Effect of air-pollutants and environmental factors on COPD exacerbations: time series analysis stratified by age and concentration of pollutants

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Abstract

Background: Chronic obstructive pulmonary disease (COPD) exacerbation (CE) is characterized by the rapid deterioration of respiratory symptoms caused by air pollution, but there have been no comprehensive studies with regard to the age-stratified effect of air pollution. We investigate the short-term effects of air pollution and environmental factors on CE. Methods: By merging the individualized environmental data and Korea's National Health Insurance cohort, we conducted Quasi-Poisson analysis to evaluate the effects of air pollutants and environmental factors on CE. Results: From January 2007 to December 2012, a total of 15110 CE events occurred, which showed seasonal dynamics in CE events, air pollutants (particulate matter less than 10 μm (PM10), NO2, SO2) and environmental factors (wind speed (WS), solar sunshine (SS)). The only factor affecting CE was PM10, and this occurred on lag days 4, 5, and 6 and had a peak hazard ratio (HR) of 1.0404 on lag day 5. PM10 also had a lag-cumulative effect on CE risk from lag day 6 to lag day 10. In subgroup analysis on age and level of parameters, each factor had a different significant effect on CE on different lag days. Conclusions: PM10 uniquely affects CE at lag-specific day 5 (from lag day 4 to lag day 6). PM10 also had a lag-cumulative effect on CE risk which showed a pattern proportional to the concentration of PM10. Considering the subgroup analysis, we need to devise different strategies for air pollutants and age for patients with COPD exacerbation.

Abbreviations

COPD, Chronic Obstructive Pulmonary Disease; CE, COPD exacerbation; HR, hazard ratio; PM10, Particulate matter less than 10 μm; SO_2, Sulfur dioxide; NO_2, Nitrogen dioxide; O_3, ozone; WS, Wind speed; SS, Solar sunshine; KNHIS-NSC, Korea National Health Insurance Service-National Sample Cohort; DLNM, Distributed Lag Linear and Non-Linear Model; QAIC, quasi Akaike information criterion; PACF, partial autocorrelation function; DOW, Day of Week; RR, Risk ratio; CO, Carbon monoxide; DTR, diurnal temperature range; HM, humidity.

Introduction

Chronic obstructive pulmonary disease (COPD) is a disease in which lung function decreases faster than other organ functions due to abnormal inflammatory reactions in the lungs. It is a heterogeneous disease, characterized by airflow limitation caused by a mixed form of parenchymal destruction (emphysema) and small airway disease (obstructive bronchiolitis). COPD is currently the fourth leading cause of death and is expected to be the third leading cause by 2020 (GOLD CRITERIA).

Symptoms of COPD include cough, sputum, and exertional dyspnea. The cause may be smoking or air pollution. For example, it has been reported that air pollution such as fine dust less than 2.5 μm/10 μm (PM2.5/10) and NO_2 affects COPD prevalence.[1]There have also been reports of significant adverse effects on lung maturation and development in children exposed to high levels of NO_2 and particulate matter less than 2.5 μm (PM2.5).[2] However, there have been no studies on the delayed effect of short-term and high peak exposure of air pollution on COPD.

COPD exacerbation (CE) is a disease that requires additional treatment due to the rapid deterioration of respiratory symptoms caused by COPD, and is a serious disease which may lead to death.[3]Some of the factors that are known to be closely related to CE include a history of two or more frequent CEs and an increase in blood eosinophil levels.[4] However, there have been no studies showing the relationship between air pollution and CE.

Therefore, in this paper, we investigated the effects of air pollution, including fine dust, and environmental factors on CE using 6 years of cohort data.

Methods

Population of this study

This study passed the scrutiny of the Institutional Review Board of Jeonbuk National University Hospital (IRB number 2020-08-012). This time series analysis was conducted using the anonymized Korea National Health Insurance Service-National Sample Cohort (KNHIS-NSC) database, and data in the period from January 1, 2007 to December 31, 2012 were analyzed. This database includes day of hospital visit, the patient's age, sex, residential area, economic level, diagnosis, medical history, and disease code. The diagnostic codes from KNHIS-NSC are based on the International Classification of Diseases, Tenth Revision (ICD-10). In 2007, the population in Korea was 49,194,085, of which 1 million cohorts of randomly stratified samples were used by the KNHIS-NSC databases.

