

The temporal relationship between air pollutants and hospital admissions for chronic obstructive pulmonary disease in Hong Kong.

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Abstract:

Aims: To assess any relationship between the levels of ambient air pollutants and the hospitalization rate due to chronic obstructive pulmonary disease (COPD) in Hong Kong.

Methods: This is a retrospective ecological study. Data of daily emergency hospital admissions to 15 major hospitals in Hong Kong for COPD and indices of air pollutants (sulphur dioxide [SO_2], nitrogen dioxides [NO_2], ozone [O_3], particulates with an aerodynamic diameter of less than $10\mu\text{m}$ [PM_{10}] and $2.5\mu\text{m}$ [$\text{PM}_{2.5}$]) and meteorological variables from January 2000 to December 2004 were obtained from several government departments. Analysis was performed by the generalized additive models with Poisson distribution. The effects of time trend, season, other cyclical factors, temperature, and humidity were adjusted. Autocorrelation and overdispersion were corrected.

Results: Significant associations were found between hospital admissions for COPD with all 5 air pollutants. Relative risks for admission for every $10\mu\text{g}/\text{m}^3$ increase in SO_2 , NO_2 , O_3 , PM_{10} and $\text{PM}_{2.5}$ were 1.007, 1.026, 1.034, 1.024 and 1.031 respectively, at a lag day ranged from lag 0 to cumulative lag 0-5. In a multi-pollutant model, O_3 , SO_2 and $\text{PM}_{2.5}$ were significantly associated with increased admissions for COPD. SO_2 , NO_2 , and O_3 had a stronger effect on COPD admissions in the cold season (December to March) than during the warm season.

Conclusion: Adverse effects of ambient concentrations of air pollutants on hospitalization rates for COPD are evident, especially during the winter season in Hong Kong. This might be due to indoor exposure to outdoor pollution through opened windows as central heating is not required in our mild winter. Measures to improve air quality are urgently needed.

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Introduction

Air pollution is a major public health problem due to emissions of air pollutants from both motor vehicles and industrial plants. Previous studies have shown that air pollution was associated with excessive respiratory and cardiovascular morbidity¹⁻⁸ as well as mortality.⁹⁻¹³

Hong Kong (HK) is a small but densely populated city. The total population was 6.88 million in mid-2004 with a population density of 6,380 people per square kilometer.¹⁴ Over the past 10 years, the air quality in HK has worsened substantially. The concentrations of particulates with an aerodynamic diameter of less than $10\mu\text{m}$ (PM_{10}) and ozone (O_3) recorded at the general air monitoring stations in HK increased by 15% and 26% respectively from 1999 to 2004.¹⁵ Nitrogen dioxide (NO_2) level also increased by 26% when the levels in 1991 and 2002 were compared.¹⁶ Because of the increase in particulate pollution, impairment in visibility in HK has also worsened over time. The percentage of time in a year with visibility < 8km (with relative humidity $\leq 80\%$) increased from 4% in 1991 to 18% in 2004.¹⁵ The major source of air pollutants in HK is attributable to air pollutant emissions from road traffic.⁵ In addition, with increased industrialization in the southern part of China, pollutants generated by motor vehicles, power plants, and various industries in the Pearl River Delta Region also contributed to the increasing air pollution in HK.¹⁶

Chronic obstructive pulmonary disease (COPD) is an important disease worldwide and acute exacerbations are associated with significant morbidity such as hospitalizations and mortality.¹⁷ In HK, COPD was the 5th leading cause of death, and accounted for at least 4% of all public hospital acute admissions in 2003. Previous studies have shown that pulmonary function and quality of life were adversely affected by frequent exacerbations, particularly in active smokers.^{18,19} A study conducted in HK a decade ago showed that air pollution was associated with a significantly increased risk for hospitalization for patients with respiratory diseases including acute exacerbations of COPD (AECOPD).⁵ With increasing air pollution, the impact of air pollutants on AECOPD may be enhanced.

