

Epidemiological study of PM_{2.5} and risk of COPD-related hospital visits in association with particle constituents in Chuncheon, Korea

Yong Suk Jo¹
Myoung Nam Lim²
Young-Ji Han³
Woo Jin Kim⁴

¹Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Kyung Hee University Medical Center, Seoul,

²Data Analysis Center, ³Department of Environmental Science, Kangwon National University, ⁴Department of Internal Medicine and Environmental Health Center, Kangwon National University Hospital, Kangwon National University School of Medicine, Chuncheon, Gangwon-do, Korea

Background and objective: Aside from smoking, which is already recognized as a strong risk factor for COPD, interest in the impact of particulate matter (PM) on COPD is increasing. This study aimed to investigate the effect of PM, especially with an aerodynamic diameter $\leq 2.5 \mu\text{m}$ (PM_{2.5}), and its chemical constituents on the exacerbation of COPD.

Methods: Data on hospital visits including admission and outpatient clinic visits for exacerbation of COPD in Chuncheon, Korea, between 2006 and 2012 were extracted from the National Health Insurance Service database. PM_{2.5} and its chemical constituents were measured on the roof of the four-story Kangwon National University Natural Sciences building once every 3 days. Meteorological data were provided by the Korean Meteorological Administration.

Results: During the study period, the mean level of PM_{2.5} was $35.0 \pm 25.2 \mu\text{g}/\text{m}^3$, and the number of daily hospital visits were 6.42 ± 4.28 and 2.07 ± 1.93 for males and females, respectively. The number of COPD-related hospital visits increased with increasing PM_{2.5} after adjusting for meteorological covariates and females tended to be more affected sooner than males. Among the PM_{2.5} constituents, Al, Si, and elemental carbon were associated with increased hospital visits and there was a difference according to sex. In males, some constituents of PM_{2.5} were related to an increased risk of a hospital visit, mainly on the first and second days of measurement (Lag1 and Lag2). In contrast, there was no significant increase in the risk of hospital visits due to any of the PM_{2.5} constituents in females.

Conclusion: Concentrations of PM_{2.5} mass and some of the PM_{2.5} constituents were associated with increased COPD-related hospital visits in Chuncheon.

Keywords: COPD, PM_{2.5}, constituents, hospital visit

Introduction

COPD is a leading cause of morbidity and mortality worldwide, and its prevalence is increasing.¹ It is characterized by progressive irreversible airflow limitation related to chronic airway inflammation.² It is currently ranked the fourth most common cause of death in the United States, and is expected to become the third most common cause by 2020.¹ Most patients with COPD experience exacerbation of respiratory symptoms and frequent hospitalization, resulting in enormous economic costs and debilitating conditions. Unfortunately, a clear pathogenesis of COPD has not been identified, and thus, it is important to identify and prevent risk factors associated with deterioration of the clinical course.

Like other systemic diseases, the development and progression of COPD is multifactorial. Smoking has been regarded as the most important risk factor for the development of COPD,^{3,4} but never-smoker COPD is reported at ~25%–45%.^{3,5,6}

Correspondence: Woo Jin Kim
Department of Internal Medicine and Environmental Health Center, Kangwon National University Hospital, Kangwon National University School of Medicine, 1 Kangwondaehak-gil, Chuncheon, Gangwon-do, 24341, Korea
Tel +82 32 258 9364
Fax +82 32 258 2404
Email pulmo2@kangwon.ac.kr

Several epidemiologic cross-sectional studies reported that elevated air pollution might be associated with the development and acute exacerbation of COPD, hospitalization, and even mortality in patients with COPD.⁷⁻¹²

Particulate matter (PM) is a complex mixture of small solid particles and liquid droplets in the air. PM with aerodynamic diameters $\leq 10 \mu\text{m}$ (PM_{10}) has been reported to be associated with increased hospitalization, emergency department visits, and mortality.¹²⁻¹⁴ Furthermore, PM with aerodynamic diameters $\leq 2.5 \mu\text{m}$ ($\text{PM}_{2.5}$) may be more directly involved as these fine particles can penetrate more deeply to approach the small airways and exert greater toxicity than PM_{10} .^{8,10,15}

According to a report recently released by the Health Effects Institute in the United States, Korea's average annual $\text{PM}_{2.5}$ concentration was $26 \mu\text{g}/\text{m}^3$ in 1990, but increased to $29 \mu\text{g}/\text{m}^3$ after 2015.¹⁶ Over the same 25 years from 1990 to 2015, the average $\text{PM}_{2.5}$ concentration in member countries of the Organisation for Economic Co-operation and Development (OECD) has dropped to $15 \mu\text{g}/\text{m}^3$, whereas in Korea, it has risen to the worst level among OECD members excluding Turkey. In Korea, $\text{PM}_{2.5}$ -related research has been increasing since the recent release of information on $\text{PM}_{2.5}$. However, most studies have been conducted in urban areas because air pollution mainly resulting from traffic and industrial processes are relatively more troublesome in urban than in rural areas.

In this study, we aimed to evaluate the association between $\text{PM}_{2.5}$ concentration and COPD-related hospital visits and to identify the influence of $\text{PM}_{2.5}$ components.

