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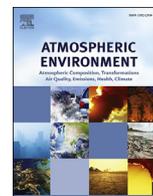
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Exposure to daily ambient particulate polycyclic aromatic hydrocarbons and cough occurrence in adult chronic cough patients: A longitudinal study

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H I G H L I G H T S

- Exposure to ambient particulate PAHs may evoke cough in adult chronic cough patients.
- Non-asthma patients have marginally stronger associations.
- Effects may occur several days after exposure.

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The specific components of airborne particulates responsible for adverse health effects have not been conclusively identified. We conducted a longitudinal study on 88 adult patients with chronic cough to evaluate whether exposure to daily ambient levels of particulate polycyclic aromatic hydrocarbons (PAH) has relationship with cough occurrence. Study participants were recruited at Kanazawa University Hospital, Japan and were physician-diagnosed to at least have asthma, cough variant asthma and/or atopic cough during 4th January to 30th June 2011. Daily cough symptoms were collected by use of cough diaries and simultaneously, particulate PAH content in daily total suspended particles collected on glass fiber filters were determined by high performance liquid chromatography coupled with fluorescence detector. Population averaged estimates of association between PAH exposure and cough occurrence for entire patients and subgroups according to doctor's diagnosis were performed using generalized estimating equations. Selected adjusted odds ratios for cough occurrence were 1.088 (95% confidence interval (CI): 1.031, 1.147); 1.209 (95% CI: 1.060, 1.379) per 1 ng/m³ increase for 2-day lag and 6-day moving average PAH exposure respectively. Likewise, 5 ring PAH had higher odds in comparison to 4 ring PAH. On the basis of doctor's diagnosis, non-asthma group had slightly higher odds ratio 1.127 (95% CI: 1.033, 1.228) per 1 ng/m³ increase in 2-day lag PAH exposure. Our findings suggest that ambient PAH exposure

Abbreviations: PM, particulate matter; DEPs, diesel exhaust particles; PM₁₀, particulate matter less than 10 μm in aerodynamic diameter; PM_{2.5}, particulate matter less than 2.5 μm in aerodynamic diameter; PAH, polycyclic aromatic hydrocarbons; TNF-α, Tumor necrosis factor-alpha; IL-8, interleukin-8; TRPA1, transient receptor potential Ankyrin 1; CYP1A1, cytochrome P450 family 1 subfamily A member 1; NO, nitric oxide; HPLC, high performance liquid chromatography; IQR, interquartile range; CI, confidence interval; CVA, cough variant asthma; AC, atopic cough; TSP, total suspended particles; GEE, generalized estimating equation; Lag 0, 24-h before health outcome; MA-2, 2-day moving average (average of lag 0–2).

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is associated with cough occurrence in adult chronic cough patients. The association may be stronger in non-asthma patients and even at low levels although there is need for further study with a larger sample size of respective diagnosis and inclusion of co-pollutants.

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1. Introduction

Exposure to ambient particulate matter (PM) increases mortality and morbidity related to respiratory diseases especially among susceptible individuals such patients with pre-existing chronic disease, children and the elderly (Anderson et al., 2012; McCreanor et al., 2007). Despite the strong association, it still remains to be determined which specific constituents of PM are responsible for the observed effects (Heo et al., 2014). Polycyclic aromatic hydrocarbons (PAH) are group of organic chemical compounds containing two or more benzene rings. PAH are widely spread in the environment and are closely linked to diesel exhaust particles (DEPs), PM_{2.5} and PM₁₀. Exposures to PAH emitted from vehicular sources, cigarette smoking, cooking and space heating have been associated with various adverse health effects in children (Al-Daghri et al., 2013; Gale et al., 2012; Jung et al., 2015; Padula et al., 2015). In particular, exposure to PAH such as benz[a]anthracene, benzo[a]pyrene, benzo[b]fluoranthene, benzo[g,h,i]perylene, chrysene and dibenz[a,h]anthracene are linked to increased cough and wheeze at age of 12 months (Miller et al., 2004). However, few longitudinal studies have been done, on its association with cough occurrence in adult chronic cough patients. Besides studies that have investigated its effects among occupationally exposed workers (Clark et al., 2012), and volunteers in controlled experiments (Behndig et al., 2006), some have reported links to wheezing and lung function in non-smoking women (Jedrychowski et al., 2007), cough and bronchial hyperreactivity among firefighters (Landrigan et al., 2004). More studies are needed to elucidate on effects of ambient exposures whose levels might be lower than those encountered in experiments or occupationally, with regard to susceptible persons such as adult chronic cough patients.

PAH may exert adverse health effects by increasing production of pro-inflammatory mediators (e.g., TNF- α , IL-8) in lung cells via oxidative stress as well as stimulation of IgE production among other mechanisms (Koike et al., 2014; Li et al., 2002; Takenaka et al., 1995). Alternatively, recent studies have shown correlation between responses to environmental PM that contains PAH, with activation of airway sensory neurons that express Transient Receptor Potential Ankyrin-1 (TRPA1), and substance P (Deering-Rice et al., 2012; Shapiro et al., 2013). This has led to the suggestion that activation of TRPA1 considered as a probable target for DEP and DEP-associated electrophilic combustion by-products in the respiratory tract may mediate responses such as cough, dyspnea, neurogenic inflammation (Deering-Rice et al., 2012). However, epidemiological evidence that supports the hypothesis is scarce with only one study performed among adult workers (Smit et al., 2012).

