alzheimer's disease; SD, Standard deviation; IQR, interquartile range.
[a] Significance of group differences in characteristics, tested using paired *t*-tests and chi-square tests.

creatinine levels (μg/g creatinine) [18].

2.3. Covariates

We considered several potential confounders, including age (in years), years of education, body mass index (BMI), smoking status (lifelong non-smoker or former or current smokers), alcohol consumption (currently drinking or not drinking), and history of diseases (angina or myocardial infarction, diabetes mellitus, hypertension, and dyslipidemia). The BMI of each participant was calculated and subsequently categorized as normal weight (18.5–22.9 kg/m^2), overweight (23.0–24.9 kg/m^2), or obese (≥25.0 kg/m^2) according to Asian population criteria [19]. Participants' disease history was determined based on self-reported information.

2.4. Statistical analyses

Descriptive statistics included means or medians with standard deviation (SD) or interquartile range (IQR) for continuous variables and frequencies and percentages for categorical variables. Differences in characteristics between the cases and their matched controls were evaluated using independent *t*-tests or chi-squared tests. A conditional logistic regression model was employed to investigate the association between urinary PAH metabolite concentrations and the risk of aMCI and AD. The fully adjusted model included age, years

Table 2
Differences in urinary PAH metabolite concentrations between individuals with neurodegenerative diseases (aMCI and AD) and matched healthy controls.

	aMCI vs. Healthy controls			AD vs. Healthy controls		
	aMCI (n = 212)	Healthy controls (n = 848)	*p*-value[a]	AD (n = 267)	Healthy controls (n = 1068)	*p*-value[a]
Urinary PAH metabolite (μg/g creatinine), GMs (95 % CI)						
1-OHP	0.075 (0.061–0.091)	0.040 (0.036–0.045)	<0.001	0.061 (0.051–0.072)	0.039 (0.035–0.043)	<0.001
1-OHPhe	0.061 (0.053–0.070)	0.047 (0.045–0.050)	<0.001	0.053 (0.047–0.059)	0.048 (0.046–0.050)	0.09
2-OHFlu	0.079 (0.068–0.092)	0.057 (0.053–0.061)	<0.001	0.058 (0.050–0.066)	0.056 (0.052–0.059)	0.67
2-NAP	0.538 (0.400–0.724)	0.198 (0.170–0.231)	<0.001	0.460 (0.351–0.603)	0.196 (0.171–0.224)	<0.001

Abbreviations: aMCI, amnestic mild cognitive impairment; AD, Alzheimer's disease; GMs, geometric mean; CI, confidence interval; PAH, polycyclic aromatic hydrocarbon; 1-OHP, 1-hydroxypyrene; 1-OHPhe, 1-hydroxyphenanthrene; 2-OHFlu, 2-hydroxyfluorene; 2-NAP, 2-naphthol.
[a] Significance of group differences in urinary PAH metabolite concentrations, tested using a paired *t*-test.

Table 3
Association of urinary concentrations of PAH metabolites with risk of neurodegenerative diseases (aMCI and AD).

Urinary PAH metabolite	aMCI vs. Healthy controls		AD vs. Healthy controls	
	Crude model	Fully adjusted model[a]	Crude model	Fully adjusted model[a]
	OR (95 % CI)	OR (95 % CI)	OR (95 % CI)	OR (95 % CI)
1-OHP	1.27 (1.17–1.38)	1.15 (1.05–1.26)	1.21 (1.11–1.31)	1.16 (1.07–1.26)
1-OHPhe	1.33 (1.15–1.53)	1.16 (0.99–1.35)	1.15 (1.00–1.32)	1.08 (0.94–1.25)
2-OHFlu	1.29 (1.15–1.45)	1.11 (0.98–1.26)	1.09 (0.97–1.23)	1.02 (0.90–1.14)
2-NAP	1.19 (1.13–1.26)	1.11 (1.05–1.19)	1.16 (1.10–1.23)	1.13 (1.07–1.19)

Abbreviations: aMCI, amnestic mild cognitive impairment; AD, Alzheimer's disease; PAH, polycyclic aromatic hydrocarbon; 1-OHP, 1-hydroxypyrene; 1-OHPhe, 1-hydroxyphenanthrene; 2-OHFlu, 2-hydroxyfluorene; 2-NAP, 2-naphthol; OR, odds ratio; CI, confidence interval.
Note: Risk ratios (per one-unit increase in the log-transformed concentrations of urinary PAH metabolites) were obtained using conditional logistic regression models.
[a]Fully adjusted models for age, years of education, body mass index category, smoking status, alcohol consumption status, and history of diseases (hypertension, angina or myocardial infarction, diabetes mellitus, and dyslipidemia).

