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Association between Cough and Ambient Polycyclic Aromatic Hydrocarbons in Patients with Chronic Cough: An Observational Study in Two Regions of Japan

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Abstract: Ambient polycyclic aromatic hydrocarbons' (PAHs) specific components are likely involved in respiratory disease development and exacerbation in children and adults. Airborne PAH exposure's effects on cough symptoms in children and adults with chronic coughs in Kanazawa and Fukuoka, Japan, were investigated in this longitudinal study. A total of 98 patients with chronic coughs were enrolled and followed up between 1 April and 31 May 2020. The enrolled patients were non-smoking adults and children aged 3–83 years. Cough diaries were used to record and collect daily cough symptoms. High-performance liquid chromatography coupled with a fluorescence detector was used to determine the particulate PAH content in daily total suspended particles collected on quartz fiber filters. Ambient concentrations of fine particulate matter, nitrogen dioxide, and sulfur dioxide were obtained from local monitoring sites. Generalized estimated equations were used to estimate the association between daily PAHs and cough symptoms. Among nine PAHs measured, benz[*a*]anthracene (BaA) was significantly associated with cough symptoms for both lag4 and lag5 PAH exposure. These findings suggest that airborne specific PAHs, especially BaA, affect cough symptoms in children and adults with chronic cough. Further studies are needed to develop effective measures to prevent respiratory diseases against specific PAHs.

Keywords: polycyclic aromatic hydrocarbon; particulate matter; chronic cough; children; adult; asthma; respiratory diseases

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Citation: Hara, A.; Odajima, H.; Matsuzaki, H.; Fujimura, M.; Toma, T.; Wada, T.; Ohkura, N.; Zhao, J.; Pham, K.-O.; Suzuki, K.; et al. Association between Cough and Ambient Polycyclic Aromatic Hydrocarbons in Patients with Chronic Cough: An Observational Study in Two Regions of Japan. *Appl. Sci.* **2022**, *12*, 12505. https://doi.org/10.3390/app122412505

Academic Editor: Simone Morais

Received: 2 November 2022
Accepted: 28 November 2022
Published: 7 December 2022

1. Introduction

Chronic cough is defined as a cough that lasts for 8 weeks or more, and its estimated global prevalence is 2–18% [1]. People with chronic cough report many physical and psychological effects, which can lead to quality of life impairment [1]. Chronic cough is often triggered by low thermal, mechanical, or environmental chemical exposure levels [1]. In addition to the effects of gaseous pollutants such as sulfur dioxide (SO_2) and nitrogen

dioxide (NO_2) [2], ambient particulate matters (PM), especially those with diameters 2.5 μm and smaller ($PM_{2.5}$), have been reported to be involved in the development and exacerbation of respiratory diseases including bronchial asthma (BA) in both children and adults [2,3] among these environmental factors.

Polycyclic aromatic hydrocarbons (PAHs) are known to be important organic PM constituents for their toxic potential through their cytotoxicity, mutagenicity, and carcinogenicity [3]. PAHs are a group of hydrocarbons with two or more fused aromatic rings, and they are produced by the incomplete combustion of coal and various organic materials such as fossil fuels and cigarette smoke [3,4]. Low-molecular-weight PAHs (two and three rings) occur in the atmosphere predominantly in the gas phase, whereas high-molecular-weight PAHs (five rings or more) are largely bound to PM. Intermediate-molecular-weight PAHs (four rings) are partitioned between the gas and particulate phases, depending on the atmospheric temperature [5]. The main sources of PAHs include plants, air, water, food and soil, and routes of exposure to humans include inhalation, ingestion or percutaneous penetration [4,5]. Among these routes, inhalation has been considered more important for the respiratory effects of PAHs [3]. PAHs are now shown to be involved in the development and exacerbation of respiratory diseases, such as childhood and adult BA, chronic obstructive pulmonary disease, and others accompanied by cough symptoms, in addition to affecting respiratory function [3,4,6,7]. However, a few epidemiological studies have demonstrated the possible association between airborne PAH exposure and respiratory symptoms, such as cough prevalence in people with chronic respiratory diseases, including asthma [6,7].

Heterogeneity exists in the association between PAH and cough symptoms or respiratory diseases, including asthma, in previous epidemiological studies, in addition to the small number of relevant studies. A US population-based cross-sectional study has reported an inverse association between urinary PAH metabolites and adult asthma, while the relationship between those and cough was not observed [8], contrary to PAH's positive association with respiratory diseases and symptoms. Another cross-sectional study in Mexican communities has shown no association between urinary metabolite 1-hydroxypyrene concentrations and respiratory function [9]. A previous cross-sectional study has reported that there were no associations between ambient PAH and respiratory functions among asthmatic children [10] as these are adult population studies. These inconsistent results might be due to differences in race, age, site, underlying disease, and measured PAHs type, in addition to the sample size of each study. Actually, the specific composition and organic chemicals amount are highly dependent on the fuel burned and combustion technology worldwide [3].

This study's purpose was to examine the airborne PAH exposure effects on cough symptoms in children and adults with respiratory disease accompanied by chronic cough in two Japanese cities, taking into account other pollutants of SO_2, NO_2, and $PM_{2.5}$ which may affect respiratory diseases based on these backgrounds.

2. Materials and Methods

2.1. Participants

The data used in the present study were from a longitudinal study conducted between 1 April and 31 May 2020 on 98 patients with chronic respiratory diseases who underwent treatment at Kanazawa University Hospital, Ishikawa Prefecture; National Hospital Organization Nanao Hospital, Ishikawa Prefecture; and National Hospital Organization Fukuoka National Hospital, Fukuoka Prefecture, Japan. Enrolled patients were non-smoking adults and children aged between 3 and 83 years old who at least had a physician-diagnosed BA, cough-variant asthma (CVA), atopic cough (AC), sinobronchial syndrome (SBS), and/or gastroesophageal reflux-associated cough during the study period. BA diagnosis was made according to the Japan Asthma Prevention and Management Guidelines 2011 [11]. CVA, AC, and SBS were diagnosed according to the diagnostic criteria previously described [12]. The total number of BA, CVA, AC, and SBS was 60, 44, 15, and 34, respectively, while

there were patients who had multiple diagnoses. Patients continued to receive standard treatment for each disease during the study period. Patients with BA and CVA were treated with medications such as bronchodilators and/or inhaled corticosteroids (ICS), and those with AC were treated with histamine H1 antagonists and/or ICS. No patients were previously diagnosed with chronic obstructive pulmonary diseases or other cardiorespiratory disorders.