Chronic cough is a common reason for seeking medical consultation with a primary care or respiratory physician, and can lead to decreased quality of life in the event of unsuccessful control (Chung and Pavord, 2008). Asthma, post-nasal drip or rhinosinusitis, and gastro-oesophageal reflux disease are recognizable clinical conditions that are related to chronic cough (Groneberg et al., 2004). Asthma is a chronic airway inflammatory condition characterized by repetitive cough, wheezing, dyspnea, reversible airway narrowing and airway hyperresponsiveness (Ohta et al., 2011).

Furthermore, cough variant asthma (CVA) considered as a precursor of asthma (Corrao et al., 1979), and atopic cough (AC) are major causes of non-productive cough in Japan (Fujimura et al., 2003). With the prevalence of asthma is said to have increased over the past decade (Ohta et al., 2011) as well as rising cases of cough variant asthma and atopic cough amongst Japanese adults (Higashi et al., 2014), there is need to assess whether exposure to ambient PAH is related to cough occurrence in such subgroup of patients. It is suggested that chronic cough may result from hypersensitive response to environmental factors such as chemicals, cold air, smoke and Asian dust (Higashi et al., 2014; Matsumoto et al., 2012; Ternesten-Hasséus et al., 2011). Currently limited information is available about susceptibility of adult patients with asthma, cough variant asthma and/or atopic cough to ambient PAH. Information of any association with aggravating factors could be helpful during evaluation of patient history as well as in management of the condition (Pavord and Chung, 2008).

In the present study we hypothesized that exposure to ambient particulate PAH may activate TRPA1 in the lung cells of patients with chronic cough that could lead to increased cough occurrence. To test our hypothesis, a group of adult patients in Kanazawa city diagnosed with asthma, CVA and/or AC were followed for a period of 6 months. Kanazawa is the headquarters of Ishikawa prefecture located in the central area bordering the Sea of Japan on the west side. Previous studies have suggested automobiles and long-range transport as the major contributors of atmospheric PAH (Tang et al., 2005; Yang et al., 2007). It has also been reported higher concentrations occur in winter attributable to temperature inversion phenomenon. However, it could be considered among the regions that records fairly low air pollution levels throughout the year. For these reasons assessment on relation between exposure to daily ambient PAH level with information on daily cough symptoms, atopy and exhaled nitric oxide (marker of airway inflammation) was performed.

2. Methods

2.1. Participants

Data used was from a longitudinal study performed from 4th January–30th June 2011 on 88 out of 99 (89%) patients who had given informed consent before participating in the study. Participants were recruited from outpatients receiving treatment at Kanazawa University Hospital, Ishikawa Prefecture, Japan. Medical Ethics Committee of Kanazawa University issued study approval. All were adult patients aged over 20 years and were physician-diagnosed to have at least asthma, CVA and/or AC during the study period. The composition included asthma (56%), asthma and AC (6%), CVA (9%), AC (18%), and both CVA and AC (11%). We divided them into two; asthma group (asthma, asthma and AC) and non-asthma group (CVA, AC, CVA and AC).

Diagnosis of asthma patients was made on basis of the Japan Asthma Prevention and Management Guidelines 2011 (Ohta et al., 2011). Cough variant asthma was diagnosed using the criteria of the Japanese Cough Research Society (Kohno et al., 2006). Atopic cough was diagnosed according to previously reported criteria

(Fujimura et al., 2005), based on bronchodilator-resistant cough and the resolution of the cough with the use of histamine H1 antagonists and/or inhaled corticosteroids (ICS).

Patients continued to take their usual medications, according to the standard medical treatment of each disease during the study period. Patients with asthma and cough variant asthma took medications such as bronchodilator and/or ICS, and patients with atopic cough took medications such as histamine H1 antagonists and/or ICS. No patient experienced symptoms suggestive of chronic obstructive pulmonary diseases or other potentially confounding cardiorespiratory disorders.

2.2. Health surveys

Each participant was issued with cough diary at the first consultation day during the study period and requested to record his/her daily symptoms. The time period of study for each participant was from his/her first consultation day to the end of study, June 30 for all. To minimize dropout due to lack of compliance with recording, participants were asked to show their diaries to the doctor when they visited the hospital during the study period. Participants returned the diaries in person or mailed back to the hospital at the end of the study. We used the information to create a daily binary variable (symptoms/no symptoms) for each individual and daily occurrence were computed by dividing the number of participants with symptoms by the number of participants who recorded on that day.

Other collected information included standard demographics, smoking status, clinical data related to asthma, cough variant asthma and atopic cough including atopy, exhaled nitric oxide.

2.3. Atopy

Specific IgE (sIgE) antibody to 15 aeroallergens (pollen, grass, dust mite, dog and cat dander) were measured by radioallergo-sorbent tests and defined atopy as having at least one sIgE > 0.35 IU/mL.

2.4. NO measurement

Exhaled NO concentrations were measured by the online method using a chemiluminescence analyser (Model 280, Sievers Instruments, Boulder, CO, USA) according to the American Thoracic Society (ATS) guidelines (American Thoracic Society; European Respiratory Society, 2005). Expiratory flow was 0.05 L/s as recommended by the guidelines and exhalation pressure was 16 cm H₂O. Measurement of exhaled NO was repeated until three reproducible NO plateau values were achieved and the mean of these values was used as exhaled NO. Exhaled nitric oxide values were divided into two levels with a cut point set at 50 ppb on the basis of the recommendation by American Thoracic Society (Dweik et al., 2011). All participants had one measurement performed.