As over 90% of the HK citizens are dependent on the public hospital healthcare resources, data on COPD admissions can be retrieved from the central computer system of the Hospital Authority Head Office (HAHO) in HK. In this study, we assessed the effect of air pollutants, including NO₂, sulphur dioxide (SO₂), O₃, PM₁₀ and particulates with an aerodynamic diameter of less than 2.5μm (PM_{2.5}), over a period of 5 years (from January 2000 to December 2004) on emergency admission rates of COPD. Data were collected from 15 major hospitals and 14 air quality monitoring stations in HK over the same period.

Methods

This is a retrospective ecological study. Data on emergency hospital admissions for COPD to 15 major hospitals from January 2000 to December 2005 inclusive were obtained from the HAHO in HK. The daily number of hospital admissions with the following codes 491, 492 and 496, based on the Ninth Revision of the International Classification of Diseases (ICD-9)²⁰ as the primary diagnosis, was recorded.

Air quality and weather data

Hourly concentrations of NO₂, SO₂, O₃, PM₁₀ and PM_{2.5} between January 2000 and December 2004 were obtained from the Environmental Protection Department.²¹ The 14 air quality monitoring stations were located in 8 districts interspersed in different districts throughout HK. All the monitoring stations measured levels of NO₂, SO₂, O₃ and PM₁₀. However, PM_{2.5} was measured by three stations only. SO₂ was measured by ultraviolet fluorescence, NO₂ by chemiluminescence and O₃ by ultraviolet absorption. Both PM₁₀ and PM_{2.5} were measured by the Tapered Element Oscillating Microbalance (TEOM) method. The 24-hour mean concentrations of NO₂, SO₂, PM₁₀ and PM_{2.5} were calculated. Since the formation of O₃ is dependent on sunlight, a daytime (9am to 5pm) mean concentration was used for analysis. The mean daily temperatures and relative humidity for the same period were obtained from the HK Observatory.

Statistical modeling

The statistical model, developed from the "Air Pollution and Health: A European Approach 2" (APHEA 2) protocol for the time series analyses of mortality and hospital admissions in Europe²², was used in this study. A generalized additive model²³ using a Poisson distribution with log-link function was used to construct a core model. This regressed the daily numbers of COPD admissions on the time variable (day), day of the week variable, daily mean temperature and humidity, and holiday indicator. Smoothing of the time variable was used to control for the long-term seasonal patterns of COPD visits and smoothing splines were used as smoothers. The quasi-likelihood method was used to correct for over-dispersion. Each core model was chosen based on the degree of freedom that gave the minimum Akaike's Information Criterion (AIC) value.²⁴ Autocorrelation was adjusted by adding autoregressive terms to the model. After the confounding effects of seasonality, days of the week, and climatic variables had been controlled, daily concentrations of PM₁₀, NO₂, SO₂, O₃ and PM_{2.5} were then added to the core model, to determine the relative risk (RR) of COPD admissions for a 10µg/m³ increase in each of these air pollutants. Concentrations of all the air pollutants for the same day (lag 0) up to five lag days (lag 5) and cumulative lags by two (average of lag 0 and 1), three (average of lag 0, 1 and 2), to six days (average of lag 0 to 5), were tested in each model. The lag day with the air pollutant concentration that yielded the largest χ^2 value, obtained from the change in deviances²³ was chosen.

Multi-pollutant models were run for air pollutants that were significant in the single pollutant analysis, and the lag that had the strongest univariate effect was tested. The correlation coefficients of the individual air pollutants were examined and only those air pollutants with $r < 0.7$ were entered into the model. Pairwise analyses by entering each pollutant, cold season

indicator and their interaction term into the core model were performed. December to March of the year were considered as the cold season in HK with a mean daily temperature below 20°C.⁵ The standard errors of the estimates were computed using the supplementary program used in the re-analysis of the National Morbidity, Mortality, and Air Pollution Study.²⁵ All calculations were performed with the software S-plus 4.0 using a more stringent convergence criteria in the gam(.) function to prevent the convergence problem.²⁶

Results

There were totally 119,225 admissions for AECOPD from January 2000 to December 2004 with a mean (SD) yearly and daily admission of 23,845 (3645) and 65.3 (18.91) respectively. Figure 1 shows a plot of daily admissions over the 5-year period with the Pearson residuals. The seasonal or long term pattern was not apparent in the residuals.