of education, BMI category, smoking and alcohol consumption status, history of hypertension, angina, myocardial infarction, diabetes mellitus, and dyslipidemia. Risk was expressed as odds ratios (ORs) with 95 % confidence intervals (CIs) per 1-unit increase in the log-transformed levels of urinary PAH metabolites. Considering the potential impacts of sex and smoking on the association between urinary PAH metabolites and the risk of aMCI and AD [6], additional analyses were conducted by stratifying participants by sex (men and women) and smoking status (lifelong non-smokers or former or current smokers). The significance of the differences between subgroups was assessed using the method outlined by Altman and Bland [20], yielding *p*-values for the interaction. All statistical analyses were performed using SAS 9.4 software (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. General characteristics of study participants

A total of 212 patients with aMCI and 848 matched controls were included in the analyses to estimate the risk of aMCI associated with PAH exposure (Table 1). The mean (SD) age of patients with aMCI and the matched healthy controls was 71.7 (8.4) and 69.3 (6.3) years, respectively. Among the patients with aMCI, 25.9 % (n = 55) were current smokers, whereas 5.4 % (n = 46) of the healthy individuals in the control group were current smokers.

To analyze the risk of AD associated with PAH exposure, 267 patients with AD and 1068 matched controls were included. The mean (SD) age of patients with AD and matched controls was 75.5 (9.5) and 70.2 (5.8) years, respectively. Among the patients with AD, 42 (15.7 %) were current smokers and 45 (16.9 %) were former smokers. Most healthy participants in the control group were lifelong non-smokers (n = 812, 76.0 %).

Patients with aMCI exhibited significantly higher levels of 1-OHP, 1-OHPhe, 2-OHFlu, and 2-NAP (all $p < 0.001$) than the healthy participants (Table 2). Patients with AD demonstrated significantly elevated levels of 1-OHP and 2-NAP (both $p < 0.001$) compared to the healthy participants.

3.2. Associations of urinary PAH metabolites with aMCI and AD

In the crude models, an increase of 1 unit in log-transformed levels of urinary 1-OHP, 1-OHPhe, 2-OHFlu, and 2-NAP were linked to an increased risk of aMCI (Table 3). Similarly, an increase of 1 unit in log-transformed levels of urinary 1-OHP and 2-NAP was

Table 4
Association of urinary concentrations of PAH metabolites with risk of neurodegenerative diseases (aMCI and AD) stratified by sex.

Urinary PAH metabolite	aMCI vs. Healthy controls			AD vs. Healthy controls		
	Men (n = 445)	Women (n = 615)	*p*-interaction	Men (n = 425)	Women (n = 910)	*p*-interaction
	OR (95 % CI)	OR (95 % CI)		OR (95 % CI)	OR (95 % CI)	
1-OHP	1.10 (0.96–1.26)	1.17 (1.03–1.33)	0.51	1.20 (1.03–1.39)	1.15 (1.04–1.27)	0.66
1-OHPhe	1.04 (0.82–1.33)	1.24 (1.01–1.51)	0.28	1.06 (0.84–1.34)	1.11 (0.92–1.33)	0.77
2-OHFlu	1.05 (0.87–1.26)	1.22 (1.01–1.46)	0.25	1.07 (0.86–1.32)	1.04 (0.89–1.20)	0.83
2-NAP	1.11 (1.01–1.22)	1.12 (1.03–1.22)	0.89	1.17 (1.06–1.30)	1.12 (1.04–1.19)	0.41

Abbreviations: aMCI, amnestic mild cognitive impairment; AD, Alzheimer's disease; PAH, polycyclic aromatic hydrocarbon; 1-OHP, 1-hydroxypyrene; 1-OHPhe, 1-hydroxyphenanthrene; 2-OHFlu, 2-hydroxyfluorene; 2-NAP, 2-naphthol; OR, odds ratio; CI, confidence interval.
Note: Risk ratios (per one-unit increase in log-transformed concentrations of urinary PAH metabolites) were obtained from conditional logistic regression models adjusted for age, years of education, body mass index category, smoking status, alcohol consumption, and history of diseases (hypertension, angina or myocardial infarction, diabetes mellitus, and dyslipidemia).

Table 5
Association between urinary concentrations of PAH metabolites and risk of neurodegenerative diseases (aMCI and AD) stratified by smoking status.