The inclusion criteria of the CE population from this database were: 1) patients assigned code J441 in the ICD-10 classification at the time of the hospital visit; 2) patients taking oral steroids; and 3) patients with chest computed tomography scans.[5,6] Individuals were divided into four age groups: preschool age (0 to 4 years old), school age (5 to 19 years old), adult (20 to 59 years old), and elderly ([?]60 years old).

Air pollution and environmental factors

Particulate matter less than 10 μm (PM10), sulfur dioxide (SO_2), nitrogen dioxide (NO_2), ozone (O_3), and carbon monoxide (CO) are factors affecting COPD exacerbation.[7] These air pollutants are known to have a direct harmful effect or a lag day effect on COPD exacerbation. Wind speed (WS), solar sunshine (SS), humidity (HM), diurnal temperature range (DTR) are also important daily ecological factors. In this study, the lag effect affecting COPD exacerbation was considered using SO_2, NO_2, O_3, PM10, WS, SS, HM, CO, and DTR as the main variables.

Individualization

Korea's administrative districts are divided into eight provinces, 77 cities, and 240 local districts. In this study, the place of residence of patients with CE was individualized using the KNHIS-NSC database, and the environmental factors in these individualized addresses were used as input variables. It was thought that these individualized data would reflect the environmental setting of each region much better than the national average for each environmental indicator.

Data source of Air pollutants

As of 2010, there were 239 air quality monitoring stations for the entire Korea according to the city measurement network. Since air quality measurements from these stations were too coarse to represent geographic variations of air pollutants across the study area, we applied the Kriging method, a widely-used statistical approach for spatial interpolation, in order to obtain refined estimates of spatial distributions of air quality.

The estimated results were then summarized to the spatial resolution of the local district and were used as an input for the dlnm modeling of this study.

Model construction

In general, since there is no clear criterion for configuring the optimal DLNM model[8], various approaches can be taken to construct this. Many studies use Akaike's information criterion to select the model with the best performance.[9]Therefore, we also considered a quasi Akaike information criterion (QAIC) and a partial autocorrelation function (PACF) to choose the optimal construction for the DLNM model. The quasi Akaike information criterion (QAIC)[10], the quasi-likelihood adjustments of Akaike's information criterion (AIC)[11], provides important information on the explanatory power of quasi Poisson models that is used for overdispersed count data. The partial autocorrelation function (PACF) evaluates the level of partial autocorrelation in model residuals. We compared the mean of the absolute values of PACF (mPACF) for the first 100 days of the models.

Table 1 shows the values of QAIC and mPACF for various models we compared. Each model was selected by forward selection using a greedy approach. The M5 model was selected because its QAIC was the lowest (3289.498) while its PACF value was the second lowest (0.02849), which was greater than the lowest by only 0.00002.

Statistical analysis

The Distributed Lag Linear and Non-Linear Model (DLNM) was used to view the direct and delayed effect of air pollution and environmental factors on CE. Considering the distribution of number of daily CE events, the Quasi-Poisson model is a more suitable model than the Poisson model. Quasi-Poisson is usually used when the variance is greater than the average, and this was the reason why we used this model. It was used in combination with a DLNM to investigate the lagged and non-linear effects. For all variables, the maximum lag day L was considered up to 10 days.

The multivariate DLNM model for the air pollutants is:

$$\log \mathrm{E}\left(Y_t\right) = s\left(PM10_t; \eta_{\mathrm{PM10}}\right) + s\left(NO2_t; \eta_{NO2}\right) + s\left(SO2_t; \eta_{SO2}\right) + s\left(\mathrm{WS}_t; \eta_{\mathrm{WS}}\right) + s\left(\mathrm{SS}_t; \eta_{\mathrm{SS}}\right) + ns\left(time, (4 \times 6 + 4)\,\mathrm{df}\right) + DOW$$

Results

Baseline data

From January 2007 to December 2012, a total of 15110 CE events occurred over the 6 years. CE increased from year to year: 2018 in 2007, 2232 in 2008, 2443 in 2009, 2385 in 2010, 2854 in 2011, and 3178 in 2012. By age group, there were 97 boys and 41 girls of preschool age, 59 boys and 106 girls of school age, 1643 men and 1076 women aged 20–59, and 7778 men and 4310 women over 60 years of age(Figure 1A).

Seasonal dynamics of COPD exacerbation and outdoor environmental factors

We noted seasonal changes in CE that differed by age group (Figure 1B). COPD exacerbation was predominantly in winter and less frequent in summer, and this tendency was particularly severe in those aged 60 or older.