The means, standard deviations, ranges and percentiles of the daily counts of hospital admissions, daily levels of NO₂, SO₂, PM₁₀ and PM_{2.5} and the levels of O₃ from 9:00am to 5:00pm are shown in Table 1. Correlations of the pollutants are shown in Table 2 and showed a close correlation between PM₁₀ and PM_{2.5} ($r = 0.95$, $p < 0.001$).

There was a statistically significant association between hospital admissions for AECOPD and an increase in 10 $\mu\text{g}/\text{m}^3$ of all the 5 pollutants (NO₂, PM₁₀, O₃, SO₂ and PM_{2.5}) and the results are illustrated in Table 3. A lag effect (cumulative from day 0 to ≥ 2 days) was found for all the pollutants assessed except SO₂. The strongest effect on COPD admissions observed for SO₂ (RR 1.007, 95% CI 1.001-1.014) was on lag 0 (i.e. no lag days), whereas for NO₂ (RR 1.026, 95% CI 1.022-1.031), it was on cumulative lag 0-3 as indicated by the greatest χ^2 score ("best" lag). A more delayed effect on COPD admission was observed for O₃ (RR 1.034, 95% CI 1.030-1.040), PM₁₀ (RR 1.024, 95% CI 1.021-1.028) and PM_{2.5} (RR 1.031, 95% CI 1.026-1.036) with the "best" cumulative lag days of 0-5. The overdispersion parameter (ϕ) and the autocorrelations coefficients were 1.295 and -0.02163 respectively. The inter-correlation between the coefficients (betas) of the pollutants in the multi-pollutant model, based on the covariance matrix²⁵, ranged from -0.4161 to 0.2005.

We noted a sharp drop in the number of daily admissions in April 2003 and this was most likely due to the major outbreak of severe acute respiratory syndrome (SARS) in HK at that time.^{27,28} As a sensitivity analysis, we constructed separate models for hospital admissions in 2000-02, 2003 and 2004 by analyzing the data before, during and after the SARS epidemic in 2003. The RRs before 2003 were lower than that after 2003 for NO₂, O₃, PM₁₀ and PM_{2.5}, but the results were largely similar to those when the entire period was used for the model (data available in the supplemental table 1).

The multi-pollutant model was constructed and the results are shown in Table 4. SO₂ and O₃ and PM_{2.5} stood out as the more important pollutants (statistically) related to COPD admissions. Among all the pollutants, O₃ had the highest χ^2 score and this indicated that it contributed to the greatest risk of COPD admission (RR 1.029, 95% CI 1.022-1.036). There was only moderate correlation ($r < 0.5$) between most air pollutants, except that between NO₂ and SO₂ ($r = 0.66$), and between PM_{2.5} and PM₁₀ ($r > 0.9$). Since PM_{2.5} is widely believed to be more damaging to health and had a higher relative risk for AECOPD admission than PM₁₀, the former was selected into the statistical model instead.

There was also seasonal effect on the air pollutants. Using 20°C as the cut off temperature, a lower temperature was associated with a higher level of mean daily PM₁₀, PM_{2.5} and NO₂ but a lower level of mean 8-hour O₃ level. In addition, the mean number of daily

admissions was also higher with a lower temperature (74.5 vs 61.9, $p < 0.0001$). The interaction between seasons and individual pollutants is shown in Table 5. Additive effect of the cold weather on the pollutants on COPD admissions was observed for NO₂, O₃ and SO₂ (RR [95%CI] 1.016 [1.009 - 1.024], 1.020 [1.008 - 1.031] and 1.0201 [1.008 - 1.033] for NO₂, O₃ and SO₂ respectively).

Discussion

This study assessed the effects of air pollution specifically on hospitalizations due to AECOPD. All five air pollutants (NO_2 , SO_2 , O_3 , PM_{10} and $\text{PM}_{2.5}$) had a positive association with AECOPD hospitalizations with different magnitudes in terms of the relative risks and the number of lag days. Previous time series studies in Asia did not focus on COPD alone, but on all respiratory diseases admissions or all cause mortality.^{5,10,11,29} As the time frame chosen in this study was recent and for an extended duration (from Jan 2000 to Dec 2004), this study could provide updated information on the effects of air pollutants specifically on COPD.