Methods

COPD-related hospital admission data

COPD-related health care use including hospital visits and admissions from Korean National Health Insurance Service (KNHIS) data have been reported.¹⁷

Data on COPD-related health care use in Chuncheon, Gangwon-do, between January 1, 2006 and December 31, 2012, were used. The KNHIS has managed a computerized database for all medical facilities since its implementation in 1998 and provides a unique and helpful approach for evaluating the nationwide magnitude of various diseases and related health care use. Medical institutions must report standard computerized claim documents for medical expenses and diagnostic codes for each admission based on the International Classification of Disease 10th (ICD-10) revision. We obtained information on the daily number of hospital visits for COPD according to the ICD-10 codes J44.x. All the KNHIS data used in this study were anonymous

and did not contain any personally identifiable information, therefore no patient consent was needed.

Air pollution and meteorological information

Daily levels of $\text{PM}_{2.5}$ were measured on the roof of the four-story Kangwon National University Natural Sciences building in Chuncheon once every 3 days from 2006 to 2012. To measure $\text{PM}_{2.5}$ mass and metallic components, a 37 mm Teflon filter was used. Carbonaceous compounds were collected on a quartz filter at a flow rate of 16.7 L/min. Ionic components of $\text{PM}_{2.5}$ were collected using a three-stage Teflon filter pack after ionic gases (SO_2 , HNO_3 , HNO_2 , and NH_3) were removed by denuders to prevent both positive and negative artifacts. All ionic components were first collected on a Zefluor filter, and HNO_3 and NH_3 volatilized from the Zefluor filter were collected on a nylon filter and paper filter soaked in 1% citric acid, respectively.

For $\text{PM}_{2.5}$ mass monitoring, the Teflon filter was stored in temperature- and humidity-controlled conditions for at least 24 hours before and after sampling and then passed through a static electric eliminator (2U500) before being weighed at least twice using an analytical balance. Metallic elements and ionic compounds were analyzed using energy-dispersive X-ray fluorescence (Spectro X-Lab Pro, Kleve, Germany) and ion chromatography (Waters Corporation, Milford, MA, USA), respectively. Carbonaceous compounds including elemental carbon (EC) and organic carbon were analyzed using National Institute for Occupational Safety and Health method 5040.¹⁸ Detailed sampling and analysis methods can be found in previous studies.¹⁹⁻²²

Meteorological data including temperature, humidity, and precipitation were obtained from the Korean Meteorological Administration. Meteorological data and hospital visits were matched to the dates of $\text{PM}_{2.5}$ measurement.

Statistical analysis

Descriptive data are presented as the mean \pm standard deviation, minimum, lower quartile, median, upper quartile, and maximum. The response variable was the frequency of COPD-related hospital visits. Hospital visits occurred sporadically and followed an irregular distribution consisting of various numbers starting with zero. The majority of subjects did not visit a hospital, which may lead to underestimation of the impact of air pollutants on COPD-related hospital visits. Therefore, we applied a zero-inflated Poisson model, which is suitable for rare events with variable lengths of time followed.

The PM_{2.5} constituents-specific risk of hospital visits was analyzed by a Poisson model and expressed as relative risk (RR) with 95% confidence interval (CI). The relationship of PM_{2.5} and its constituents with COPD-related hospital visits was adjusted for covariates including temperature, humidity, precipitation, season, day of the week, and holiday status. Environmental effects may be delayed over a period of several days, and thus, we considered the lagged effects of the day of the event and up to 5 days (from Lag0 to Lag5). All analyses were two-sided and performed at a significance level of 0.05 unless otherwise noted. $P < 0.05$ was considered statistically significant. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

This study was approved by the Institutional Review Board of Kangwon National University Hospital (IRB No 2013-12-011).

Results

Meteorological information

For the period of 6 years from 2006 to 2012, the mean PM_{2.5} concentration was $35.0 \pm 25.16 \mu\text{g}/\text{m}^3$ (range $1.46\text{--}146.99 \mu\text{g}/\text{m}^3$) and mean temperature and humidity were $11.36^\circ\text{C} \pm 9.47^\circ\text{C}$ (range -8.99°C to 28.33°C) and $70.92\% \pm 12.81\%$ (range $38.38\% \text{--} 94.54\%$), respectively.

There are four distinct seasons in Korea: spring (March through May), summer (June through August), fall (September through November), and winter (December through February). The PM_{2.5} level showed an obvious seasonal variation, with a lower level in summer ($19.42 \pm 1.39 \mu\text{g}/\text{m}^3$) and higher level in winter ($42.71 \pm 2.08 \mu\text{g}/\text{m}^3$). Within a 12-month period, the PM_{2.5} concentration was the highest in December ($48.23 \pm 3.28 \mu\text{g}/\text{m}^3$) and lowest in August ($13.43 \pm 1.48 \mu\text{g}/\text{m}^3$).

Risk of hospital visit for COPD according to PM_{2.5} concentration

The mean numbers of hospital visits for COPD-related respiratory difficulty are presented in Table 1. Hospital visits including both admissions and outpatient clinic visits were more prevalent for males than for females. Mean hospital admission and outpatient clinic visit rates expressed by number per day for COPD were 0.21 ± 0.43 and 8.25 ± 5.36 for males and 0.04 ± 0.19 and 6.21 ± 4.23 for females, respectively.