2.2. Surveillance of Daily Cough

Each patient was issued a cough diary during the study period and requested to record his/her daily cough symptoms. The study period was conducted when a cough diary of each patient could be recorded and collected during the monitoring period of ambient air from December 2019 to August 2021. Participants were asked to show their diaries to physicians when they visited the hospital during the study period to minimize dropout due to lack of adherence to diary recording. Cough diaries were returned from the study participants to their physicians at the end of the study. We used the daily binary variable of the presence or absence of cough for each participant, and cough prevalence was defined as the days with cough symptoms divided by the observation period in each participant.

2.3. Other Clinical Information

Other collected information included age, sex, height, and weight. We calculated and ranked the body mass of study participants using height and weight: for participants aged ≥16 years, body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2) and ranked as lean (BMI < 18.5), normal (BMI of ≥18.5 and <25.0), and overweight/obesity (BMI ≥ 25.0) [13]. The Kaup index (body weight [g]/height [cm]/height [cm] × 10) was calculated using the same equation as that for BMI for participants aged from 3–5 years and ranked as lean (<14.5), normal (≥14.5 and <16.5) and overweight (≥16.5) [14]. The Rohrer index (weight (kg)/height $(m)^3$ × 10) was calculated for those aged from 6–15 years and ranked as lean (<115), normal (≥115 and <145), and overweight (≥145) [15].

2.4. Ambient Air Sampling

Sampling sites and methods details were previously described [16]. The total suspended particles (TSP) samples were collected on the roofs of 2 buildings in residential areas: the Graduate School of Medical Science of Kanazawa University, Kanazawa City, Ishikawa (36.6° N, 136.7° E) and National Hospital Organization Fukuoka National Hospital, Fukuoka City, Fukuoka (33.53° N, 130.41° E). Kanazawa City (population of 461,000), the capital of Ishikawa prefecture, is a commercial city located on the Japan seacoast side of Central Honshu Island, Japan. The capital of Fukuoka prefecture, Fukuoka City (population of 1,620,000), is a commercial port city located on the Japanese seacoast side of Kyushu. Samples for measuring TSP were obtained daily using high-volume air samplers (HR-RW, Shibata, Japan) equipped with quartz fiber filters at a 1000 L/min flow rate during the study period. Among them, 61 samples collected from 1 April to 31 May 2020 were used in the present study. Filters were covered in aluminum foil and balanced in a dark desiccator for at least 24 h before and after the sampling. TSP concentration was calculated from filter weights before and after sampling.

2.5. Measurement of PAHs

Based on the chemical characteristics of the binding of PAHs to PM among 16 PAHs classified as priority pollutants [4], Fluoranthene (Flt), pyrene (Pyr), benz[*a*]anthracene (BaA), chrysene (Chr), benzo[*b*]fluoranthene (BbF), benzo[*k*]fluoranthene (BkF), benzo[*a*]pyrene (BaP), benzo[*ghi*]perylene (BghiP) and indeno[1,2,3-*cd*]pyrene (IcdP) were included in the nine individual PAH compounds measured using high-performance liquid chromatography (HPLC) equipped with fluorescence detection, as described previously [16]. In brief, each filter was cut into approximately 1 cm^2 in a glass flask, and an aliquot of the PAH internal standards (Pyr-d_{10} and BaP-d_{12}) was added. A total of 80 mL ethanol:benzene (purity

99.5%; FUJIFILM Wako Pure Chemical Industries Ltd., Osaka, Japan) (*v*/*v* 1:4) was used to extract PAHs by sonication, and the extract was cleaned with a buffer with 5% NaOH and 20% H_2SO_4. The organic phase was evaporated under nitrogen gas until 100 µL before reconstituting with 900 µL acetonitrile and filtering into a vial. During the HPLC procedures, SS EPA 610 PAH Mix (Supelco, Bellefonte, PA, USA) was used as a standard of PAHs. To check the quality assurance/control of the data, the recovery test was performed by spiking the standard internal mixture with known concentrations on blank and sample filters. As a result, the recovery was 110–120%. Also, the reproductivity test was conducted by analyzing the same samples using the same methods at two facilities at Kanazawa University. The reproductivity range was 90–115%. Furthermore, at each sequence of analysis, a standard mixture was run and compared with the previous analysis. The relative standard deviation was within 15%. Total PAH concentrations were defined as the sum of these 9 PAHs.

2.6. Daily Ambient Concentrations of SO_2, NO_2, and $PM_{2.5}$

Information on hourly concentrations of SO_2, NO_2, and $PM_{2.5}$ obtained from the 2 monitoring sites of Kodatsuno, Kanazawa City (136.7° E, 36.6° N) and Fukuoka city, Fukuoka (130.4° E, 33.5° N) were collected using the atmospheric environmental regional observation system provided by the Ministry of the Environment Government of Japan [17], and the 24-h daily averages were calculated.