The total number of hospital admissions in this study was high (total 119,225 admissions) when compared to other US national multicity studies (for example, a US multicity study by Medina-Ramon et al included a total of 578, 006 admissions²). As we had noted a sharp decline in the number of daily admissions in April 2003, which was most likely due to the major outbreak of SARS,^{27,28} we constructed separate models analyzing hospital admissions and air pollution data for the periods before, during and after the SARS epidemic in 2003. Although the RRs before 2003 were lower than that after 2003 for NO_2 , O_3 , PM_{10} and $\text{PM}_{2.5}$, the results were similar to those when the entire period was used for the model. Not only has this confirmed the robustness of the general additive model in correcting the potential effects caused by an epidemic that might affect the number of hospital admissions, it has shown that the relationship between air pollution and COPD admissions was not affected by an event that reduced only hospital admissions but not air pollution.

The concentrations of PM_{10} and $\text{PM}_{2.5}$ in HK were high in 2000-2004 when compared to other western countries. The mean (SD) level of PM_{10} was $50.1(23.9)\mu\text{g}/\text{m}^3$ in this current study, whereas the level from a study involving 36 American cities² in 1986 – 1999 was $30.4(5.1)\mu\text{g}/\text{m}^3$. Our median level of PM_{10} ($44.5\mu\text{g}/\text{m}^3$) was also higher than those in several European studies (median level for Stockholm, Birmingham, London and Netherlands were 13.6, 21.5, 24.9 and $33.4\mu\text{g}/\text{m}^3$ respectively). For $\text{PM}_{2.5}$, the median (IQR) level in this current study was $31.7\mu\text{g}/\text{m}^3$ (19.4–46.7), which was much higher than the level of $13.4(11.3\text{--}15.2)\mu\text{g}/\text{m}^3$ in a national US study¹. Our study had comparable levels of SO_2 , O_3 and NO_2 to the western European city such as Rome.⁷

We found that a $10\mu\text{g}/\text{m}^3$ increase in PM_{10} was associated with a 2.4% increase in hospital admission for AECOPD at a cumulative lag days of 0–5. The effect of PM_{10} on respiratory admission appeared to have a lesser magnitude in other studies. For example, in the National Mortality, Morbidity and Air Pollution Studies (NMMAPS) focused on the 20 largest metropolitan areas in the US in 1987–1994, every $10\mu\text{g}/\text{m}^3$ increase in PM_{10} level was associated with 1.5% (1.0–1.9) increase in COPD admissions.^{30–32} The NMMAPS statistical model is over-specified with regard to long-wave controlling variables for season and weather placed in the model (along with the pollution), relative to the more generally accepted methods published in the literature.^{25,33,34} This has apparently led to smaller estimates of pollution effects in publications deriving from the NMMAPS study, and the difference in estimates can be up to 2-fold.³⁴ Indeed we have found that by applying the more aggressive adjustment model of NMMAPS, the effects

of PM₁₀, NO₂, O₃ and PM_{2.5} on COPD admissions were of smaller magnitudes when compared to the APHEA2 statistical model. Our observations of underestimation of pollution effects with the NMMAPS model were similar to those reported by Schwartz et al.³³ and Ito et al.³⁴ The APHEA-2 study, which assessed the hospital admissions in 8 European cities in the mid 1990s, found an 1.0% (0.4-1.5%) increase in asthma and COPD admissions among people aged >65 years per 10 $\mu\text{g}/\text{m}^3$ increase in PM₁₀ level. However, COPD was not assessed separately in the APHEA-2 study.⁶ Our results have shown that the effect of PM₁₀ on COPD admission was similar to the NMMAPS study³⁰⁻³² based on the same method for analysis. In comparisons to the APHEA-2 study,⁶ the effect of PM₁₀ on combined COPD and asthma hospitalization in Europe were of lesser magnitude than our study.