There were definite seasonal variations in NO_2, PM10, SO_2, WS and SS (Figure 1C). Contaminants such as NO_2, PM10, and SO_2 mainly showed a cyclic seasonal pattern with highs in winter and lows in summer. Environmental factors such as WS and SS also showed cyclic patterns with highs in late winter and early spring and lows in the autumn. Table 2 shows the median values for the air pollutants and environmental factors. We used these median values when calculating the risk ratio (RR).

Estimated lag day effect and lag-cumulative effect of outdoor environmental factors on COPD exacerbation

Of the three air pollutants and two external environmental factors, the only factor affecting COPD exacerbation was PM10 (Figure 2A-E). In particular, PM10 affected COPD exacerbation on lag days 4, 5, and 6 and had a hazard ratio (HR) of 1.0404 (95% CI [1.0089, 1.0729]) at lag day 5 (Table 3). PM10 also had a cumulative effect from lag day 6 to lag day 10 (Figure 2A). The remaining factors NO_2, SO_2, SS, and WS did not influence COPD exacerbation (Figure 2B-E).

Subgroup analysis – calculated RR stratified by concentration of air pollutants and patient age

As a subgroup analysis, we calculated the RR values according to the concentration of air pollutants (Table 3). From this, the concentrations of air pollutants NO_2 and SO_2 were not correlated with COPD exacerbation risk, nor were the environmental factors WS and SS. Only PM10 showed an increase in HR with concentration: 1.0253 at 30 $\mu g/m^3$, 1.0704 at 80 $\mu g/m^3$, and 1.1370 at 150 $\mu g/m^3$(Table 3, Figure 3A, B).

In addition, we examined the RR values for COPD exacerbation according to patient age by time series (Table 4). Individuals aged under 20 years (preschool, school age) did not have significant RR values for any of the air pollutants or environmental factors. In adults (20–59 years), PM10 at lag day 3 (which was significant from lag day 3 to 4) had an RR value of 1.0372 and NO_2 at lag day 0 had a significant RR value of 1.4613. For the environmental factors, WS and SS had significant RR values at lag day 0 (1.1320, 0.9444, respectively). This pattern was the same in the elderly over 60 years of age. In the case of air pollutants, PM10 at lag day 3 (which was significant from lag day 6) had an RR value of 1.0372, and NO_2 at lag day 6 had a significant RR value of 1.0774. SO_2 did not show significant RR values in any of the age groups. For the environmental factors, WS and SS in the elderly group had significant RR values at lag day 0 (1.1320 and 0.9444, respectively).

Discussion

Various air pollutants such as PM10, NO_2, and SO_2 pose a great danger to public health, in particular to the respiratory system of individuals.[12] It is known that, for every increase of PM10 by 10 $\mu g/m^3$, mortality from all causes, cardiopulmonary diseases and lung cancer rises by 4%, 6% and 8%, respectively.[13] Carbon monoxide (CO) and nitrogen dioxide (NO_2) from diesel engines are known to raise the risk of lung cancer from 15% to 40%.[14] These environmental pollutants are known to have a significant adverse effect on public health including mortality rates. As a result of increased residence times in the air and higher concentrations of pollutants, mortality rates are significantly affected and public health generally deteriorates.[15] These air pollutants are closely affected by environmental factors such as wind speed and sunlight.

In our study, air pollutants such as PM10, NO_2, and SO_2 showed seasonal variations. In Korea, the use of coal or oil increases during cold weather, mainly in winter, and atmospheric pollution increases leading to high air pollution indicators (PM10, SO_2, NO_2) in winter (Figure 1C). In our study, the same sinusoidal pattern appeared in the frequency of COPD exacerbations (Figure 1B). During the entire 6-year observation period, 15110 individuals suffered COPD exacerbation, of which 17.9% were adults in their 20s, and 80% were elderly individuals older than 60 years of age (Figure 1A). When the distribution of the entire patient population was drawn in a time series, the number of individuals affected tended to be particularly high in winter, which is consistent with the pattern of major air pollution indicators (Figure 1B).