2.7. Statistical Analysis

Descriptive characteristics at baseline were compared according to monitoring sites and daily cough extent. Student's *t*-test was used to examine the comparison of the means of continuous variables, and the chi-square test was used to examine the comparison of proportions of categorical variables. The Pearson correlation analysis was used to examine the correlation between daily concentrations of air pollutants, including PAH and TSP. The generalized estimating equations (GEEs) were used to examine the relationship between cough occurrence and PAH exposure [6]. GEE models for same-day (lag 0 defined as 24 h period before the health response) through 5 day lag were constructed with adjustments for potential confounders; monitoring sites, gender, age, body mass ranking, and the presence or absence of asthma. Daily concentrations of SO_2, NO_2, and $PM_{2.5}$ were further adjusted to discriminate specific effects of PAHs from other air pollutants, which have been shown to be associated with asthma exacerbation in children and adults in addition to these site- and subject-specific variables [18]. Model regression parameters were presented as the regression coefficients with 95% confidence intervals. SPSS Version 26 (IBM Corp., Tokyo, Japan) was used for all analyses. $p < 0.05$ was considered statistically significant.

3. Results and Discussion

3.1. Characteristics of Study Patients According to Monitoring Sites

Table 1 shows the study participants' characteristics by study region. The median age in Kanazawa was higher than that in Fukuoka (63.0 vs. 9.0 years). The prevalence of men in Kanazawa was smaller than that in Fukuoka (28.8% vs. 56.4%). The median height and weight in Kanazawa were additionally larger than those in Fukuoka. The proportion of overweight/obese subjects in Kanazawa was greater than that in Fukuoka (28.1% vs. 8.3%) in terms of body mass. The cough prevalence during the monitoring period in Kanazawa was higher than that in Fukuoka (8.2% vs. 0%).

Table 1. Baseline characteristics of study participants in Kanazawa and Fukuoka.

	Total (n = 98)	Kanazawa (n = 59)	Fukuoka (n = 39)	p Value
Age, years	42.0 (9.0, 66.0)	63.0 (43.0, 70.0)	9.0 (8.0, 15.0)	**<0.001**
Men, n	39 (39.8)	17 (28.8)	22 (56.4)	**0.006**
Asthma, n	60 (61.2)	21 (35.6)	39 (100)	**<0.001**
Height, cm	156.0 (135.8, 162.8)	157.0 (152.6, 163.8)	133.5 (126.9, 158.6)	**<0.001**
Weight, kg	51.4 (30.3, 62.3)	56.5 (48.4, 67.0)	30.3 (26.4, 50.9)	**<0.001**
Body mass rank (n = 93)				**0.004**
Lean	14	3	11	
Normal	57	38	19	
Overweight/obese	22	16	6	
Cough prevalence, %	1.8 (0.0, 37.7)	8.2 (0.0, 68.5)	0.0 (0.0, 6.6)	**0.002**

Data are expressed as median (interquartile range) or n (percentage), as appropriate. The p values of <0.05 are highlighted in bold.

3.2. Characteristics of Study Patients According to the Cough Prevalence

Table 2 shows the study participants' characteristics by cough frequency during the monitoring period. The median age in the group with frequent cough was higher than in those with less cough (56.0 vs. 16.0 years). BA prevalence in the frequent cough group was smaller than that in the less cough group (48.8% vs. 70.9%). These findings are consistent with the previous studies. A worldwide survey has shown that the most common age for the presentation was 60–69 years [19]. A Finnish adult community-based study has additionally reported that the mean age in subjects with chronic cough was 50.5 years and that age was a risk factor for chronic cough [20]. Other underlying diseases, including AC, SBS, and gastroesophageal reflux disease besides CVA, are common causes in adults, especially in Japanese [12,21–23], while BA/CVA has been reported to be the most common cause in children with regard to the etiology of chronic cough [24]. There might be a higher cough response condition in middle-aged individuals with chronic cough compared to children and young adults with allergic asthma even under usual care taken together with a recent review [25], which has described that one of the clinical characteristics of adult-onset airway diseases is treatment resistance, compared with childhood-onset conditions.

Table 2. Baseline characteristics of study participants according to the cough prevalence.

	Less Cough (n = 55)	Frequent Cough (n = 43)	p Value
Age, years	16.0 (9.0, 63.0)	56.0 (15.0, 70.0)	**0.018**
Men, n	25 (45.5)	14 (32.6)	0.196
Asthma, n	39 (70.9)	21 (48.8)	**0.026**
Height, cm	153.8 (130.2, 162.6)	157.0 (150.2, 163.0)	0.147
Weight, kg	48.0 (29.0, 60.5)	53.0 (46.5, 62.5)	0.127
Body mass rank (n = 93)			0.504
Lean	9	5	
Normal	28	29	
Overweight/obese	13	9	
Cough prevalence, %	0.0 (0.0, 0.0)	50.0 (13.1, 87.0)	**<0.001**

Data are expressed as median (interquartile range) or n (percentage), as appropriate. The p values of <0.05 are highlighted in bold.

No differences in gender or body mass rank distribution were found between the two groups. While chronic cough has been known to be more prevalent in women than in men worldwide, this gender effect is suggested to be modulated by environmental and social influences, resulting in mixed results with regional differences [1]. As for body mass, obesity is a known risk factor for chronic cough and asthma [1,4], but some modifications due to environmental and social influences might attenuate the differences among study participants in the two Japanese regions.