The risk of a COPD-related hospital visit including admissions and outpatient clinic visits according to PM_{2.5} concentration is presented in Table 2. For every $10 \mu\text{g}/\text{m}^3$ increase in PM_{2.5} concentration, total hospital visits increased by 0.26% on Lag2 and Lag3 and by 0.25% on Lag4. When divided by

Table 1 Descriptive statistics of hospital visits in Chuncheon, Korea, from 2006 to 2012

N/day	Mean \pm SD	Min	Percentiles					Max
			5th	25th	50th	75th	95th	
Total	8.49 \pm 5.42	1.00	1.00	5.00	8.00	11.00	18.00	36.00
Male	6.42 \pm 4.28	0.00	1.00	3.00	6.00	9.00	15.00	23.00
Female	2.07 \pm 1.93	0.00	0.00	1.00	2.00	3.00	5.00	14.00
Admission	0.24 \pm 0.48	0.00	0.00	0.00	0.00	0.00	1.00	2.00
Male	0.21 \pm 0.43	0.00	0.00	0.00	0.00	0.00	1.00	2.00
Female	0.04 \pm 0.19	0.00	0.00	0.00	0.00	0.00	0.00	1.00
Outpatient visit	8.25 \pm 5.36	0.00	1.00	4.00	8.00	11.00	18.00	35.00
Male	6.21 \pm 4.23	0.00	1.00	3.00	6.00	8.00	14.00	23.00
Female	2.04 \pm 1.91	0.00	0.00	1.00	2.00	3.00	5.00	14.00

sex, total hospital visits by males significantly increased by 0.32% and 0.25% on Lag3 and Lag4 but increased by 0.40% and 0.58% on Lag1 and Lag2. Hospital admissions were not affected by an increase in PM_{2.5} concentration, but the risk of an outpatient visit increased as the PM_{2.5} concentration increased, similar to total hospital visits.

Risk of hospital visit for COPD according to PM_{2.5} constituents

The relationship between PM_{2.5} constituents and the risk of COPD-related hospital visits is shown in Table 3. Among the constituents, Al and Si increased COPD-related hospital visits on Lag1 (RR, 1.0; 95% CI, 1.00–1.00, for both) and EC did so on Lag2 (RR, 1.14; 95% CI, 1.02–1.28). The influence of constituents on hospital visits analyzed according to sex is shown in Table 4. In males, Mg, Al, Si, Ti, As, Br, and EC were related to high risk for hospital visits in COPD patients, and especially, As was found to have a greater effect than other constituents (RR, 2.39; 95% CI, 1.00–5.69). However, no significantly associated constituents were found for females.

Discussion

We observed that COPD-related hospital visits including outpatient clinic visits and admissions increased as the PM_{2.5} concentration increased and that some constituents of PM_{2.5} were related to an increased risk of hospital visits in Chuncheon, Korea. Our results demonstrated sex-specific effects on association between exposure to air pollutants and the risk of a hospital visit; females visited the hospital sooner than males and the risk of a hospital visit increased considerably more in females than in males. In our study, 79.9% of males and 96.5% of females did not visit a hospital for aggravation of COPD. This is consistent with the expectation

Table 2 Percentage increase in hospital visits and 95% CI as PM_{2.5} increases 10 µg/m³

	Lag1		Lag2		Lag3		Lag4		Lag5	
	% increase	95% CI								
Total	0.11	-0.07, 0.30	0.26*	0.06, 0.46	0.26*	0.04, 0.44	0.25*	0.05, 0.44	0.10	-0.08, 0.28
Male	0.02	-0.20, 0.23	0.15	-0.07, 0.38	0.32*	0.10, 0.53	0.25*	0.02, 0.48	0.07	-0.14, 0.28
Female	0.40*	0.01, 0.78	0.58*	0.17, 0.99	0.09	-0.27, 0.44	0.25	-0.14, 0.63	0.17	-0.19, 0.53
Admission	0.17	-0.89, 1.23	0.51	-0.72, 1.72	0.99	-0.33, 2.29	0.36	-0.86, 1.57	-0.68	-1.78, 0.41
Male	0.19	-0.90, 1.29	0.77	-0.70, 2.22	0.83	-0.59, 2.24	0.93	-0.72, 2.56	0.99	-0.19, 2.19
Female	0.40	-0.01, 0.81	0.11	-0.21, 0.42	0.02	-0.45, 0.50	0.05	-0.22, 0.32	0.08	-0.23, 0.40
Outpatient visit	0.11	-0.07, 0.30	0.25	-0.05, 0.45	0.24*	0.06, 0.43	0.25*	0.05, 0.45	0.12	-1.66, 1.88
Male	0.28	-1.89, 2.41	0.13	-0.09, 0.36	0.30*	0.08, 0.52	0.24	-0.01, 0.47	0.10	-0.11, 0.32
Female	0.36	-0.03, 0.74	0.62*	0.20, 1.03	0.44	-0.38, 1.10	0.28	-0.12, 0.67	0.17	-0.20, 0.53

Notes: * $P \leq 0.05$, which represents statistically significant changes as time progressed. Environmental effects may be delayed over a period of several days, and thus, we considered the lagged effects of the day of the event and up to 5 days (from Lag0 to Lag5).

Abbreviations: CI, confidence interval; PM_{2.5}, particulate matter with aerodynamic diameters ≤ 2.5 µm.

that admission due to deterioration of COPD is a rare event, which might result in underestimation of the impact of PM_{2.5} and its constituents on the risk of exacerbation.