2.5. Ambient air monitoring

Daily ambient air monitoring was performed to correspond with the period the subjects were recording their daily symptoms. Six individual PAH compounds which included fluoranthene, pyrene, chrysene, benzo[b]fluoranthene, benzo[k]fluoranthene, and benzo[a]pyrene were measured. The sums of the individual PAH were used as proxies for 4 ring PAH (fluoranthene, pyrene, chrysene), 5 ring PAH (benzo[b]fluoranthene, benzo[k]fluoranthene, benzo[a]pyrene) and total particulate PAH concentration. These were measured as part of total suspended particles (TSP) on a 24-h basis from January 4th–June 30th, 2011 at Kanazawa University, Japan

(136.7°E, 36.6°N). TSP was collected on borosilicate glass fiber filter coated with fluorocarbon (FIBERFILM T60A20, 8 × 10 in, Pallflex, Putnam, CT, U.S.A) using high volume air sampler (120SL, KIMOTO Electric Co. Ltd, Japan) at a flow rate of 1000 L min⁻¹.

Extraction of PAH was done using a method previously described (Yang et al., 2007) with some modifications. In brief, it involved using 5 cm² of each filter cut into smaller pieces and placed in 10 ml test-tube. Pyrene-d₁₀ and benzo[a]pyrene-d₁₂ were added into the test-tube as internal standards for PAH. Addition of 625 μl ethanol, 1.88 ml dichloromethane, and sonicated for 15 min to extract PAH were repeated twice. Extract was passed through membrane filters (polytetrafluoroethylene, hydrophobic[pore size, 0.45 μm]; GL Science Inc., Tokyo, Japan) and evaporated to dryness under nitrogen gas. PAH were analyzed using HPLC-Fluorescence detector (RF-20A; SHIMADZU, Kyoto, Japan and a reversed-phase column (Intersil ODS-P, 4.6 × 250 mm, 5 μm, GL Sciences Inc., Tokyo, Japan). EPA 610 PAHs mix containing fluoranthene, pyrene, chrysene, benzo[b]fluoranthene, benzo[k]fluoranthene and benzo[a]pyrene (Sigma-Aldrich K.K., Tokyo, Japan), pyrene-d₁₀ (ISOTEC International, Canton, GA, USA) and benzo[a]pyrene-d₁₂ (Wako pure Chemical Industries, Ltd, Osaka, Japan) were used for calibration of HPLC system and quantification of the extracted PAH. Other reagents used were acetonitrile (HPLC grade), dichloromethane (HPLC grade), and ethanol for residual pesticides analysis (Wako pure Chemical Industries, Ltd, Osaka, Japan). The detection frequency ranged 80–110% for the 6 PAH analyzed in the current study.

Hourly average temperature and humidity data obtained from Kanazawa Local Meteorological Office – Japan Meteorological Agency (136.6°E, 36.6°N) were used to calculate the 24-h daily averages corresponding to PAH concentration.

2.6. Statistical analysis

Analyses were restricted to participants who provided information on cough symptoms at any given day within the study period, information about their smoking status and daily PAH concentrations were available. Eleven patients were excluded from the current analyses due to lack of information on smoking status (3%), no cough information for entire study period (3%), and current smokers (5%) with a final sample size of 88 (Table 1).

Spearman correlation coefficients were computed to examine the association between pollutants of interest and weather parameters (temperature and humidity) as they may influence concentrations of ambient PAH. We created a dichotomy variable to represent presence of cough or no cough using the individual participant's recorded information for each day. To analyze the relationship between cough occurrence and PAH exposure (continuous variable), we used generalized estimating equations (GEE) for panel data (Delfino et al., 2002; Higashi et al., 2014; Janes et al., 2008; Schildcrout et al., 2006). We specifically used marginal approach GEE with autoregressive working correlation matrix (AR1), in order to account for possible correlations between repeated measures on the same subject (Delfino et al., 2002).

Separate logistic regression models for same day (lag 0 defined as 24 h period before the health response) through to 7- day lag and 2 through to 7 day moving average (where MA-2 defined as average of lag 0–2) were constructed, without and with controlling for potential confounders; gender, smoking status, age, disease group, BMI, atopy, exhaled NO, day of week, temperature and humidity. Stratification by disease with adjustments was performed to assess whether there was effect modification in the estimates. We also conducted sensitivity analyses by excluding the 5 patients who were diagnosed as having both asthma and atopic cough.

Model regression parameters are presented as symptom odds

Table 1
Descriptive statistics for study subjects for study period 4th January–30th June 2011, Kanazawa city.^a

	Total, n = 88	Asthma, n = 54	Non-asthma, n = 34
Median age (age range, years)	66 (23–84)	67 (23–84)	62 (29–79)
Gender: males (females)			
Males (%)	28 (32)	18 (33)	9 (26)
Females (%)	60 (68)	36 (67)	25 (74)
BMI (SD, Kg/m ²)	22.73 (3.42)	22.49 (2.89)	23.12 (4.10)
Disease			
Asthma (%)	49 (56)	49 (91)	–
CVA (%)	8 (9)	–	8 (24)
AC (%)	16 (18)	–	16 (47)
Asthma and AC (%)	5 (6)	5 (9)	–
CVA and AC (%)	10 (11)	–	10 (29)
Smoking status			
Never smoked (%)	62 (70)	33 (61)	29 (85)
Ex-smoker (%)	26 (30)	21 (39)	5 (15)
Number of recorded days	130.2	135.7	121.5
Cough prevalence(day range) ^b	36.1% (10–178)	23.0% (10–178)	60.2% (57–178)
Time period of study (days) ^c	144.2	152.0	131.8
Atopy (%) ^d	45 (51)	30 (56)	15 (44)
Exhaled NO (%) ^e	13 (15)	12 (22)	1 (3)

Abbreviations: SD, standard deviation; non-asthma (cough variant asthma and atopic cough); CVA, cough variant asthma; AC, atopic cough; NO, nitric oxide.