3.3. Daily Ambient Air Pollutant Concentrations in Kanazawa and Fukuoka

Figure 1 shows the daily mean ambient PAH and TSP concentrations at Kanazawa and Fukuoka, Japan, in the examined period. Patterns of the PAH and TSP concentrations course were different between the two sites during the study period. As shown in Table 3, the mean total PAH concentrations over the 2-month period were lower in Kanazawa compared to those in Fukuoka (0.26 ± 0.15 vs. 0.52 ± 0.34 ng/m^3). Similar results were observed for the nine individual PAHs. Mean TSP concentrations were higher in Kanazawa than those in Fukuoka (23.0 ± 12.4 vs. 15.9 ± 7.5 μg/m^3). Pearson's correlation matrix of air pollutants during the study period in Kanazawa and Fukuoka is shown in Tables S1 and S2, respectively. Daily total PAH concentrations were associated with TSP concentration both in Kanazawa (r = 0.564, $p < 0.001$) and Fukuoka (r = 0.366, $p = 0.004$), which were similar to the findings in the non-Asian dust period, as previously reported [16]. The monthly mean $PM_{2.5}$ concentration in Kanazawa was lower than that in Fukuoka (6.6 ± 3.7 vs. 12.4 ± 4.2 μg/m^3), contrary to the TSP levels. Atmospheric PM and PAH concentrations in Kanazawa are known to show seasonal variations. The period covered by this study is spring, which is the season when PM concentrations are greatest, and PAH concentrations are second highest after winter [26]. Furthermore, Hayakawa and his colleagues have calculated the contributions of vehicles and coal combustion and the effects of long-range transport from China on atmospheric pollutants in Kanazawa using the 1-nitropyrene-pyrene method. They have reported that the average annual contributions of coal heating facilities and vehicles to combustion-derived particulates in the $PM_{2.5}$ (Pc) were 69% and 31%, respectively, and that high concentrations of Pc and PAHs in the winter and during the Asian dust event in the spring were largely attributed to the long-range transport of emissions from coal heating facilities in China [26]. In addition, the differences in TSP and PAH concentrations between Kanazawa and Fukuoka in the study period may be due to differences in transboundary transport routes from the Asian continent to Japan in addition to the local TSP and PAH sources in each city, as reported in a previous study [16]. These results might be a part of the source responsible for respiratory diseases with chronic cough, as discussed previously [16].

Additionally, the 2-month mean NO_2 and SO_2 concentrations in Kanazawa were lower than those in Fukuoka. For both regions, the mean air pollution exposures were lower than the daily limits of Japan for $PM_{2.5}$ (35 μg/m^3), NO_2 (40 ppb), and SO_2 (40 ppb). However, regarding the annual air quality guideline values that were recommended in 2021 by the World Health Organization (WHO) ($PM_{2.5}$: 5 μg/m^3; NO_2: 10 μg/m^3), only the mean exposure to NO_2 was below the limit.

3.4. Associations between Ambient PAH and Cough

The analysis of the association between daily PAH concentrations and cough results using the GEE is shown in Table 4. After adjusting for potential confounders, including SO_2, NO_2, and $PM_{2.5}$, a positive association was found between BaA levels and cough in the lag 4 model [B: 8.407, 95% confidence interval (CI): 1.260–15.554] and lag 5 model (B: 9.406, 95% CI: 0.678–18.134) among the lag 0 to lag 5 models, and a similar trend was observed in cases of Pyr and BghiP, while total PAH and TSP levels were not associated with cough. Previous studies have found that exposure to specific PAHs, including BaA, is associated with adverse respiratory outcomes. Serum BaA levels were associated with childhood asthma biomarkers, including resistin and IgE, as well as interleukin-10 [27] in a pediatric case-control study. Urine 1-hydroxypyrene levels were associated with childhood asthma [28] in another case-control study. Furthermore, a recent case-control adult study demonstrated that 2-hydroxyfluorene, 1- and 4-hydroxyphenanthrene, and 1-hydroxypyrene concentrations were associated with a greater adult asthma exacerbation risk among 12 urinary PAHs metabolites [29]. These findings, including the present study, suggested that low-molecular-weight PAHs, including BaA, are associated with respiratory diseases with chronic cough both in children and adults.

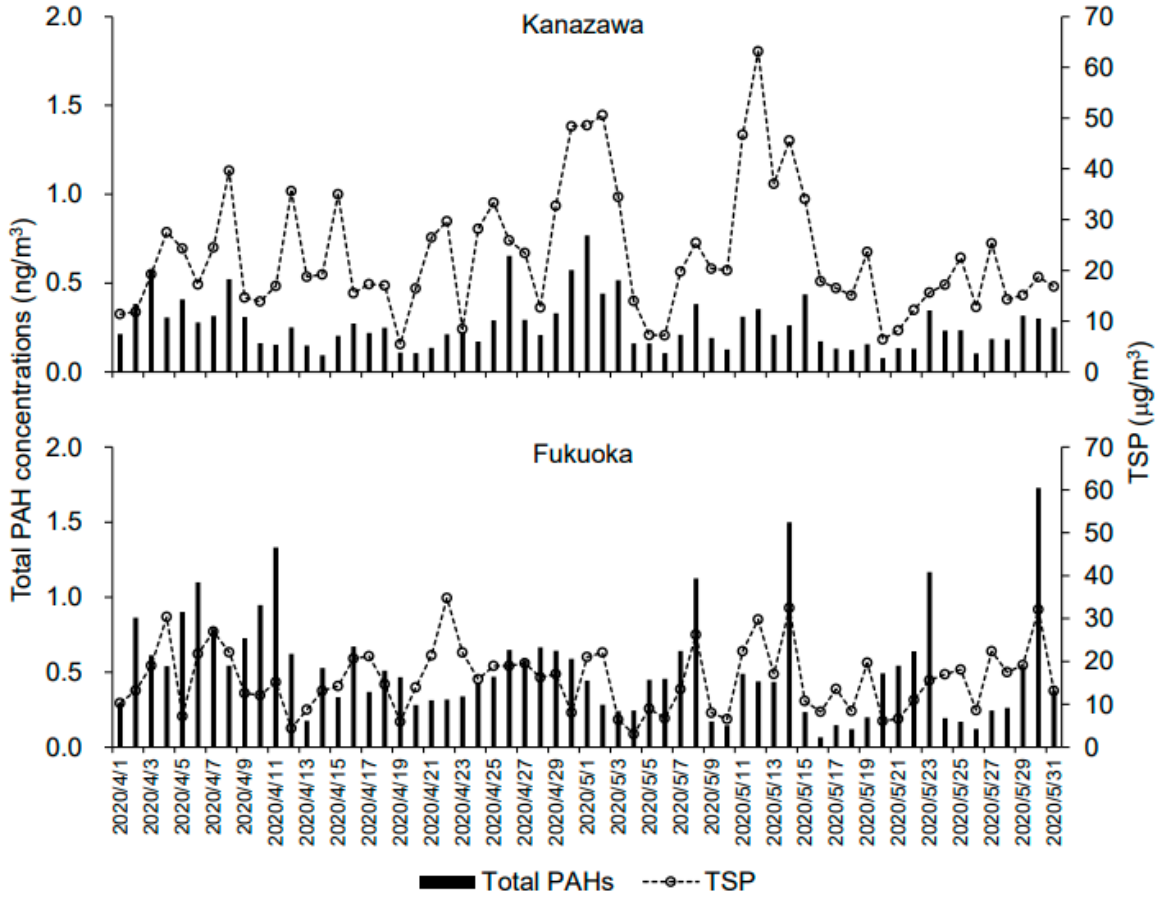

Figure 1. The course of the concentrations of total PAH and TSP in Kanazawa and Fukuoka during the study period. PAH, polycyclic aromatic hydrocarbons; TSP, total suspended particles.