PM, a major component of air pollution, consists of solid and liquid particles that float around in air.²³ Although PM₁₀ is usually trapped in the upper airway, PM_{2.5} could approach the terminal bronchiole and alveolar space, and water-soluble pollutants might penetrate alveolar capillaries and then enter the systemic circulation.²⁴ In this process, inflammatory signals become active and several inflammatory cytokines are released and even pollutants themselves might cause oxidative stress,^{25,26} which contributes to the development and exacerbation of chronic respiratory diseases.²⁷

The influence of PM levels on respiratory disease has been reported in several studies, and focused on PM_{2.5}; there are epidemiologic data regarding the harmful impact of PM_{2.5} on the higher prevalence,²⁸ increase of exacerbation and emergency room visits,²⁹ and mortality of COPD.³⁰ As the interest in fine dust increases, PM-related studies are on the rise, especially in East Asia, and in China in particular.^{8,28} In Korea, information about PM_{2.5} was released in 2014, and thus, there have been several recent studies related to this. Most of the previous studies were performed in big urban city areas where the sources of PM, including traffic, industry, biomass, and long-range transport, are abundant.^{14,31} However, Chuncheon is a relatively small city comprising <1% of the population in Korea with 0.28 million inhabitants living mostly in rural areas outside the central district. Because there are no industrial complexes and there is not much traffic, the amount of pollution generated in the area itself is expected to be low, but because Chuncheon is located northeast from Seoul, the capital of Korea, drifting of dust from metropolitan areas over to Chuncheon with westerly winds may be possible.

Furthermore, because the city is surrounded by mountains, dust cannot efflux to different locations easily. The World Health Organization defined the daily limit of exposure for PM_{2.5} and PM₁₀ as 25 and 50 µg/m³, respectively.³² Considering that the expected amount of dust created in Chuncheon is low, meteorological and geographical factors might explain the high concentration of dust in Chuncheon. Furthermore, a recent study from a rural area of England showed that in a pattern similar to an urban city area, increases in CO and nitrogen oxides concentrations are related to a higher risk of hospital admission for exacerbation of COPD.³³

After adjustment for meteorological factors that could influence variation of respiratory symptoms, including humidity, temperature, precipitation, and season, we found that PM_{2.5} and some constituents are meaningfully associated with an increment in hospital visits in patients with COPD. However, because the number of hospital admissions during the study period was too low, we found no significant effect of PM_{2.5} on the risk of hospital admission.

Li et al³⁴ reported an association between PM and its constituents and health-related outcomes and showed K⁺, Ca²⁺, NO³⁻, and SO₄²⁻ were associated with increased mortality in a 5 year study in Beijing. Son et al³⁵ estimated the effects of PM_{2.5} and its chemical components on mortality in Seoul and found that Mg, NO₃, SO₄, and chlorine exhibited significant associations with mortality. In the present study, some constituents including Al, Si, and EC were related to an increased risk of COPD-related hospital visits; especially, the influence of EC was marked at Lag2. The results of this study are meaningful both clinically and ecologically since the effect of each constituent of PM_{2.5} on COPD-related prognosis was significant. Although COPD is influenced by multiple environmental factors,³⁶ control of PM_{2.5} emission will

Table 3 Percentage increase in COPD-related hospital visits and 95% CI in all participants as each particle constituent increased 10 µg/m³

	Lag1		Lag2		Lag3		Lag4		Lag5	
	% increase	95% CI	% increase	95% CI	% increase	95% CI	% increase	95% CI	% increase	95% CI
Na	-0.024	-0.086, 0.037	-0.022	-0.128, 0.085	-0.005	-0.077, 0.068	-0.029	-0.085, 0.027	0.072	-0.091, 0.234
Mg	0.044	-0.006, 0.094	0.100	-0.372, 0.572	0.366	-0.455, 1.188	-0.300	-0.610, 0.010	0.679	-1.371, 2.730
Al	0.016*	0.000, 0.031	0.065	-0.055, 0.185	0.028	-0.066, 0.121	-0.108	-0.220, 0.005	-0.066	-0.253, 0.120
Si	0.007*	0.000, 0.014	0.031	-0.020, 0.082	0.014	-0.024, 0.052	-0.053	-0.107, 0.000	-0.033	-0.119, 0.053
Cl	-0.034	-0.162, 0.094	0.009	-0.138, 0.156	-0.058	-0.231, 0.113	-0.059	-0.199, 0.080	-0.056	-0.280, 0.167
K	0.017	-0.027, 0.061	0.038	-0.040, 0.115	0.027	-0.046, 0.100	-0.080	-0.153, 0.007	-0.054	-0.202, 0.095
Ca	0.021	-0.001, 0.043	0.073	-0.126, 0.272	0.041	-0.154, 0.236	-0.164	-0.339, 0.010	-0.134	-0.461, 0.193
Ti	0.242	-0.008, 0.493	0.729	-0.443, 1.900	0.396	-0.529, 1.320	-1.546	-2.964, -0.127	-0.988	-3.370, 1.394
V	3.370	-1.184, 7.925	-1.994	-8.585, 4.594	-4.433	-11.317, 2.451	4.309	-3.170, 11.788	-1.129	-10.709, 8.451
Cr	2.113	-1.997, 4.229	2.278	-1.846, 4.711	3.212	-3.023, 5.401	0.717	-0.908, 2.342	1.546	-1.366, 4.458
Mn	0.706	-0.150, 1.563	0.571	-1.681, 2.823	-0.143	-1.959, 1.674	-0.745	-2.585, 1.095	-0.535	-3.016, 1.946
Fe	0.023	-0.001, 0.048	0.050	-0.074, 0.174	0.008	-0.084, 0.101	-0.064	-0.165, 0.036	-0.043	-0.188, 0.101
Ni	-4.014	-7.642, -0.384	-1.827	-6.302, 2.647	-1.834	-5.771, 2.102	-0.192	-4.485, 4.101	4.409	-9.373, 18.192
Cu	-0.332	-0.797, 0.131	0.292	-0.290, 0.873	0.553	-0.120, 1.227	-1.109	-1.912, 0.307	-0.527	-2.092, 1.039
Zn	0.016	-0.349, 0.383	0.114	-0.355, 0.584	-0.026	-0.389, 0.337	-0.137	-0.511, 0.237	-0.130	-0.623, 0.363
As	-2.260	-5.777, 1.256	3.153	-2.681, 8.987	1.446	-3.053, 5.946	-5.162	-10.553, 0.227	-3.303	-12.073, 5.468
Se	-2.700	-8.540, 3.139	-1.011	-7.361, 5.338	-3.695	-10.738, 3.350	0.500	-6.347, 7.348	-1.123	-10.604, 8.359
Br	-0.685	-2.850, 1.481	1.674	-1.137, 4.485	1.414	-1.160, 3.987	-4.834	-8.618, -1.049	-3.932	-11.641, 3.779
Pb	0.196	-0.660, 1.052	0.023	-1.162, 1.208	-0.447	-1.918, 1.024	-0.463	-1.598, 0.672	-0.320	-2.248, 1.608
OC	-0.172	-0.474, 0.129	0.118	-0.145, 0.382	0.042	-0.244, 0.329	0.044	-0.311, 0.398	-0.118	-0.451, 0.216
EC	0.751	-0.404, 1.906	1.336*	0.218, 2.455	0.417	-0.873, 1.706	-0.862	-2.229, 0.504	0.223	-0.959, 1.406