Urinary PAH metabolite	aMCI vs. Healthy controls			AD vs. Healthy controls		
	Smokers or former smokers (n = 376)	Lifelong non-smokers (n = 684)	*p*-interaction	Smokers or former smokers (n = 343)	Lifelong non-smokers (n = 992)	*p*-interaction
	OR (95 % CI)	OR (95 % CI)		OR (95 % CI)	OR (95 % CI)	
1-OHP	1.21 (1.06–1.38)	1.17 (1.02–1.33)	0.72	1.15 (0.99–1.34)	1.17 (1.06–1.29)	0.86
1-OHPhe	1.21 (0.97–1.50)	1.21 (0.97–1.51)	0.99	1.11 (0.86–1.42)	1.11 (0.93–1.32)	0.99
2-OHFlu	1.18 (1.00–1.39)	1.20 (0.99–1.46)	0.88	1.09 (0.91–1.31)	1.03 (0.88–1.20)	0.63
2-NAP	1.14 (1.04–1.25)	1.14 (1.05–1.25)	0.98	1.13 (1.03–1.24)	1.14 (1.06–1.21)	0.88

Abbreviations: aMCI, amnestic mild cognitive impairment; AD, Alzheimer's disease; PAH, polycyclic aromatic hydrocarbon; 1-OHP, 1-hydroxypyrene; 1-OHPhe, 1-hydroxyphenanthrene; 2-OHFlu, 2-hydroxyfluorene; 2-NAP, 2-naphthol; OR, odds ratio; CI, confidence interval.
Note: Risk ratios (per one-unit increase in log-transformed concentrations of urinary PAH metabolites) were obtained from conditional logistic regression models adjusted for age, years of education, body mass index category, alcohol consumption, and history of diseases (hypertension, angina or myocardial infarction, diabetes mellitus, and dyslipidemia).

associated with an increased risk of AD. In the fully adjusted models, an increase of 1 unit in log-transformed levels of urinary 1-OHP and 2-NAP remained significantly associated with an increased risk of aMCI. Additionally, an increase of 1 unit in log-transformed levels of urinary of 1-OHP and 2-NAP remained associated with an increased risk of AD.

3.3. Stratified analysis by sex

Among men, an increase in urinary levels of 2-NAP was significantly associated with the risk of aMCI (Table 4). Similarly, urinary levels of 1-OHP and 2-NAP were significantly associated with the risk of AD. Among women, increases in urinary levels of all the four metabolites, 1-OHP, 1-OHPhe, 2-OHFlu, and 2-NAP, were significantly associated with the risk of aMCI. Additionally, urinary levels of 1-OHP and 2-NAP were significantly associated with an increased risk of AD. There were no statistically significant differences in the association between urinary levels of PAH metabolites and the risk of neurodegenerative diseases based on sex.

3.4. Stratified analysis by smoking status

Among lifelong non-smokers, increases in urinary levels of 1-OHP and 2-NAP were significantly associated with the risk of aMCI (Table 5). Similarly, the urinary level of 2-NAP was significantly associated with the risk of AD. Among current or former smokers, increases in urinary levels of 1-OHP and 2-NAP were significantly associated with the risk of aMCI. Additionally, urinary levels of 1-OHP and 2-NAP were significantly associated with the risk of AD. There were no significant interactive effects of smoking on the association of urinary levels of PAH metabolites with the risk of aMCI or AD.

4. Discussion

In this study, we investigated the effects of PAH exposure on the risk of aMCI and AD. By including patients diagnosed with neurodegenerative diseases and carefully matched corresponding cognitively healthy controls, we were able to evaluate the association between urinary levels of PAH metabolites and the risk of aMCI and AD. Upon adjusting for potential confounding factors, we observed that increased urinary levels of PAH metabolites, specifically 1-OHP and 2-NAP, were significantly associated with an elevated risk of aMCI and AD. An increase of 1 unit in log-transformed 1-OHP level was associated with a 1.15- and 1.16-times higher risk of aMCI and AD, respectively. Additionally, an increase of 1 unit in log-transformed 2-NAP level was associated with a 1.11- and 1.13-times higher risk of aMCI and AD, respectively. These associations did not differ significantly between the sexes or based on smoking status.

Several prior studies have linked PAH exposure to adverse neuropsychological outcomes in adults. For instance, a cross-sectional study involving 454 adults in the United States demonstrated that urinary 1-OHP levels were related to decreased psychomotor speed, attention, and visuoperceptual function [8]. Similarly, another cross-sectional study involving 949 Korean adults demonstrated an association between urinary 1-OHP levels and decreased memory and verbal learning [6]. Additionally, occupational studies have shown that urinary 1-OHP and 2-NAP levels were related to decreased verbal learning and auditory memory in coke oven workers [9,10]. However, there is limited empirical support for the association between PAH exposure and the risk of MCI or AD. To the best of our knowledge, only one previous study has reported an association between urinary PAH metabolites and the risk of the MCI, without distinguishing between amnestic and non-amnestic MCI [11]. Therefore, the present study makes a substantial contribution to this area of research by including a large cohort of patients with aMCI or AD (diagnoses confirmed by neurologists) as well as a large number of cognitively healthy controls from a community-based cohort. Our findings provide novel evidence regarding the increased risk of AD associated with PAH exposure, expanding our knowledge of the impact of such exposure on neuropsychological functions.