The high PM_{2.5} level in this current study was associated with a higher impact on COPD admissions when compared to other studies. A 10 $\mu\text{g}/\text{m}^3$ increase in PM_{2.5} was associated with a 3.1% increase in COPD admissions with a cumulative lag of 0-5 in our current study (using the APHEA2 statistical model) in contrast to a recent US study (using the NMMAPS statistical model), which showed the largest effect per 10 $\mu\text{g}/\text{m}^3$ increase in PM_{2.5} occurring at lag 0 and 1 with a risk of about 0.9%.¹ Analysis of our data using the NMMAPS model has shown that each 10 $\mu\text{g}/\text{m}^3$ increase in PM_{2.5} was associated with 2.0% increase in COPD admission, and the effect of PM_{2.5} was higher than that reported by Dominici et al.¹ The higher impact on PM_{2.5} level on respiratory admissions as noted in our study may possibly be due to a higher level of PM_{2.5} in our community and a dose-response effect of the pollutants on respiratory morbidity. The effect of particulate matter on respiratory morbidity remained a focus of research. The leading hypothesis emphasized inflammatory responses in the lungs and release of cytokines with local and systemic consequences. Particulate matters may promote inflammation and thereby exacerbating underlying lung diseases and reducing the efficacy of lung-defense mechanisms.^{12,35}

Despite several previous reports in HK addressing the issue of increasing air pollution^{15,16}, the average values detected by the air quality monitoring stations for NO₂, SO₂, O₃ and PM₁₀ did not differ much when compared to a previous study conducted by Wong et al⁵ in HK in 1994-5 on the effect of air pollutants on all respiratory admissions. In fact, the effect of individual pollutants on COPD was also similar when our current study was compared to Wong's study.⁵ However, the cumulative effect for NO₂, SO₂ and PM₁₀ was assessed for up to 4 days (lag 0-3) only in the previous study⁵ whereas this study has extended the cumulative lag to 6 days (lag 0-5) for all the pollutants. We noted the most statistically significant effect of PM₁₀ on COPD admissions was at lag 0-5, in contrast to lag 0-3 as in Wong's study.⁵ Concerning the use of cumulative lags in analyzing the effects of pollutants on COPD hospitalization, the RR's derived from two different averaging period variables must be interpreted with caution. For example, it requires a longer duration of exposure to effect a change of 1 $\mu\text{g}/\text{m}^3$ in a 5-day average (ie., a 1 $\mu\text{g}/\text{m}^3$ increase on 5 consecutive days) than for that for a 1-day average increase of 1 $\mu\text{g}/\text{m}^3$ (i.e., one day increase of 1 $\mu\text{g}/\text{m}^3$ on a single day only). Our study has provided additional information on the effect of PM_{2.5} on COPD admissions whereas this aspect was not addressed in the previous study.⁵ Furthermore, multi-pollutant model specific for

AECOPD was not constructed in Wong's study.⁵ In this current study, when multiple pollutants (NO_2 , SO_2 , O_3 and $\text{PM}_{2.5}$) were analyzed together, all pollutants except NO_2 were retained in the model. As expected, the RRs of the individual pollutants were smaller than those in the single pollutant models. The effect of O_3 on COPD admissions was the greatest among the pollutants.

There were differences in the maximum effect of the individual air pollutants on COPD hospitalizations in terms of the number of cumulative lag days in this current study. Despite the use of the "best" lag calculated according to statistical criteria, these differences could possibly be explained by the chemical and toxicological properties of the individual pollutants on the airway. SO_2 is very soluble in the upper respiratory tract⁵ and thus may produce immediate irritant effect on respiratory mucosa and account for no lag days observed for SO_2 in our current study. In contrast, O_3 and NO_2 are much less soluble, enabling them to penetrate deeply into the lungs. Besides, these two gaseous pollutants and PM_{10} are highly reactive oxidants and can cause inflammation of the respiratory epithelium at high concentration.^{36,37,38} Experimental chamber exposure study has demonstrated a decrement in lung function after exposure to O_3 .³⁹ On the other hand, NO_2 exposure could enhance the recruitment of macrophages and T-lymphocytes to the airway, as evident by increased CD45RO+ lymphocytes, B-cells, and natural killer (NK) cells in the broncho-alveolar lavage of healthy volunteers.⁴⁰ As oxidant-induced airway inflammation takes time to develop, this may account for some cumulative lag days rather than an immediate effect on AECOPD admissions due to O_3 , NO_2 and PM_{10} .