Notes: *P≤0.05, which represents statistically significant changes as time progressed. Environmental effects may be delayed over a period of several days, and thus, we considered the lagged effects of the day of the event and up to 5 days (from Lag0 to Lag5).

Abbreviations: CI, confidence interval; EC, elemental carbon; OC, organic carbon.

Table 4 Percentage increase in COPD-related hospital visits and 95% CI in males and females as each particle constituent increased 10 µg/m³

	Lag1		Lag2		Lag3		Lag4		Lag5	
	% increase	95% CI	% increase	95% CI	% increase	95% CI	% increase	95% CI	% increase	95% CI
Male										
Na	-0.031	-0.106, 0.045	-0.023	-0.152, 0.106	0.003	-0.081, 0.087	-0.042	-0.107, 0.022	0.130	-0.094, 0.355
Mg	0.059*	0.001, 0.116	0.376	-0.291, 1.043	0.711	-0.546, 1.968	-0.373	-0.724, -0.023	1.316	-1.291, 3.923
Al	0.021*	0.002, 0.039	0.182*	0.002, 0.361	0.010	-0.097, 0.117	-0.126	-0.265, 0.014	-0.122	-0.367, 0.123
Si	0.009*	0.001, 0.018	0.078*	0.008, 0.148	0.008	-0.035, 0.052	-0.063	-0.133, 0.005	-0.060	-0.178, 0.057
Cl	-0.077	-0.225, 0.070	0.036	-0.137, 0.209	-0.142	-0.343, 0.060	-0.068	-0.231, 0.094	-0.119	-0.397, 0.158
K	0.021	-0.032, 0.075	0.110	-0.006, 0.227	0.013	-0.072, 0.098	-0.096	-0.186, -0.008	-0.099	-0.294, 0.097
Ca	0.028*	0.002, 0.053	0.229	-0.063, 0.521	-0.018	-0.243, 0.208	-0.192	-0.401, 0.016	-0.234	-0.658, 0.190
Ti	0.324*	0.031, 0.617	1.699*	0.197, 3.202	0.310	-0.741, 1.362	-1.981	-3.916, -0.045	-1.886	-5.375, 1.603
V	3.355	-2.110, 8.819	-3.661	-11.135, 3.814	-7.785	-15.965, 0.398	5.262	-3.669, 14.193	-3.829	-15.626, 7.968
Cr	1.708	-1.336, 4.049	2.035	-1.350, 4.720	2.735	-2.297, 5.174	-0.056	-2.130, 2.010	-0.493	-4.570, 3.584
Mn	0.855	-0.177, 1.886	1.371	-1.394, 4.134	-0.825	-2.890, 1.239	-0.754	-2.920, 1.412	-1.192	-4.253, 1.869
Fe	0.030*	0.001, 0.059	0.137	-0.037, 0.311	-0.020	-0.126, 0.086	-0.069	-0.189, 0.052	-0.083	-0.267, 0.100
Ni	-5.920	-10.281, -1.561	-3.030	-8.205, 2.147	-2.283	-6.722, 2.158	-0.910	-5.944, 4.123	7.795	-18.351, 22.811
Cu	-0.359	-0.919, 0.201	0.601	-0.064, 1.265	0.746	-0.030, 1.523	-1.514	-2.584, -0.445	-0.189	-2.165, 1.788
Zn	-0.079	-0.511, 0.352	0.279	-0.295, 0.853	-0.164	-0.577, 0.249	-0.139	-0.578, 0.301	-0.270	-0.884, 0.346
As	-3.351	-7.512, 0.809	8.714*	0.045, 17.383	0.530	-4.614, 5.673	-6.099	-12.773, 0.576	-6.173	-17.761, 5.418
Se	-5.232	-11.914, 1.448	-1.564	-8.819, 5.692	-7.275	-15.630, 1.077	0.490	-7.550, 8.530	-3.745	-15.376, 7.885
Br	-0.856	-3.447, 1.734	3.876*	0.340, 7.410	1.302	-1.635, 4.238	-6.840	-12.238, -1.442	-8.630	-22.321, 5.063
Pb	0.091	-0.926, 1.107	0.179	-1.208, 1.567	-1.205	-2.942, 0.533	-0.569	-1.890, 0.751	-0.858	-3.227, 1.513
OC	-0.122	-0.458, 0.216	0.120	-0.163, 0.404	-0.012	-0.336, 0.310	-0.135	-0.582, 0.312	-0.260	-0.632, 0.111
EC	0.888	-0.454, 2.230	1.489*	0.206, 2.770	0.443	-1.004, 1.890	-1.458	-3.046, 0.130	0.165	-1.078, 1.407
Female										
Na	-0.009	-0.090, 0.073	-0.017	-0.179, 0.145	-0.040	-0.133, 0.053	-0.001	-0.073, 0.071	0.055	-0.158, 0.268
Mg	0.016	-0.060, 0.091	-0.189	-0.857, 0.479	0.000	-0.964, 0.964	-0.119	-0.517, 0.279	0.467	-2.299, 3.232
Al	0.006	-0.017, 0.030	-0.066	-0.244, 0.112	0.087	-0.036, 0.210	-0.085	-0.227, 0.057	-0.051	-0.298, 0.196
Si	0.003	-0.008, 0.013	-0.030	-0.112, 0.051	0.034	-0.016, 0.084	-0.042	-0.108, 0.024	-0.026	-0.138, 0.086
Cl	0.080	-0.126, 0.285	-0.052	-0.281, 0.176	0.144	-0.103, 0.390	-0.045	-0.230, 0.140	-0.034	-0.339, 0.270
K	0.014	-0.048, 0.076	-0.041	-0.153, 0.071	0.072	-0.024, 0.168	-0.054	-0.146, 0.038	-0.041	-0.238, 0.156
Ca	0.009	-0.024, 0.041	-0.103	-0.385, 0.179	0.201	-0.057, 0.459	-0.117	-0.342, 0.108	-0.102	-0.539, 0.336
Ti	0.092	-0.282, 0.465	-0.726	-2.692, 1.242	0.791	-4.421, 2.002	-1.148	-2.856, 0.559	-0.795	-3.833, 2.243
V	3.705	-3.125, 10.534	0.677	-10.871, 12.225	2.487	-7.761, 12.736	2.344	-7.348, 12.037	-0.022	-13.145, 13.100
Cr	3.209	-2.155, 6.263	3.132	-1.362, 0.602	4.270	-3.066, 7.474	2.130	-5.500, 4.760	4.074	-0.580, 8.727
Mn	0.496	-0.736, 1.727	-0.812	-4.202, 2.577	1.729	-0.744, 4.204	-0.796	-3.206, 1.614	-0.296	-3.664, 3.072
Fe	0.011	-0.024, 0.047	-0.058	-0.238, 0.120	0.090	-0.034, 0.213	-0.060	-0.190, 0.070	-0.029	-0.225, 0.167
Ni	-0.290	-5.747, 5.166	0.234	-7.304, 7.773	-1.931	-7.358, 3.495	1.026	-4.286, 6.339	4.300	-12.344, 20.944
Cu	-0.270	-0.964, 0.425	-0.303	-1.387, 0.783	0.301	-0.681, 1.283	-0.579	-1.537, 0.378	-0.668	-2.780, 1.444