^a Study participants after excluding 5 current smokers, 3 with no smoking status, 3 with no cough symptom information.

^b Number of participants with cough symptom/number of participants who recorded for that day (minimum, maximum recorded days), Mann-Whitney *U* test for difference in cough prevalence between asthma and non-asthma group, *P* < 0.001.

^c From entry (first consultation day during study period for each subject) to the end of study period (June 30th for all).

^d Number of subjects with at least one sIgE ≥ 0.35 IU/mL.

^e Number of subjects with Exhaled NO value > 50 ppb on basis of recommendations by American Thoracic Society.

ratios per unit change in PAH. All statistical analyses were performed using the SPSS software program for MS Windows, version 19.0 (SPSS, Inc., New York, NY, U.S.A.) and plots made using R software. Significance was set at *p* < 0.05 for all analyses.

3. Results

Table 1 shows descriptive summary of study subjects. A total of 12,473 observations were available for analysis from repeated measurements on 88 participants (68% females). The composition of subgroups based on physician diagnoses was asthma (61%) and non-asthma (39%). No significant differences were observed between age, BMI among the two groups. During the entire study period, daily prevalence of cough was higher among non-asthma than asthma group that was significant *P* < 0.001, (Fig. 1).

Daily ambient PAH level, temperature and humidity are summarized in Table 2. For the entire study period PAH concentrations had 8% missing data due to technical problem with high volume air sampler used in collection of TSP while temperature and humidity had 0.5% missing data. No imputation of missing data was performed. Table 3 shows Spearman's correlation matrix of PAH with weather parameters during the entire study period.

Odds ratios of cough occurrence per unit increases in PAH (4 ring, 5 ring and total) for the entire study population are shown in Tables 4a and 4b, lagged and moving average exposures respectively. These estimates are from regression models fitted for each pollutant without and with adjustments for age, gender, BMI, atopy, smoking status, exhaled NO, disease group, day of week, temperature, humidity. Lags (2-, 3-, 5- and 6-day) showed evidence of positive relation with cough occurrence. Most robust effects were for 2- and 6-day lag (OR (95 percent CI); 1.088 (1.031, 1.147); 1.087(1.001, 1.179), *P* < 0.05) per 1 ng/m³ change in PAH. We also found that 7-day lag had a negative relation with cough occurrence that was significant (*P* < 0.05). In addition, for cumulative health effects we observed a general trend of positive associations with robust effect for 6-day moving average (OR, (95 percent CI); 1.209 (1.060, 1.379), *P* < 0.05).

Tables 5a and 5b shows the adjusted estimates of cough

occurrence stratified by disease group for lagged and moving average exposures respectively. For asthma group, lags (2-, 3-, 5- and 6-day) revealed a tendency of positive association. Both lag 2- and 6-day had robust associations (*P* < 0.05), while 7-day lag showed evidence of negative association with cough outcome. For non-asthma group lag (0, 2, 4, 5, and 6-day) had positive tendency, however, only lag 2 had significant relation 1.127 (95 percent CI: 1.033, 1.228, *P* < 0.05) per unit increase in PAH. Both subgroups displayed positive trends for the case of moving average. However, only 6-day moving average had significant relation with non-asthma having slight high ORs compared to asthma group.

The estimates of cough occurrence were higher for 5 ring PAH in comparison to 4 ring PAH for all the exposure metrics as shown in Tables 4 and 5. No significant differences were observed in the sensitivity analyses (results not shown).

4. Discussion and conclusions

In this longitudinal study the main aim was to assess relationship between cough occurrence in adult chronic cough patients and daily ambient particulate PAH exposure. Our results show moderate association between 1 ng/m³ increase in PAH exposure and odds of cough occurrence among the patients for the entire study period. The association was still present even after adjustments for age, gender, BMI, smoking status, atopy, exhaled NO, disease group, day of week, temperature and humidity were made. On the basis of doctor's diagnoses, our results suggest non-asthma group had a slightly increased tendency of cough occurrence compared to asthma patients. To the best of our knowledge, this is the first epidemiologic study to investigate the relationship of ambient PAH (as 4 ring, 5 ring and their sum) with cough symptom in adult patients with asthma, cough variant asthma and/or atopic cough.

We found exposure to ambient PAH (according to benzene rings and their total) was linked to cough occurrence in adult patients with chronic cough that appeared a few days after exposure. Despite scarcity of studies that directly link exposure to ambient PAH and cough occurrence in adult chronic cough patients, there are published articles that have illustrated its association with