So which of the three air pollutants, at what concentrations and for how long, were individuals affected by COPD exacerbation? We utilized "DLNM packages" using R to analyze these factors. In conclusion, of the various air pollutants, only PM10 was significantly related to COPD exacerbation (Figure 2A), and it was found to affect lag-specific days 4 to 6. In particular, on lag-specific day 5, the risk of COPD exacerbation reached peak values (Figure 2A, Table 3). For a PM10 concentration of 30 $\mu g/m^3$, which is the upper limit of "acceptable" fine dust levels, the risk of COPD exacerbation increased by 2.5%. At the median concentration of normal PM10 (46.98 $\mu g/m^3$), it increased by 4.0%. When it was 80 $\mu g/m^3$, which is the lower limit of

"unacceptable" fine dust levels, the risk of COPD exacerbation increased by 7.0%. In the case of PM10 over 150 $\mu g/m^3$, which is an extremely unacceptable level of PM10, CE risk increased by 13.7% (Table 3, Figure 3A, B). In addition, for the lag-cumulative effect of PM10, we calculated the risk of COPD exacerbation, and it was found that it continued to affect CE risk from lag day 6 to lag day 10 after exposure to PM10 (Figure 2B).

We analyzed the entire patient group in four age subgroups. (Table 4) For preschool age (less than 5 years old) and school age (less than 20 years old) individuals, the number of COPD exacerbations was small, so the confidence interval of the RR value was large and so did not produce meaningful results.

In the group of adults 20 years or older, PM10 level significantly increased the risk of COPD exacerbation on lag days 3 and 4. At lag day 0, NO_2 and WS levels significantly increased the risk of COPD, and SS level significantly decreased the risk of COPD exacerbation.

Similar results were found in older people over the age of 60 with PM10 significantly increasing CE risk at lag days 3, 4, 5, and 6, and NO_2 significantly increasing CE risk at lag day 6, WS increasing CE risk at lag day 0, and SS lowering CE risk at lag day 0.

Through this, it can be considered that CE risk was not high in adults over 20 years of age on a clear day without wind. On the other hand, on windy days when it was not sunny, CE risk increased in adults over 20 years of age. Unlike air pollutants, all these climate factors were found to affect CE risk only on the lag-specific day, not the lag days (after lag day 1).

The limitations of this paper are: 1) The study only covers data since 2007 when fine dust (PM10) measurement started in Korea. 2) Detailed indicators, such as PM2.5, were not tested at the time and were not included in the study.

Nevertheless, this paper has the following advantages. 1) This is a large-scale cohort study of patients in Korea. 2) Modeling considers each of the air pollutants and environmental factors in combination with linear, non-linear and lagged effect. 3) The study attempts to analyze each age group and the concentrations of pollution indicators.

Conclusion

Among air pollutants, PM10 uniquely affects CE at lag-specific day 5 (from lag day 4 to lag day 6). For the lag-cumulative effect of PM10, CE risk showed a pattern proportional to the concentration of PM10. When we look at how other air pollutants and environmental factors affect each age group differently, we need to devise different strategies for air pollutants and age of COPD patients.

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Author contributions

EJL, JSK, DHK, MHL contributed to the study design, protocol and study materials. HSS, JSK, SWY collected study data. HSS, SWY, SHK, SJN designed the statistical plan and data analysis. HSS, SWY performed the statistical analysis. EJL, MGK, JSK, HSS, wrote the first draft of the manuscript. All authors contributed to interpretation of the data and revision of the manuscript.

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Figure legends

Figure 1. A. CE counts by age and sex. B. Seasonal variations according to age group. C. Seasonal variations of air pollutants and environmental factors according to time series.

Figure 2. Lag-specific effect and lag-cumulative effect of air pollutants. A. PM10. B. NO_2. C. SO_2. D. SS. E. WS.

Lag day 0: current day; Lag day 1: 1 day previously, to Lag day 10: 10 days previously.

Figure 3. A. Heat-map of PM10 stratified by concentration and lag day effect. B. 3D image of PM10 stratified by concentration and lag day effect.

Lag day 0: current day; Lag day 1: 1 day previously, to Lag day 10: 10 days previously.