Zn	0.258	-0.303, 0.819	-0.177	-0.887, 0.534	0.351	-0.144, 0.845	-0.148	-0.638, 0.341	-0.076	-0.744, 0.591
As	0.058	-5.147, 5.263	-3.097	-11.747, 5.552	4.315	-1.576, 10.207	-3.941	-10.738, 2.858	-2.334	-13.955, 9.288
Se	4.160	-5.759, 14.080	-0.632	-11.233, 9.971	4.039	-6.413, 14.491	0.276	-8.751, 9.304	-0.063	-13.049, 12.922
Br	-0.206	-3.281, 2.869	-1.723	-6.486, 3.040	2.230	-1.160, 5.620	-2.973	-7.354, 1.406	-3.042	-12.438, 6.353
Pb	0.515	-0.760, 1.791	-0.331	-2.188, 1.525	1.263	-0.864, 3.390	-0.288	-1.795, 1.219	-0.101	-2.734, 2.532
OC	-0.356	-0.965, 0.254	0.098	-0.465, 0.660	0.273	-0.203, 0.749	0.318	-0.176, 0.812	0.256	-0.257, 0.768
EC	0.340	-1.692, 2.372	1.099	-1.079, 3.277	0.552	-1.813, 2.919	0.193	-1.892, 2.279	0.366	-1.664, 2.396

Notes: * $P \leq 0.05$, which represents statistically significant changes as time progressed. Environmental effects may be delayed over a period of several days, and thus, we considered the lagged effects of the day of the event and up to 5 days (from Lag0 to Lag5).

Abbreviations: CI, confidence interval; EC, elemental carbon; OC, organic carbon.

benefit patients from increased hospital visits. For effective regulation, understanding of toxic components and sources of PM_{2.5} is needed. In addition, studies on the mechanism of air pollution in the development and exacerbation of COPD will be helpful for prevention strategies.