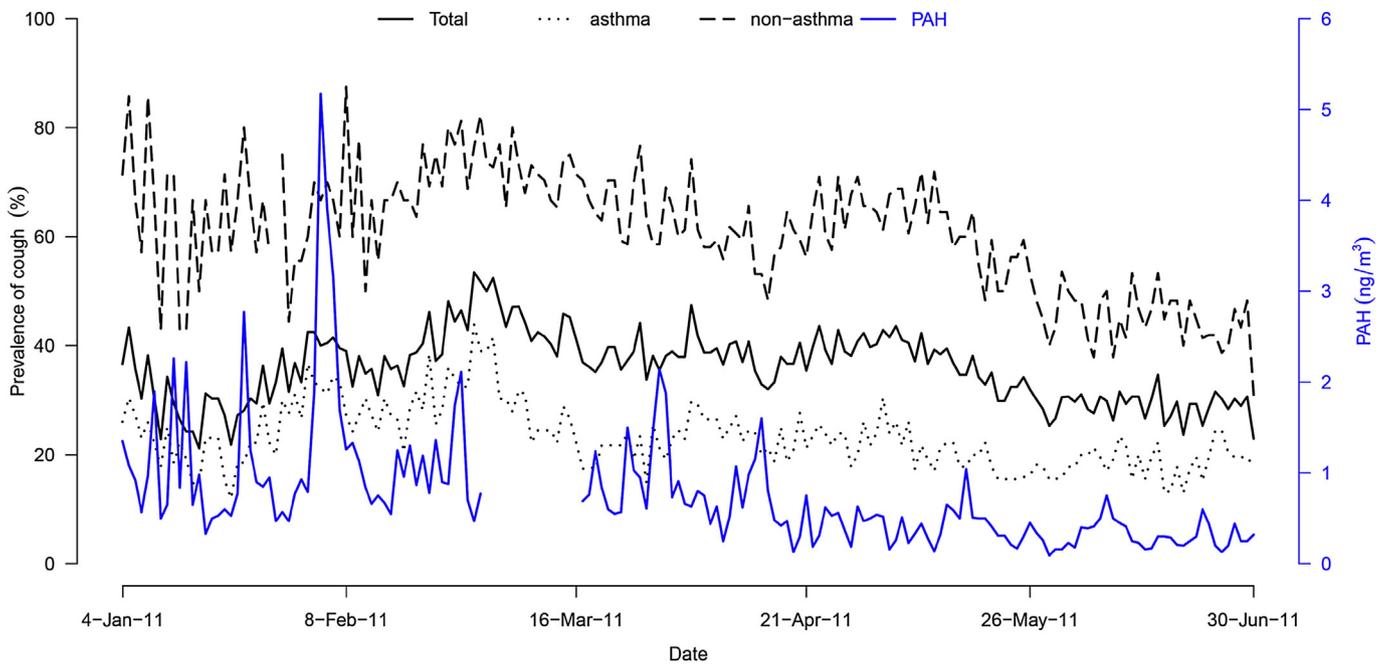


Fig. 1. Daily time-series plot of prevalence of cough for total, asthma and non-asthma patients (%) versus PAH concentrations (ng/m^3) in Kanazawa city during 4th January–30th June 2011 study period.

Table 2

Summary of daily PAH concentrations, temperature and humidity measurements for study period, 4th January–30th June 2011, Kanazawa city.^a

Exposure	No. observations	Mean (SD)	Min/max	IQR
4 ring PAH (ng/m^3) ^b	163	0.49 (0.45)	0.03/3.34	0.39
5 ring PAH (ng/m^3) ^b	163	0.25 (0.23)	0.02/1.83	0.18
PAH (ng/m^3) ^b	163	0.75 (0.67)	0.09/5.17	0.57
Temperature ($^{\circ}\text{C}$) ^c	177	10.7 (8.05)	-1.8/28.6	14.4
Humidity (%) ^c	177	68.36(11.37)	36/91	16.0

Abbreviations: IQR, interquartile range; SD, standard deviation; Min, minimum; max, maximum; PAH, polycyclic aromatic hydrocarbons; 4 ring PAH includes fluoranthene, pyrene, chrysene, 5 ring PAH includes of benzo[b]fluoranthene, benzo[k]fluoranthene, benzo[a]pyrene; PAH includes both 4 ring PAH and 5 ring PAH.

^a Measurements used were from 2 central monitoring sites.

^b Measurement were taken at Kanazawa University site and 15 days are missing due to equipment failure.

^c Measurement were taken from Kanazawa Local Meteorological Office -Japan Meteorological Agency, temperature and humidity 1 day missing data.

Table 3

Daily PAH concentrations, temperature and humidity correlation matrix for study period 4th January–30th June 2011, Kanazawa city.^a

	4 ring-PAH	5 ring-PAH	PAH	Temperature	Humidity
4 ring-PAH ^b		0.984 [†]	0.995 [†]	-0.660 [†]	-0.341 [†]
5 ring-PAH ^c			0.991 [†]	-0.648 [†]	-0.309 [†]
PAH ^d				-0.635 [†]	-0.332 [†]
Temperature					-0.102

Abbreviation: PAH, polycyclic aromatic hydrocarbons.

[†] $P < 0.001$.

^a Spearman's correlation coefficients.

^b Sum of fluoranthene, pyrene, chrysene.

^c Sum of benzo[b]fluoranthene, benzo[k]fluoranthene, benzo[a]pyrene.