Table 1. DLNM model selection process through quasi Akaike information criterion (QAIC) and a partial autocorrelation function (PACF) (Abbreviations: M1, model 1; M2, model 2; M3, model 3; M4, model 4; M5, model 5; M6, model 6; M7, model 7; M8, model 8; M9, model 9; PM10, Particulate matter less than 10 μm; NO_2, Nitrogen dioxide; SO_2, Sulfur dioxide; WS, Wind speed; SS, Solar sunshine; O_3, ozone; HM, humidity; CO, Carbon monoxide; DTR; diurnal temperature range; QAIC, quasi Akaike information criterion; PACF, partial autocorrelation function; DOW, Day of Week; RR, Risk ratio

	Model	QAIC	mPACF
M1	PM10	3305.782	0.02962
M2	PM10+NO_2	3303.790	0.02862
M3	PM10+NO_2+SO_2	3292.022	0.02899
M4	PM10+NO_2+SO_2+SS	3294.994	0.02847
M5	**PM10+NO_2+SO_2+SS+WS**	**3289.498**	**0.02849**
M7	PM10+NO_2+SO_2+SS+WS+O_3	3327.636	0.02919
M8	PM10+NO_2+SO_2+SS+WS+O_3+HM	3318.287	0.02931
M9	PM10+NO_2+SO_2+SS+WS+O_3+HM+CO	3324.240	0.02953
M10	PM10+NO_2+SO_2+SS+WS+O_3+HM+CO+DTR	3348.394	0.03135

Table 2. Summary of outdoor air pollutants and environmental factors

Factor	Daily median [range]
Outdoor air pollutant (data from Ministry of Environment)	
PM10 (μg/m^3)	46.9794 [8.2000, 626.1082]
NO_2 (ppb)	23.245 [5.33000, 71.17143]
SO_2 (ppb)	4.80625 [1.60000 17.32143]
O_3 (ppb)	34.27667 [4.55, 99.04]
CO (ppb/24hr)	480.05 [239.8, 1357]
Weather condition (data from Korea Meteorological Administration)	
WS (m/s)	2.04125 [1.011688 7.186957]
SS (h)	5.917177 [0.00, 12.26]
HM (%)	68.7424 [30.4688, 91.9677]
DTR ([?]C)	9.6687 [2.8012, 18.4892]

PM10, Particulate matter less than 10 μm; SO2, Sulfur dioxide; NO2, Nitrogen dioxide; O3, ozone; WS, Wind speed; SS, Solar sunshine; CO, Carbon monoxide; HM, humidity; DTR, diurnal temperature range.

Table 3. HR of CE according to representative value of air pollutants and environmental factors

Factor	Lag day	Median	**HR** Mean [LL, UL]	Concentration	HR	Concentration	HR	Concentration	HR
Outdoor air pollutant									
PM10 (μg/m^3)	5	46.98	**1.0404 [1.0089, 1.0729]***	30	**1.0253 [1.0056, 1.0454]***	80	**1.0704 [1.0153, 1.1285]***	150	**1.1 [1. 1.2**
NO_2 (ppb)	0	23.25	1.0554 [0.9140, 1.2187]	30	1.0737 [0.8883, 1.2979]	50	1.1278 [0.8186, 1.5537]		
SO_2 (ppb)	1	4.81	1.0198 [0.9473, 1.0979]	10	1.0452 [0.8854, 1.2339]	20	1.0979 [0.7734, 1.5586]		
Weather condition									
WS (m/s)	1	2.04	1.0181 [0.9779, 1.0598]						
SS (h)	7	5.92	1.0213 [0.9934, 1.0500]						

Abbreviations: CE, chronic obstructive pulmonary disease exacerbation; HR, hazard ratio; [LL, UL], 95% confidence interval [lower limit, upper limit].

***: statistically significant.**

Lag day 0: current day; Lag day 1: 1 day previously to Lag day 10: 10 days previously.

Table 4. HR of CE according to stratified age and lag days

Factor	Concentration (median)	Preschool age	Preschool age	School age	School
		Lag day	HR [LL, UL]	Lag day	HR [L
Outdoor air pollutant					
PM10 (μg/m^3)	46.98	5	1.0296 [0.0951, 11.142]	0	0.9797
NO_2 (ppb)	23.25	5	1.4613 [0.1080, 19.769]	0	1.4613
SO_2 (ppb)	4.81	1	1.0884 [0.0177, 66.736]	0	1.0884
WS (m/s)	2.04	1	1.0215 [0.1542, 6.7653]	1	1.0215
SS (h)	5.92	4	1.0148 [0.3907, 2.6359]	1	0.9748

Abbreviations: CE, chronic obstructive pulmonary disease exacerbation; HR, hazard ratio; [LL, UL], 95% confidence interval [lower limit, upper limit].

***: statistically significant.**

Lag day 0: current day; Lag day 1: 1 day previously, to Lag day 10: 10 days previously.