Table 3. Concentrations of PAHs and other air pollutants in Kanazawa and Fukuoka between April and May 2020.

	Kanazawa		Fukuoka		*p* Value
	Mean	**SD**	**Mean**	**SD**	
Total PAHs (ng/m^3)	0.264	0.146	0.523	0.343	**<0.001**
Flt (ng/m^3)	0.053	0.037	0.100	0.084	**<0.001**
Pyr (ng/m^3)	0.046	0.025	0.082	0.056	**<0.001**
BaA (ng/m^3)	0.007	0.002	0.013	0.008	**<0.001**
Chr (ng/m^3)	0.024	0.015	0.059	0.042	**<0.001**
BbF (ng/m^3)	0.036	0.020	0.082	0.059	**<0.001**
BkF (ng/m^3)	0.012	0.007	0.026	0.019	**<0.001**
BaP (ng/m^3)	0.018	0.011	0.039	0.029	**<0.001**
BghiP (ng/m^3)	0.039	0.019	0.062	0.034	**<0.001**
IcdP (ng/m^3)	0.027	0.014	0.051	0.032	**<0.001**
TSP (μg/m^3)	23.016	12.360	15.946	7.531	**<0.001**
$PM_{2.5}$ (μg/m^3)	6.557	3.699	12.426	4.166	**<0.001**
SO_2 (ppb)	0.330	0.473	1.330	0.926	**<0.001**
NO_2 (ppb)	2.460	0.976	8.570	3.294	**<0.001**

SD, standard deviation. *p* values less than 0.05 are highlighted in bold. PAH, polycyclic aromatic hydrocarbons; Flt, fluoranthene; Pyr, pyrene; BaA, benz[*a*]anthracene; Chr, chrysene; BbF, benzo[*b*]fluoranthene; BkF, benzo[*k*]fluoranthene; BaP, benzo[*a*]pyrene; BghiP, benzo[*ghi*]perylene; IcdP, indeno[1,2,3-*cd*]pyrene; TSP, total suspended particles; $PM_{2.5}$, particulate matter with diameters 2.5 μm and smaller; SO_2, sulfur dioxide; NO_2, nitrogen dioxide.

Table 4. Adjusted estimates of cough symptoms by each PAH exposure.

Pollutants	Lag	Coefficient (B)	95% CI	*p* Value
Total PAHs	0	−0.011	−0.250, 0.228	0.929
	1	0.066	−0.166, 0.298	0.575
	2	0.083	−0.135, 0.301	0.454
	3	0.142	−0.052, 0.336	0.152
	4	0.193	−0.038, 0.424	0.101
	5	0.149	−0.076, 0.373	0.195
Flt	0	0.219	−0.776, 1.214	0.666
	1	0.481	−0.541, 1.502	0.356
	2	0.422	−0.500, 1.345	0.370
	3	0.537	−0.249, 1.323	0.180
	4	0.768	−0.226, 1.762	0.130
	5	0.446	−0.463, 1.354	0.336
Pyr	0	0.208	−1.305, 1.720	0.788
	1	0.766	−0.765, 2.297	0.327
	2	0.775	−0.619, 2.169	0.276
	3	1.054	−0.153, 2.260	0.087
	4	1.386	−0.088, 2.859	0.065
	5	1.007	−0.397, 2.411	0.160
BaA	0	−2.765	−10.015, 4.485	0.455
	1	−0.535	−11.288, 10.219	0.922
	2	3.190	−5.982, 12.362	0.495
	3	8.696	−0.554, 17.945	0.065
	4	8.407	1.260, 15.554	**0.021**
	5	9.406	0.678, 18.134	**0.035**
Chr	0	0.195	−1.836, 2.227	0.851
	1	0.656	−1.393, 2.704	0.531
	2	0.716	−1.113, 2.544	0.443
	3	0.984	−0.605, 2.573	0.225
	4	1.396	−0.570, 3.362	0.164
	5	0.640	−1.245, 2.524	0.506
BbF	0	−0.541	−1.721, 0.639	0.369
	1	−0.018	−1.187, 1.151	0.976
	2	0.315	−0.871, 1.501	0.602
	3	0.499	−0.584, 1.583	0.366
	4	0.704	−0.381, 1.788	0.203
	5	0.761	−0.415, 1.936	0.205
BkF	0	−0.646	−4.881, 3.590	0.765
	1	0.827	−3.354, 5.007	0.698
	2	1.056	−2.764, 4.875	0.588
	3	1.816	−1.629, 5.260	0.302
	4	3.123	−0.923, 7.169	0.130
	5	1.769	−2.171, 5.709	0.379
BaP	0	−1.067	−3.798, 1.663	0.444
	1	−0.056	−2.787, 2.675	0.968
	2	0.048	−2.349, 2.445	0.969
	3	0.935	−1.388, 3.257	0.430
	4	1.964	−0.642, 4.570	0.140
	5	0.743	−1.902, 3.389	0.582
BghiP	0	0.370	−2.169, 2.910	0.775
	1	0.659	−1.464, 2.782	0.543
	2	0.724	−1.553, 3.000	0.533
	3	1.539	−0.690, 3.769	0.176
	4	2.043	−0.257, 4.342	0.082
	5	2.248	−0.069, 4.565	0.057
IcdP	0	−0.841	−3.504, 1.821	0.536
	1	−0.376	−2.574, 1.821	0.737
	2	0.071	−2.086, 2.228	0.948
	3	0.909	−1.199, 3.018	0.398
	4	0.788	−1.521, 3.098	0.504
	5	1.094	−1.536, 3.724	0.415

CI, confidence interval. The *p* values of <0.05 are highlighted in bold. Adjusted for monitoring sites, sex, age, body mass ranking, asthma, and daily concentrations of $PM_{2.5}$, SO_2 and NO_2.