^d Sum of 4 ring PAH and 5 ring PAH. n is 163 days for PAH and 177 days for temperature and humidity.

adverse respiratory effects in adults. Increased cough and bronchial hyperreactivity linked to exposure to World Trade Center dust was reported in firefighters who took part in rescue exercise after

Table 4a

Odds ratios and 95% CI estimates for cough symptoms per 1 ng/m^3 increase in lagged PAH exposure for entire group during study period, 4th January–30th June 2011, Kanazawa city.^a

Pollutant	Lag	Unadjusted ^b		Adjusted ^c	
		OR	95% CI	OR	95% CI
4 ring PAH	Lag 0	0.980	0.911,1.055	0.999	0.914,1.092
	Lag 1	0.951	0.880,1.028	0.951	0.867,1.044
	Lag 2	1.083	1.018,1.151	1.122	1.039,1.211
	Lag 3	1.032	0.952,1.120	1.045	0.948,1.152
	Lag 4	0.962	0.878,1.054	0.931	0.833,1.040
	Lag 5	1.027	0.960,1.100	1.037	0.956,1.124
	Lag 6	1.127	1.017,1.248	1.140	1.009,1.289
5 ring PAH	Lag 7	0.920	0.847,0.999	0.883	0.798,0.978
	Lag 0	0.964	0.833,1.116	0.996	0.839,1.181
	Lag 1	0.885	0.756,1.036	0.904	0.748,1.092
	Lag 2	1.205	1.059,1.373	1.291	1.095,1.522
	Lag 3	1.027	0.883,1.195	1.047	0.876,1.252
	Lag 4	0.955	0.810,1.127	0.887	0.730,1.077
	Lag 5	1.039	0.907,1.189	1.056	0.901,1.237
PAH	Lag 6	1.196	0.979,1.462	1.233	0.972,1.564
	Lag 7	0.859	0.738,0.999	0.793	0.657,0.957
	Lag 0	0.983	0.936,1.032	0.994	0.937,1.055
	Lag 1	0.965	0.917,1.016	0.970	0.911,1.032
	Lag 2	1.061	1.018,1.107	1.088	1.031,1.147
	Lag 3	1.013	0.959,1.070	1.019	0.955,1.087
	Lag 4	0.975	0.919,1.035	0.954	0.888,1.025
Lag 5	1.017	0.971,1.064	1.023	0.970,1.080	
Lag 6	1.077	1.006,1.153	1.087	1.001,1.179	
Lag 7	0.948	0.898,1.000	0.923	0.863,0.986	

Abbreviations: OR, odds ratio; CI, confidence interval; PAH, polycyclic aromatic hydrocarbons; 4 ring PAH is sum of fluoranthene, pyrene, chrysene; 5 ring PAH is sum of benzo[b]fluoranthene, benzo[k]fluoranthene, benzo[a]pyrene; PAH is sum of 4 ring PAH and 5 ring PAH.

^a Values in bold are statistically significant ($P < 0.05$).

^b Only pollutant without adjustments.

^c With adjustments for age, gender, BMI, atopy, smoking status, exhaled NO, disease group, day of week, temperature, humidity; models involved 88 subjects.

September attack (Landrigan et al., 2004). The same study reported new onset cough (33%), wheeze (18%) and phlegm production

Table 4b

Odds ratios and 95% CI estimates for cough symptoms from 1 ng/m³ increase in moving average PAH exposure for entire group during study period, 4th January–30th June 2011, Kanazawa city.^a

Pollutants		Unadjusted ^b		Adjusted ^c	
		OR	95% CI	OR	95% CI
4 ring PAH	MA-2	1.019	0.933,1.113	1.057	0.954,1.171
	MA-3	1.045	0.927,1.177	1.096	0.953,1.260
	MA-4	1.045	0.910,1.199	1.051	0.901,1.226
	MA-5	1.082	0.912,1.284	1.090	0.900,1.321
	MA-6	1.315	1.083,1.597	1.348	1.102,1.649
	MA-7	0.920	0.847,0.999	1.146	0.907,1.449
	5 ring PAH	MA-2	1.071	0.904,1.268	1.175
MA-3		1.072	0.854,1.346	1.196	0.918,1.557
MA-4		1.132	0.876,1.462	1.141	0.863,1.507
MA-5		1.148	0.832,1.583	1.170	0.817,1.675
MA-6		1.560	1.093,2.227	1.633	1.136,2.346
MA-7		1.346	0.903,2.007	1.251	0.804,1.946
PAH		MA-2	1.020	0.962,1.082	1.052
	MA-3	1.029	0.950,1.114	1.066	0.971,1.170
	MA-4	1.031	0.942,1.129	1.038	0.938,1.149
	MA-5	1.050	0.937,1.176	1.060	0.933,1.204
	MA-6	1.187	1.045,1.349	1.209	1.060,1.379
	MA-7	1.124	0.980,1.290	1.096	0.939,1.281

Abbreviations: OR, odds ratio; CI, confidence interval; PAH, polycyclic aromatic hydrocarbons; MA, moving average; 0–7 number of days; 4 ring PAH is sum of fluoranthene, pyrene, chrysene; 5 ring PAH is sum of benzo[b]fluoranthene, benzo[k]fluoranthene, benzo[a]pyrene; PAH is sum 4 ring PAH and 5 ring PAH.

^a Values in bold are statistically significant ($P < 0.05$).

^b Only pollutant without adjustments.

^c With adjustments for age, gender, BMI, atopy, smoking status, exhaled NO, disease group, day of week, temperature, humidity; models involved 88 subjects.