Some studies have shown sex-specific effects of air pollution on health-related outcomes. Kan et al³⁷ found that females are more vulnerable to air pollution (PM₁₀; SO₂, NO₂, and O₃) than males, and Zanobetti and Schwartz³⁸ observed that air pollution-related mortality was higher in females than in males. Clear reasons for the adverse effects of air pollution on females are not well known. Sex-specific differences with respect to the effects of air pollution may be related to smaller airways, greater airway reactivity, lung structural differences, and greater deposition of particles in the lungs of females.³⁹⁻⁴¹ A difference in gene expression due to chronic air pollution exposure between males and females has also been reported.⁴²

Our study has several limitations to consider. First, the number of hospital visits was obtained from the KNHIS database based on the claimed diagnosis of COPD defined by ICD-10 codes, which may not reflect the patient's actual problem during that hospital visit. Second, the PM_{2.5} concentration was measured in only one place, which thus did not take into account any effect of the distance between the PM_{2.5} measurement site and the residence or principal locus of daily activity. Therefore, the impact of PM_{2.5} might be overestimated or underestimated depending on the distance from the measurement site. Third, there was a lack of demographic information that could influence hospital visits of COPD patients, such as age, smoking history, lung function, perceived quality of life, dyspnea scale, and previous exacerbation history. Fourth, we could not account for indoor air pollutants. Lastly, the low number of hospitalized events in COPD patients could have resulted in an underestimation of the effects of PM_{2.5} and its constituents as well.

Conclusion

In summary, we found a significant association between PM_{2.5} and the risk of COPD-related hospital visits. Furthermore, various constituents of PM_{2.5} might have a positive influence to increase the risk of hospital visits in COPD patients. In addition, there was a difference according to sex in the time until the COPD-related health care event occurred.

Acknowledgment

This study was supported by a grant from the Ministry of Environment, Republic of Korea.

Disclosure

The authors report no conflicts of interest in this work.