The present finding that the association between atmospheric BaA and cough symptoms was significant in the lag 4 and lag 5 models of GEE analysis might be important in considering the mechanisms underlying the association between PAHs, particularly BaA, and chronic cough. BaA is a carcinogenic chemical classified into Group 2A as "prob-

ably carcinogenic to humans" by the International Agency for Research on Cancer [30]; its metabolite BaA-dihiydrodiols has been reported to induce oxidative DNA damage, resulting in carcinogenesis [31]. PAHs on combustion PM and in the gas phase are known to be involved in the respiratory disease pathogenesis through three main mechanisms with regard to its relationship with respiratory diseases other than cancer; (i) induction of local pulmonary inflammation through the exposure of inflammatory and resident cells to PAHs in airways, (ii) autonomic nervous system reflexes induction by stimulating a receptor group in the autonomic nervous system in the respiratory tract, and (iii) crossing the epithelial barrier to cause responses in remote tissues and cells [3]. In addition to IgE-mediated actions, oxidative stress pathways are known to be involved in the pathogenesis and asthma exacerbation induced by PAHs: in this model, PAHs metabolites by cytochrome P450 may activate inflammatory signaling pathways and lead to transcriptional gene up-regulation involved in the regulation of immune responses, resulting in the development and exacerbation of both atopic and non-allergic asthma [4]. A previous cohort study of Japanese adults with chronic cough revealed that patients without BA were more likely to have increased cough prevalence related to ambient pollutants, including PAH, than those with BA supporting these combined mechanisms, with the largest associations observed in lag 2 and lag 02 [6]. Furthermore, the development of immune dysfunction in people with asthma has been suggested to be mediated through epigenetic remodeling [32] in addition to the transcriptional levels. Atmospheric BaA might contribute to the development and progression of airway inflammation through various pathways, which in turn leads to cough symptoms, although the detailed mechanisms by which specific PAHs cause respiratory diseases and concomitant cough symptoms are yet to be determined.

For other air pollutants used as covariates in the GEE, significant associations were observed between SO_2 levels and cough in the lag 3 model (Table S3) and between $PM_{2.5}$ levels and cough in the lag 3 and lag 4 models (Tables S3 and S4, respectively). Although it is not clear why $PM_{2.5}$ was negatively associated with cough, this finding is consistent with a previous study that reported SO_2 to be associated with cough in an analysis using the lag model in adults with chronic cough [6]. With regard to associations with characteristics of study participants, no statistically significant associations were found between age, body mass or asthma and cough symptoms (Tables S3 and S4).

4. Conclusions

This study's aim was to determine the association between airborne PAHs, a PM component, and cough symptoms in patients with chronic coughs in two regions of Japan. Airborne BaA was associated with cough symptoms exacerbation in patients with chronic cough.

Of note, this study has several limitations; first, the sample size and observational time are relatively limited compared to previous studies, and the background characteristics of participants were different between the two areas. Accordingly, it was not possible to perform a stratified analysis by age or body size. Second, indoor air pollutants were not measured. People tended to spend more time indoors and might be exposed to indoor air pollutants during the COVID-19 pandemic. Indoor air PAH sources include not only solid fuel combustion for cooking and heating as a source of indoor air PAHs but also secondhand smoke [33]. However, the indoor air pollutants' impact might be extremely small based on the environment surrounding the study subjects. Third, air pollutant concentrations in each region were regarded as the same as those measured at the central monitoring station of Kanazawa and Fukuoka City. Therefore, there is a possibility of misclassification of exposure, especially for people who live far from these monitoring sites. A higher number of sampling sites should be considered in future studies. Fourth, information on educational and socioeconomic status as risk factors for chronic cough [34] and prenatal exposure to PAH in children has not been collected.

Taken together, further studies are needed to examine the association between specific PAHs and chronic cough on a larger scale and in longer periods in order to develop effective

prevention measures in the future. This approach could lead to the optimized management of the PAHs sources and concentrations to reduce the onset and exacerbation of respiratory diseases associated with chronic cough.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/app122412505/s1. Table S1: Daily air pollutant concentrations correlation matrix for study period 1 April–31 May 2020, Kanazawa city; Table S2: Daily air pollutant concentrations correlation matrix for study period 1 April–31 May 2020, Fukuoka city; Table S3: Adjusted estimates of cough symptoms in total PAH exposure in the GEE lag 3 model; Table S4: Adjusted estimates of cough symptoms in total PAH exposure in the GEE lag 4 model.

Author Contributions: Conceptualization, H.N.; methodology, A.H. and H.N.; formal analysis, A.H., K.-O.P. and K.S.; resources, H.O., A.T., K.H. and H.N.; data curation, A.H., H.O., M.F., T.T. and N.O.; writing—original draft preparation, A.H.; writing—revising and editing, H.O., H.M., M.F., T.T., T.W., N.O., J.Z., K.-O.P., K.S., H.T., A.T., K.H. and H.N.; supervision, K.H. and H.N.; project administration, H.T., H.N.; funding acquisition, H.N. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the Environment Research and Technology Development Fund (JPMEERF20195051) of the Environmental Restoration and Conservation Agency of Japan.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Medical Ethics Committee of Kanazawa University (approval number: 1630).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Acknowledgments: The authors thank Yuko Katsuragi for her assistance with data management and Andrew E. Schneider, a native English speaker, for his English editing of the manuscript. K.-O.P. currently belongs to Data Management Department, Asia Center for Air Pollution Research, Niigata, Japan.

Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

References

1. Morice, A.; Dicpinigaitis, P.; Mcgarvey, L.; Birring, S.S. Chronic Cough: New Insights and Future Prospects. *Eur. Respir. Rev.* **2021**, *30*, 210127. [CrossRef] [PubMed]
2. Guarnieri, M.; Balmes, J.R. Outdoor Air Pollution and Asthma. *Lancet* **2014**, *383*, 1581–1592. [CrossRef]
3. Låg, M.; Øvrevik, J.; Refsnes, M.; Holme, J.A. Potential Role of Polycyclic Aromatic Hydrocarbons in Air Pollution-Induced Non-Malignant Respiratory Diseases. *Respir. Res.* **2020**, *21*, 299. [CrossRef] [PubMed]
4. Karimi, P.; Peters, K.O.; Bidad, K.; Strickland, P.T. Polycyclic Aromatic Hydrocarbons and Childhood Asthma. *Eur. J. Epidemiol.* **2015**, *30*, 91–101. [CrossRef]
5. Srogi, K. Monitoring of Environmental Exposure to Polycyclic Aromatic Hydrocarbons: A Review. *Environ. Chem. Lett.* **2007**, *5*, 169–195. [CrossRef] [PubMed]
6. Anyenda, E.O.; Higashi, T.; Kambayashi, Y.; Thi, T.; Nguyen, T.; Michigami, Y.; Fujimura, M.; Hara, J.; Tsujiguchi, H.; Kitaoka, M.; et al. Associations of Cough Prevalence with Ambient Polycyclic Aromatic Hydrocarbons, Nitrogen and Sulphur Dioxide: A Longitudinal Study. *Int. J. Environ. Res. Public Health* **2016**, *13*, 800. [CrossRef] [PubMed]
7. Anyenda, E.O.; Higashi, T.; Kambayashi, Y.; Thao, N.T.T.; Michigami, Y.; Fujimura, M.; Hara, J.; Tsujiguchi, H.; Kitaoka, M.; Asakura, H.; et al. Exposure to Daily Ambient Particulate Polycyclic Aromatic Hydrocarbons and Cough Occurrence in Adult Chronic Cough Patients: A Longitudinal Study. *Atmos. Environ.* **2016**, *140*, 34–41. [CrossRef]
8. Shiue, I. Urinary Polyaromatic Hydrocarbons Are Associated with Adult Emphysema, Chronic Bronchitis, Asthma, and Infections: US NHANES, 2011–2012. *Environ. Sci. Pollut. Res* **2016**, *23*, 25494–25500. [CrossRef]
9. Rodríguez-Aguilar, M.; Díaz De León-Martínez, L.; García-Luna, S.; Gómez-Gómez, A.; Karen González-Palomo, A.; Javier Pérez-Vázquez, F.; Díaz-Barriga, F.; Trujillo, J.; Flores-Ramírez, R. Respiratory Health Assessment and Exposure to Polycyclic Aromatic Hydrocarbons in Mexican Indigenous Population. *Environ. Sci. Pollut. Res.* **2019**, *26*, 25825–25833. [CrossRef]