Table 5a

Odds ratios and 95% CI estimates for occurrence of cough symptoms per 1 ng/m³ increase in lagged exposure concentrations for two subgroups, 4th January–30th June 2011.^a

Pollutant		Asthma		Non-asthma		
		OR	95% CI	OR	95% CI	
4 ring PAH	Lag 0	0.952	0.845,1.073	1.125	0.961,1.318	
	Lag 1	0.942	0.828,1.072	0.970	0.856,1.098	
	Lag 2	1.107	1.002,1.223	1.183	1.038,1.349	
	Lag 3	1.086	0.996,1.184	0.976	0.752,1.267	
	Lag 4	0.894	0.783,1.021	1.026	0.817,1.289	
	Lag 5	1.026	0.937,1.123	1.077	0.895,1.295	
	Lag 6	1.108	0.981,1.251	1.265	0.925,1.730	
	Lag 7	0.967	0.874,1.070	0.729	0.595,0.894	
	5 ring PAH	Lag 0	0.928	0.751,1.147	1.186	0.829,1.698
		Lag 1	0.877	0.671,1.145	0.967	0.747,1.25
Lag 2		1.254	1.014,1.551	1.443	1.121,1.859	
Lag 3		1.135	0.956,1.348	0.908	0.586,1.407	
Lag 4		0.806	0.632,1.028	1.125	0.778,1.625	
Lag 5		1.088	0.904,1.309	1.020	0.735,1.417	
Lag 6		1.115	0.889,1.398	1.649	0.906,3.004	
Lag 7		0.957	0.799,1.146	0.546	0.379,0.785	
PAH		Lag 0	0.964	0.891,1.043	1.072	0.961,1.196
		Lag 1	0.962	0.883,1.049	0.986	0.907,1.072
	Lag 2	1.078	1.007,1.155	1.127	1.033,1.228	
	Lag 3	1.053	0.993,1.116	0.957	0.810,1.131	
	Lag 4	0.927	0.850,1.011	1.021	0.882,1.183	
	Lag 5	1.020	0.962,1.083	1.041	0.919,1.179	
	Lag 6	1.060	0.980,1.146	1.179	0.956,1.454	
	Lag 7	0.980	0.919,1.047	0.814	0.714,0.929	

Abbreviations: OR, odds ratio; CI, confidence interval; PAH, polycyclic aromatic hydrocarbons; 4 ring PAH is sum of fluoranthene, pyrene, chrysene; 5 ring PAH is sum of benzo[b]fluoranthene, benzo[k]fluoranthene, benzo[a]pyrene; PAH is sum of 4 ring PAH and 5 ring PAH.

^a Values in bold are statistically significant ($P < 0.05$). Adjusted for age, gender, BMI, atopy, smoking status, exhaled NO, disease group, day of week, temperature and humidity. Models involved 54 and 34 subjects for asthma and non-asthma groups respectively.

Table 5b

Odds ratios and 95% CI for occurrence of cough symptoms per 1 ng/m³ increase in moving average exposure concentration for two subgroups, 4th January–30th June 2011.^a

Pollutant		Asthma		Non-asthma	
		OR	95% CI	OR	95% CI
4 ring PAH	MA-2	1.034	0.909,1.176	1.131	0.939,1.362
	MA-3	1.117	0.963,1.297	1.097	0.805,1.494
	MA-4	1.035	0.861,1.243	1.157	0.849,1.576
	MA-5	1.079	0.860,1.354	1.192	0.814,1.745
	MA-6	1.311	1.043,1.647	1.578	1.030,2.418
	MA-7	1.259	0.978,1.620	1.065	0.657,1.726
	5 ring PAH	MA-2	1.119	0.871,1.439	1.369
MA-3		1.252	0.934,1.680	1.186	0.685,2.053
MA-4		1.087	0.788,1.500	1.454	0.794,2.664
MA-5		1.191	0.798,1.776	1.317	0.616,2.819
MA-6		1.514	1.010,2.271	2.379	1.083,5.227
MA-7		1.473	0.910,2.386	1.142	0.468,2.787
PAH		MA-2	1.038	0.951,1.132	1.100
	MA-3	1.088	0.985,1.202	1.048	0.858,1.281
	MA-4	1.035	0.919,1.165	1.090	0.888,1.339
	MA-5	1.062	0.918,1.229	1.107	0.853,1.436
	MA-6	1.184	1.021,1.373	1.352	1.025,1.783
	MA-7	1.170	0.990,1.383	1.040	0.759,1.425

Abbreviations: OR, odds ratio; CI, confidence interval; PAH, polycyclic aromatic hydrocarbons; MA, moving average; 0–7 number of days; 4 ring PAH is sum of fluoranthene, pyrene, chrysene; 5 ring PAH is sum of benzo[b]fluoranthene, benzo[k]fluoranthene, benzo[a]pyrene; PAH is sum of 4 ring PAH and 5 ring PAH.

^a Values in bold are statistically significant ($P < 0.05$). Adjusted for age, gender, BMI, atopy, smoking status, exhaled NO, disease group, day of week, temperature and humidity. Models involved 54 and 34 subjects for asthma and non-asthma groups respectively.

(24%) among 183 cleanup workers. In addition, high prevalence of wheezing and reduced lung function has been reported among non-smoking female adults associated with higher levels of fine particulate and PAH exposure (Jedrychowski et al., 2007). While the concentrations in those studies were much higher compared with the current study, PAH concentrations were within range on basis of studies done in some Japanese cities (Tang et al., 2005; Tham et al., 2008; Yang et al., 2007). Another study reported severe dry cough symptom had relationship with urinary 1-hydroxypyrene levels among exposed vulcanization workers (Jönsson et al., 2008). Elsewhere, Choi and coworkers reported 1-hydroxypyrene metabolite compromised lung function in elderly persons with haplotype-based CYP1A1 polymorphism (Choi et al., 2013). In view of the current findings together with the previous reported studies it may be considered ambient PAH is among the trigger factors of cough in adults including patients with chronic cough.