References

- Mannino DM, Braman S. The epidemiology and economics of chronic obstructive pulmonary disease. *Proc Am Thorac Soc.* 2007;4(7):502–506.
- Vogelmeier CF, Criner GJ, Martinez FJ, et al. Global strategy for the diagnosis, management and prevention of chronic obstructive lung disease 2017 report. *Respirology.* 2017;22(3):575–601.
- Salvi SS, Barnes PJ. Chronic obstructive pulmonary disease in non-smokers. *Lancet.* 2009;374(9691):733–743.
- Pauwels RA, Rabe KF. Burden and clinical features of chronic obstructive pulmonary disease (COPD). *Lancet.* 2004;364(9434):613–620.
- Kohansal R, Martinez-Cambor P, Agustí A, Buist AS, Mannino DM, Soriano JB. The natural history of chronic airflow obstruction revisited: an analysis of the Framingham offspring cohort. *Am J Respir Crit Care Med.* 2009;180(1):3–10.
- Eisner MD, Anthonisen N, Coultas D, et al. An official American Thoracic Society public policy statement: novel risk factors and the global burden of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2010;182(5):693–718.
- Anderson H, Spix C, Medina S, et al. Air pollution and daily admissions for chronic obstructive pulmonary disease in 6 European cities: results from the APHEA project. *Eur Respir J.* 1997;10(5):1064–1071.
- Ko FW, Tam W, Wong TW, et al. Temporal relationship between air pollutants and hospital admissions for chronic obstructive pulmonary disease in Hong Kong. *Thorax.* 2007;62(9):780–785.
- Andersen ZJ, Hvidberg M, Jensen SS, et al. Chronic obstructive pulmonary disease and long-term exposure to traffic-related air pollution: a cohort study. *Am J Respir Crit Care Med.* 2011;183(4):455–461.
- Tsai S-S, Chang C-C, Yang C-Y. Fine particulate air pollution and hospital admissions for chronic obstructive pulmonary disease: a case-crossover study in Taipei. *Int J Environ Res Public Health.* 2013;10(11):6015–6026.
- Zhu R, Chen Y, Wu S, Deng F, Liu Y, Yao W. The relationship between particulate matter (PM10) and hospitalizations and mortality of chronic obstructive pulmonary disease: a meta-analysis. *COPD.* 2013;10(3):307–315.
- Medina-Ramón M, Zanobetti A, Schwartz J. The effect of ozone and PM10 on hospital admissions for pneumonia and chronic obstructive pulmonary disease: a national multicity study. *Am J Epidemiol.* 2006;163(6):579–588.
- Moolgavkar SH, Luebeck EG, Anderson EL. Air pollution and hospital admissions for respiratory causes in Minneapolis-St. Paul and Birmingham. *Epidemiology.* 1997;8(4):364–370.
- Kim H, Kim Y, Hong Y-C. The lag-effect pattern in the relationship of particulate air pollution to daily mortality in Seoul, Korea. *Int J Biometeorol.* 2003;48(1):25–30.
- Slaughter JC, Kim E, Sheppard L, Sullivan JH, Larson TV, Claiborn C. Association between particulate matter and emergency room visits, hospital admissions and mortality in Spokane, Washington. *J Expo Anal Environ Epidemiol.* 2005;15(2):153–159.
- HEI, IHME. State of global air 2017: a special report on global exposure to air pollution and its disease burden. 2017. Available from: <https://www.stateofglobalair.org/report>. Accessed July 3, 2017.
- Park J, Lim MN, Hong Y, Kim WJ. The influence of Asian dust, haze, mist, and fog on hospital visits for airway diseases. *Tuberc Respir Dis.* 2015;78(4):326–335.
- Birch M, Cary R. Elemental carbon-based method for monitoring occupational exposures to particulate diesel exhaust. *Aerosol Sci Technol.* 1996;25(3):221–241.
- Han Y-J, Kim S-R, Jung J-H. Long-term measurements of atmospheric PM2.5 and its chemical composition in rural Korea. *J Atmos Chem.* 2011;68(4):281–298.
- Han Y-J, Kim H-W, Cho S-H, Kim P-R, Kim W-J. Metallic elements in PM 2.5 in different functional areas of Korea: concentrations and source identification. *Atmos Res.* 2015;153:416–428.
- Raman RS, Hopke PK, Holsen TM. Characterization of fine aerosol and its inorganic components at two rural locations in New York State. *Environ Monit Assess.* 2008;144(1–3):351–366.
- Winberry WT Jr, Ellestad T, Stevens B. *Compendium Method IO-4.2: Determination of Reactive Acidic and Basic Gases and Strong Acidity of Atmospheric Fine Particles (<2.5 μm)*. Cincinnati, OH: US Environmental Protection Agency; 1999. EPA/625/R-96/010a.
- Baldacci S, Maio S, Cerrai S, et al. Allergy and asthma: effects of the exposure to particulate matter and biological allergens. *Respir Med.* 2015;109(9):1089–1104.
- Huang S-K, Zhang Q, Qiu Z, Chung KF. Mechanistic impact of outdoor air pollution on asthma and allergic diseases. *J Thorac Dis.* 2015;7(1):23.
- Valavanidis A, Vlachogianni T, Fiotakis K, Loidas S. Pulmonary oxidative stress, inflammation and cancer: respirable particulate matter, fibrous dusts and ozone as major causes of lung carcinogenesis through reactive oxygen species mechanisms. *Int J Environ Res Public Health.* 2013;10(9):3886–3907.
- Ling SH, van Eeden SF. Particulate matter air pollution exposure: role in the development and exacerbation of chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis.* 2009;4:233–243.
- Ni L, Chuang CC, Zuo L. Fine particulate matter in acute exacerbation of COPD. *Front Physiol.* 2015;6:294.
- Liu S, Zhou Y, Liu S, et al. Association between exposure to ambient particulate matter and chronic obstructive pulmonary disease: results from a cross-sectional study in China. *Thorax.* 2017;72(9):788–795.
- Hwang S-L, Lin Y-C, Guo S-E, Chi M-C, Chou C-T, Lin C-M. Emergency room visits for respiratory diseases associated with ambient fine particulate matter in Taiwan in 2012: a population-based study. *Atmos Pollut Res.* 2017;8(3):465–473.
- Atkinson RW, Kang S, Anderson HR, Mills IC, Walton HA. Epidemiological time series studies of PM2.5 and daily mortality and hospital admissions: a systematic review and meta-analysis. *Thorax.* 2014;69(7):660–665.
- Jo E-J, Lee W-S, Jo H-Y, et al. Effects of particulate matter on respiratory disease and the impact of meteorological factors in Busan, Korea. *Respir Med.* 2017;124:79–87.
- WHO. Ambient (outdoor) air quality and health. Updated September 2016. Available from: <http://www.who.int/mediacentre/factsheets/fs313/en/>. Accessed July 10, 2017.
- Sauerzapf V, Jones AP, Cross J. Environmental factors and hospitalisation for chronic obstructive pulmonary disease in a rural county of England. *J Epidemiol Community Health.* 2009;63(4):324–328.
- Li P, Xin J, Wang Y, et al. Association between particulate matter and its chemical constituents of urban air pollution and daily mortality or morbidity in Beijing city. *Environ Sci Pollut Res Int.* 2015;22(1):358–368.
- Son JY, Lee JT, Kim KH, Jung K, Bell ML. Characterization of fine particulate matter and associations between particulate chemical constituents and mortality in Seoul, Korea. *Environ Health Perspect.* 2012;120(6):872–878.
- Kim WJ, Lee CY. Environmental exposures and chronic obstructive pulmonary disease. *Mol Cell Toxicol.* 2017;13(3):251–255.
- Kan H, London SJ, Chen G, et al. Season, sex, age, and education as modifiers of the effects of outdoor air pollution on daily mortality in Shanghai, China: the Public Health and Air Pollution in Asia (PAPA) study. *Environ Health Perspect.* 2008;116(9):1183–1188.
- Zanobetti A, Schwartz J. Race, gender, and social status as modifiers of the effects of PM10 on mortality. *J Occup Environ Med.* 2000;42(5):469–474.
- Yunginger JW, Reed CE, O'Connell EJ, Melton L, O'Fallon WM, Silverstein MD. A community-based study of the epidemiology of asthma. *Am Rev Respir Dis.* 1992;146(4):888–894.

40. Kohlhauff M, Brand P, Scheuch G, et al. Increased fine particle deposition in women with asymptomatic nonspecific airway hyperresponsiveness. *Am J Respir Crit Care Med*. 1999;159(3):902–906.
41. Hong Y, Ji W, An S, Han SS, Lee SJ, Kim WJ. Sex differences of COPD phenotypes in nonsmoking patients. *Int J Chron Obstruct Pulmon Dis*. 2016;11:1657–1662.
42. Vrijens K, Winckelmans E, Tsamou M, et al. Sex-specific associations between particulate matter exposure and gene expression in independent discovery and validation cohorts of middle-aged men and women. *Environ Health Perspect*. 2017;125(4):660–669.

International Journal of COPD

Publish your work in this journal

The International Journal of COPD is an international, peer-reviewed journal of therapeutics and pharmacology focusing on concise rapid reporting of clinical studies and reviews in COPD. Special focus is given to the pathophysiological processes underlying the disease, intervention programs, patient focused education, and self management protocols.

Submit your manuscript here: <http://www.dovepress.com/international-journal-of-chronic-obstructive-pulmonary-disease-journal>

Dovepress

This journal is indexed on PubMed Central, MedLine and CAS. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.