In contrast to this current study, previous studies found an increased risk of respiratory admissions, including COPD and pneumonia admissions, associated with ambient O_3 and PM_{10} levels predominantly in the warm season.^{2,41,42} A previous study in the US suggested that the difference in positive effect of O_3 in different seasons on respiratory admissions might be due to higher O_3 concentration and the larger amount of time spent outdoors during the warm season. Since O_3 is a highly reactive gas, its indoor concentration is extremely low in buildings with closed windows.² In HK, the situation is quite different from the western countries as our winter season is not cold enough to require central heating in most places. Windows are often opened in winter for ventilation purpose. Summers are in generally hot and humid, and most people spend more time indoor with air-conditioning. This might explain the enhanced effects of O_3 exposure, and probably for SO_2 and NO_2 exposure, in COPD patients in winter in HK. This is supported by a previous study showing that air conditioned homes had lower air exchange rates than homes with windows opened for ventilation.⁴³ The reasons for the seasonal differences we observed in this current study when compared to other western studies are not entirely clear and further studies are needed.

Similar to other ecological studies, this study was limited by the fact that precise exposure to a specific pollutant could not be assessed. The ICD coding for identifying COPD hospital admissions might be limited by the accuracy of coding. The interaction between pollutants with the collinearity issues and limitations of the time series design imposed great difficulty for assessing which particular pollutant had a direct adverse effect on the COPD patients.

In summary, air pollutant levels of SO₂, NO₂, O₃, PM₁₀ and PM_{2.5} were all associated with increased hospital admissions for AECOPD in HK. O₃ was the most important air pollutant leading to increased hospitalizations for AECOPD whereas PM₁₀ and PM_{2.5} levels in HK were higher than in other countries. The PM₁₀ concentration had exceeded the European Union recommendation (average 24 hour concentration < 40µg/m³ by 2005).³² Public health measures are urgently needed to improve air quality in HK.

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Figure Legends:

Figure 1. (A) Number of daily admissions for COPD in January 2000 to December 2004, (B) Time plot of Pearson residuals of daily admissions for respiratory diseases based on the core model

Table 1: Daily summary of the number of COPD admissions, metrological and pollutants data

	Mean	SD	Min	Q1	Median	Q3	Max
Admissions for COPD (n)	65.3	18.9	15	52	65	78	125
Temperature (°C)	23.7	4.9	8.2	19.9	25.2	27.9	31.0
Relative humidity (%)	74.4	12.8	21.1	67.6	77.0	83.0	97.0
NO₂ (µg/m³)	51.2	21.8	10.1	35.0	50.1	64.0	157.6
PM₁₀ (µg/m³)	50.1	23.9	13.6	31.9	44.5	64.1	172.2
O₃ (µg/m³)	31.0	16.2	4.8	18.1	26.7	41.0	101.3
SO₂ (µg/m³)	15.0	11.6	0.7	7.6	12.5	19.5	99.4
PM_{2.5} (µg/m³)	35.7	20.6	6.0	19.4	31.7	46.7	163.2

SD = standard deviation

Q1 = 25th percentile

Q3 = 75th percentile

Min = minimum

Max = maximum

Table 2. Correlations between different air pollutants and meteorological variables

		SO ₂	NO ₂	PM ₁₀	O ₃	PM _{2.5}	Tempera-ture	Humidity
SO ₂	r	1.00	0.659*	0.229*	-0.037*	0.282	0.084*	0.169*
	p value	---	<0.001	<0.001	0.111	<0.001	<0.001	<0.001
NO ₂	r		1.00	0.399*	0.338*	0.441	-0.268*	0.212*
	p value		---	<0.001	<0.001	<0.001	<0.001	<0.001
PM ₁₀	r			1.00	0.421*	0.952	-0.344*	-0.390*
	p value			---	<0.001	<0.001	<0.001	<0.001
O ₃	r				1.00	0.394	-0.028	-0.106*
	p value				---	<0.001	0.236	<0.001
PM _{2.5}	r					1.00	-0.356	-0.343
	p value					---	<0.001	<0.001
Temperature	r						1.00	0.127*
	p value						---	0.001
Humidity	r							1.00
	p value							---

r = Pearson Correlation

Table 3: Relative risk with 95% confidence intervals for the pollutants per 10 $\mu\text{g}/\text{m}^3$ increase in the concentration of air pollutants for hospitalizations due to acute exacerbation of COPD (single pollutant model)