The observed association between PAH exposure and the risk of AD is consistent with findings from several experimental and observational studies. Although experimental evidence on AD-specific neurotoxicity of PAH exposure is limited, animal studies have

demonstrated that PAH exposure may induce systemic inflammation, oxidative stress, and disruption of neurotransmitter systems [21,22]. An observational study involving 4378 Korean adults found that a mixture of urinary PAH metabolites was significantly associated with elevated levels of serum gamma-glutamyl transferase, as an oxidative stress marker [23]. Additionally, a recent study on coke oven workers reported associations between the total sum of urinary PAH metabolites and increased plasma levels of phosphorylated tau, a protein involved in AD pathophysiology [11,24]. Furthermore, a neuroimaging study in adults showed associations between urinary PAH metabolites and brain cortical atrophy, an indicator of neurodegeneration as well as a phenotype on the continuum of AD [6,24]. Given these previous findings, neuroinflammation and oxidative stress have been proposed as possible mechanisms for the association between PAH exposure and the risk of aMCI and AD. PAHs are metabolized by cytochrome P450 enzymes (CYPs), specifically CYP1A1/2 and CYP1B1, into reactive intermediates that covalently bind to DNA, consequently initiating redox reactions that generate reactive oxygen species (ROS) [25–27]. PAH exposure can also cause oxidative stress by affecting the regulation of ROS-generating enzymes (e.g., CYPs) via the aryl hydrocarbon receptor signaling pathway [28]. Persistent oxidative stress can disrupt the regulation of neuroinflammatory response and potentially lead to neurodegenerative diseases such as aMCI and AD [29]. However, the specific neurotoxic impacts of PAH exposure on AD remain unclear. Additional experimental and observational studies are required to explore potential AD-specific mechanisms, such as amyloid beta accumulation.

This study has several limitations. First, as a case-control study, the possibility of reverse causation cannot be ruled out. It is possible that behavioral modifications (such as smoking cessation and alcohol abstinence) among patients with aMCI or AD may have influenced PAH exposure levels. This may have led to an underestimation of the risks associated with PAH exposure for aMCI and AD. Moreover, we found no significant differences in these associations when comparing lifelong non-smokers with current and former smokers; however, the association remained significant among lifelong non-smokers. In the future, a cohort study should be employed to follow-up cognitively healthy individuals for the development of aMCI and AD. Second, the generalizability of our results to the wider population may be constrained owing to the recruitment of aMCI and AD patients from a single institution. However, the patient survey center is a university-based hospital that provides high-level specialist medical services across the entire country, minimizing the impact of geographical constraints on the patient population. Finally, the collection of only one spot of the urine sample may not fully capture the cumulative exposure to PAHs over time. However, despite their short half-lives, urinary PAH metabolite concentrations have proven to be useful indicators of chronic exposure to PAH [30–32]. Additionally, although we selected four urinary PAH metabolites as markers of PAH exposure, these metabolites have been found to be dominant in Asian populations [33], making our approach efficient for capturing PAH exposure.

5. Conclusion

In conclusion, our findings imply that PAH exposure may increase the risk of aMCI and AD in adults. Considering the widespread distribution of PAHs in the environment, reducing PAH exposure may be an effective strategy for the prevention of neurodegenerative diseases, especially in elderly adults. Further research is warranted to better understand the specific mechanisms underlying this association and to explore potential interventions to reduce PAH exposure in populations that are at risk.

Ethics approval and consent to participate

This study was conducted in accordance with the principles of the Declaration of Helsinki, and all procedures were approved by the Yonsei University Health System Institutional Review Board (IRB No. 4-2014-0359) and the Institutional Review Board of the Samsung Medical Center (SMC 2015-09-880). All participants provided written informed consent prior to enrolment.

Data availability statement

Data will be made available on request.

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CRediT authorship contribution statement

Heeseon Jang: Writing – original draft, Project administration, Methodology, Formal analysis, Conceptualization. **Jungwoo Sohn:** Validation, Resources. **Hee Jin Kim:** Validation, Resources. **Sang Won Seo:** Validation, Resources. **Young Noh:** Validation, Resources. **Sang-Baek Koh:** Validation, Resources. **Jaelim Cho:** Writing – review & editing, Funding acquisition. **Changsoo Kim:** Writing – review & editing, Supervision, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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LIST OF ABBREVIATIONS

1-OHP	1-hydroxypyrene
1-OHPhe	1-hydroxyphenanthrene
2-NAP	2-naphthol
2-OHFlu	2-hydroxyfluorene
AD	Alzheimer's disease
aMCI	amnestic mild cognitive impairment
BMI	body mass index
CI	confidence interval
EPINEF	Environmental Pollution-Induced Neurological Effects
IQR	interquartile range
LOD	limit of detection
MCI	mild cognitive impairment
OR	odds ratio
PAH	polycyclic aromatic hydrocarbon
SD	standard deviation

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