10. Padula, A.M.; Balmes, J.R.; Eisen, E.A.; Mann, J.; Noth, E.M.; Lurmann, F.W.; Pratt, B.; Tager, I.B.; Nadeau, K.; Hammond, S.K. Ambient Polycyclic Aromatic Hydrocarbons and Pulmonary Function in Children HHS Public Access. *J. Expo Sci. Environ. Epidemiol.* **2015**, *25*, 295–302. [CrossRef]
11. Ichinose, M.; Sugiura, H.; Nagase, H.; Yamaguchi, M.; Inoue, H.; Sagara, H.; Tamaoki, J.; Tohda, Y.; Munakata, M.; Yamauchi, K.; et al. Japanese Guidelines for Adult Asthma 2017. *Allergol. Int.* **2017**, *66*, 163–189. [CrossRef] [PubMed]
12. Fujimura, M.; Abo, M.; Ogawa, H.; Nishi, K.; Kibe, Y.; Hirose, T.; Nakatsumi, Y.; Iwasa, K. Importance of atopic cough, cough variant asthma and sinobronchial syndrome as causes of chronic cough in the Hokuriku area of Japan. *Respirology* **2005**, *10*, 201–207. [CrossRef] [PubMed]
13. Matsuzawa, Y.; Nakamura, T.; Takahashi, M.; Ryo, M.; Inoue, S.; Ikeda, Y.; Ohno, M.; Sakata, T.; Fukagawa, K.; Saitoh, Y.; et al. New Criteria for "obesity Disease" in Japan. *Circ. J.* **2002**, *66*, 987–992. [CrossRef]
14. Kuroiwa, M.; Sayuri, H.F.; Shiho, A.; Kime, R.; Endo, T.; Tanaka, R.; Kurosawa, Y.; Hamaoka, T. Impact of Brown Adipose Tissue Vascular Density on Body Adiposity in Healthy Japanese Infants and Children. *Obes. Sci. Pract.* **2021**, *8*, 190–198. [CrossRef] [PubMed]
15. Kimura, M.; Ikeda, A.; Suzuki, Y.; Maruyama, K.; Wada, H.; Tanigawa, T. The Association between Asthma and Anxiety in Elementary School Students in Japan. *Pediatr. Pulmonol.* **2020**, *55*, 2603–2609. [CrossRef]
16. Pham, K.-O.; Hara, A.; Zhao, J.; Suzuki, K.; Matsuki, A.; Inomata, Y.; Matsuzaki, H.; Odajima, H.; Hayakawa, K.; Nakamura, H. Different Transport Behaviors between Asian Dust and Polycyclic Aromatic Hydrocarbons in Urban Areas: Monitoring in Fukuoka and Kanazawa, Japan. *Appl. Sci.* **2022**, *12*, 5404. [CrossRef]
17. Wide-Area Monitoring System for Air Pollutants by Ministry of the Environment (Soramamekun). Available online: https://soramame.env.go.jp/ (accessed on 29 September 2022).
18. Orellano, P.; Quaranta, N.; Reynoso, J.; Balbi, B.; Vasquez, J. Effect of Outdoor Air Pollution on Asthma Exacerbations in Children and Adults: Systematic Review and Multilevel Meta-Analysis. *PLoS ONE* **2017**, *12*, e0174050. [CrossRef]
19. Morice, A.H.; Jakes, A.D.; Faruqi, S.; Birring, S.S.; Mcgarvey, L.; Canning, B.; Smith, J.A.; Parker, S.M.; Chung, K.F.; Lai, K.; et al. Worldwide Survey of Chronic Cough: A Manifestation of Enhanced Somatosensory Response. *Eur. Respir. J.* **2014**, *44*, 1149–1155. [CrossRef]
20. Lätti, A.M.; Pekkanen, J.; Koskela, H.O. Defining the Risk Factors for Acute, Subacute and Chronic Cough: A Cross-Sectional Study in a Finnish Adult Employee Population. *BMJ Open* **2018**, *8*, 1–6. [CrossRef]
21. Yamasaki, A.; Hanaki, K.; Tomita, K.; Watanabe, M.; Hasagawa, Y.; Okazaki, R.; Yamamura, M.; Fukutani, K.; Sugimoto, Y.; Kato, K.; et al. Cough and Asthma Diagnosis: Physicians' Diagnosis and Treatment of Patients Complaining of Acute, Subacute and Chronic Cough in Rural Areas of Japan. *Int. J. Gen. Med.* **2010**, *3*, 101–107. [CrossRef]
22. Niimi, A. Geography and Cough Aetiology. *Pulm. Pharmacol. Ther.* **2007**, *20*, 383–387. [CrossRef] [PubMed]
23. Watanabe, K.; Shinkai, M.; Shinoda, M.; Hara, Y.; Yamaguchi, N.; Rubin, B.K.; Ishigatsubo, Y.; Kaneko, T. Measurement of ENO with Portable Analyser Might Improve the Management of Persistent Cough at Primary Care Practice in Japan. *Clin. Respir. J.* **2016**, *10*, 380–388. [CrossRef] [PubMed]
24. Holinger, L.D.; Sanders, A.D. Chronic Cough in Infants and Children: An Update. *Laryngoscope* **1991**, *101*, 596–605. [CrossRef] [PubMed]
25. Asano, K.; Ueki, S.; Tamari, M.; Imoto, Y.; Fujieda, S.; Taniguchi, M. Adult-Onset Eosinophilic Airway Diseases. *Allergy Eur. J. Allergy Clin. Immunol.* **2020**, *75*, 3087–3099. [CrossRef]
26. Hayakawa, K.; Tang, N.; Xing, W.; Oanh, P.K.; Hara, A.; Nakamura, H. Concentrations and Sources of Atmospheric PM, Polycyclic Aromatic Hydrocarbons and Nitropolycyclic Aromatic Hydrocarbons in Kanazawa, Japan. *Atmosphere* **2021**, *12*, 256. [CrossRef]
27. Al-Daghri, N.M.; Alokail, M.S.; Abd-Alrahman, S.H.; Draz, H.M.; Yakout, S.M.; Clerici, M. Polycyclic Aromatic Hydrocarbon Exposure and Pediatric Asthma in Children: A Case-Control Study. *Environ. Health A Glob. Access Sci. Source* **2013**, *12*, 2–7. [CrossRef]
28. Wang, I.J.; Karmaus, W.J.J.; Yang, C.C. Polycyclic Aromatic Hydrocarbons Exposure, Oxidative Stress, and Asthma in Children. *Int. Arch. Occup. Environ. Health* **2017**, *90*, 297–303. [CrossRef]
29. Huang, X.; Zhou, Y.; Cui, X.; Wu, X.; Yuan, J.; Xie, J.; Chen, W. Urinary Polycyclic Aromatic Hydrocarbon Metabolites and Adult Asthma: A Case-Control Study. *Sci. Rep.* **2018**, *8*, 1–8. [CrossRef]
30. Smith, C.J.; Perfetti, T.A.; Rumple, M.A.; Rodgman, A.; Doolittle, D.J. "IARC Group 2A Carcinogens" Reported in Cigarette Mainstream Smoke. *Food Chem. Toxicol.* **2001**, *39*, 183–205. [CrossRef]
31. Seike, K.; Murata, M.; Hirakawa, K.; Deyashiki, Y.; Kawanishi, S. Oxidative DNA Damage Induced by Benz[a]Anthracene Dihydrodiols in the Presence of Dihydrodiol Dehydrogenase. *Chem. Res. Toxicol.* **2004**, *17*, 1445–1451. [CrossRef]
32. Klingbeil, E.C.; Hew, K.M.; Nygaard, U.C.; Nadeau, K.C. Polycyclic Aromatic Hydrocarbons, Tobacco Smoke, and Epigenetic Remodeling in Asthma. *Immunol. Res.* **2014**, *58*, 369–373. [CrossRef] [PubMed]
33. Matsui, E.C.; Hansel, N.N.; Mc Cormack, M.C.; Rusher, R.; Breysse, P.N.; Diette, G.B. Asthma in the Inner City and the Indoor Environment. *Immunol. Allergy Clin. N. Am.* **2008**, *28*, 665–686. [CrossRef] [PubMed]
34. Zhang, J.; Perret, J.L.; Chang, A.B.; Idrose, N.S.; Bui, D.S.; Lowe, A.J.; Abramson, M.J.; Haydn Walters, E.; Lodge, C.J.; Dharmage, S.C.; et al. Risk Factors for Chronic Cough in Adults: A Systematic Review and Meta-Analysis. *Respirology* **2022**, *27*, 36–47. [CrossRef] [PubMed]