Although ambient levels of PAH may have little impact to healthy persons whose lungs have intact epithelial lining, those with damaged epithelial lining experience increased inflammatory response. Exposure to environmental factors (e.g., chemicals, cold, and scents) has been cited as major triggers of chronic cough in adults. Ternesten-Hasséus and coworkers (Ternesten-Hasséus et al., 2011) found environmental factors had links to coughing in over 60% of patients with unexplained cough. We have previously reported that Asian dust (Kosa) was associated with cough occurrence among chronic cough patients (Higashi et al., 2014). Changes in the airway wall mucosa and epithelium may play a role in the pathogenesis of cough receptor sensitization (Niimi and Chung, 2004). It is suggested that heightened cough reflex could result from increased sensitivity of cough receptors or changes in central processing, brainstem (Chung and Pavord, 2008). Exposure to agonists of TRP ion channels expressed by neuronal and non-neuronal cells may be one possible cause for increased cough responses. Some studies have shown association between enhanced cough reflex found in patients with chronic cough and expression of TRP

ion channels. Groneberg and coworkers reported increased expression of TRPV-1 in airway epithelial nerves of patients with chronic cough (Groneberg et al., 2004). It has recently been shown TRPA1 agonists induced cough in guinea pig and human volunteers (Birrell et al., 2009). The TRPA1 receptor is a promiscuous receptor that can be activated by a wide range of stimuli such as cigarette smoke extracts, wood smoke containing PAH (Bessac and Jordt, 2008; Shapiro et al., 2013). This could be a possible explanation for the observation of increased cough occurrence in the current study. Although caution needs to be taken when interpreting the results, as we cannot exclude the contribution of other correlated pollutants such as environmental tobacco smoke and other unmeasured confounding exposures.

Important highlights of this study include use of daily concentration of 6 individual PAH compounds allowed analysis on basis of 4 ring PAH, 5 ring PAH and their sum. Some of the previous studies used PAH concentrations that were sampled only for few days (Gale et al., 2012; Jedrychowski et al., 2007) during the study period. We found increases in PAH exposures according to benzene rings were positively related to odds of cough occurrence with 5 ring PAH showing higher estimates. This is in agreement with studies that have illustrated toxicological effects of PAH related to number of benzene rings (Gale et al., 2012; Koike et al., 2014). Also all participants were diagnosed to have conditions that are related to chronic cough providing an opportunity to evaluate links between ambient PAH and cough occurrence in a subpopulation considered at risk. More so, detection of health changes from variation in daily ambient pollutants was made possible with the follow-up by use of diary during the study. Only three out of the ten confounders added in the regression models displayed some relation with cough occurrence. We found disease group had statistically significant relation to cough occurrence ($P < 0.001$, results not reported). When added in the regression model with the pollutant of interest it inflated the estimates, however, it did not change the direction of association. This could be suggestive of the influence of underlying disease with regard to occurrence of cough among the participants. Smoking status and temperature were also found to have significant relations and findings are in agreement with previous reports. For instance, temperature had a negative association in the adjusted model which may be interpreted as cold conditions might cause cough (Ternesten-Hasséus et al., 2011). Additionally, we also found the concentrations of PAH were higher during cold period (winter) as reported in previous studies (Tang et al., 2005; Tham et al., 2008). This could be attributed to temperature-PAH volatility relation especially for case of 4 ring PAH but also it could be as a result of temperature inversion phenomenon leading to poor vertical mixing during cold periods and hence high concentrations of PAH (Tang et al., 2005). On the other hand, unlike previous reports no gender influence was observed in the current study (Pavord and Chung, 2008). Likewise, higher exhaled NO concentration (a marker of airway inflammation) was not related to cough which inferred that there could be another mechanism through which PAH induced cough.

Several shortcomings that might hinder interpretation of the current results include misclassification of exposure from the assumption that all patients were exposed to same ambient levels. We cannot rule out possibility of overestimation especially for the patients that lived at far distance from the monitoring site. However, a previous study suggested that ambient fine particle concentrations could be a good estimate for personal exposure to fine particles of ambient origin (Janssen et al., 2005). It has also been previously reported that traffic sources and long-range transport are major contributors of ambient PAH in Kanazawa (Tang et al., 2005; Yang et al., 2007). Another shortcoming is small sample size that led into CVA and AC patients put together in same group.

The ideal case would have been to cluster asthma and CVA patients into one group, and non-asthma patients comprising atopic cough patients. This might have influenced the estimates between the two subgroups of asthma and non-asthma, although we still observed marginal differences between the two subgroups. Additionally, participants continued to take medication during the study, this might have masked adverse effects of PAH and we lacked detailed information to quantitatively analyze its influence. Although there were no changes in prescribed medication for all the patients that could be interpreted as in the current study no significant influence of medication use was present. Finally, it is worth to mention that exhaled NO (a marker of inflammation) measurements were performed only once for all the patients and at different times. This might not have fully captured any changes that occurred as result of inflammation and possibly led to the null association observed in this study.

In conclusion, our results suggest that exposure to ambient particulate PAH compounds according to benzene rings and their total was associated with occurrence of cough among adult chronic cough patients. These associations were largest for 2- and 6-day lags, 6-day moving average exposures. On the basis of physician-diagnoses, non-asthma group were more likely to report increase in occurrence of cough symptom compared to asthma group. Our results add to the growing evidence that ambient PAH even at lower concentrations may act as an aggravating factor and needs to be considered during clinical management of adult patients with chronic cough. Future longitudinal study that includes co-pollutants to account for any confounding effects is needed to confirm the relation. Such study would greatly benefit from taking into account spatial distribution of exposure and larger patient number.

Conflict of interest

The authors declared no conflict of interest.

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