Pollutants \ Lag days	NO ₂	PM ₁₀	O ₃ (8 hours)	SO ₂	PM _{2.5}
Lag 0	1.009 (1.005-1.013)**	1.003 (1.000-1.005)*	1.002 (0.998-1.005)	1.007 (1.001-1.014)*#	1.002 (0.998-1.001)
Lag 1	1.001 (0.997-1.005)	1.005 (1.002-1.007)**	1.011 (1.008-1.015)**	0.991 (0.981-1.001)	1.003 (0.999-1.007)**
Lag 2	1.003 (0.999-1.007)	1.010 (1.007-1.012)**	1.011 (1.008-1.020)**	0.992 (0.985-1.000)	1.011 (1.007-1.014)**
Lag 3	1.010 (1.007-1.014)**	1.011 (1.008-1.013)**	1.011 (1.012-1.019)**	1.006 (0.999-1.013)	1.013 (1.010-1.017)**
Lag 4	1.010 (1.007-1.014)**	1.008 (1.006-1.011)**	1.011 (1.008-1.015)**	1.004 (0.998-1.011)	1.011 (1.008-1.015)**
Lag 5	1.008 (1.004-1.012)**	1.007 (1.004-1.009)**	1.006 (1.003-1.010)**	1.004 (0.997-1.010)	1.009 (1.006-1.013)**
Lag 0-1	1.007 (1.003-1.011)**	1.005 (1.002-1.008)**	1.011 (1.006-1.014)**	0.998 (0.991-1.006)	1.004 (0.999-1.008)
Lag 0-2	1.009 (1.004-1.013)**	1.011 (1.008-1.014)**	1.019 (1.015-1.023)**	0.993 (0.985-1.001)	1.010 (1.006-1.015)**
Lag 0-3	1.026 (1.022-1.031)**#	1.016 (1.013-1.019)**	1.027 (1.02-1.031)**	0.998 (0.989-1.007)	1.018 (1.013-1.022)**
Lag 0-4	1.021 (1.017-1.026)**	1.020 (1.017-1.024)	1.031 (1.027-1.036)**	1.001 (0.991-1.010)	1.024 (1.019-1.029)**
Lag 0-5	1.026 (1.022-1.031)**	1.024 (1.021-1.028)**#	1.034 (1.030-1.040)**#	1.004 (0.994-1.014)	1.031 (1.026-1.036)**#

Results are presented as relative risk (95% confidence interval)

* p < 0.05

** p < 0.001

highest χ^2 score (best lag)

Table 4. Relative risk with 95% confidence intervals for the pollutants per 10 $\mu\text{g}/\text{m}^3$ increase in the concentration of air pollutants for hospitalizations due to acute exacerbation of COPD (multi-pollutant model)

	NO_2 (lag0-3)	O_3 (8 hours) (lag 0-5)	SO_2 (lag 0)	$\text{PM}_{2.5}$ (lag 0-5)
4 pollutant model	0.993 (0.985-1.001)	1.029 (1.022-1.036)*#	1.008 (1.001-1.015)*	1.014 (1.007-1.022)*
3 pollutant model		1.029 (1.022-1.034)*#	1.008 (1.001-1.015)*	1.011 (1.004-1.017)*

* p<0.05

highest χ^2 score in the pollutant model

Table 5. Interaction between season and individual pollutant. Cold season is defined as the period from December to March of each year.

Pollutant	RR	95%CI	p-value	t-score
NO ₂ (lag 0-3)	1.0164	1.0086 - 1.0243	<0.0001*	4.150476
O ₃ (lag 0-5)	1.0195	1.0081 -1.0309	0.0007*	3.379242
SO ₂ (lag 0)	1.0205	1.0078 - 1.0334	0.0015*	3.178459
PM _{2.5} (lag 0-5)	0.9983	0.9891-1.0076	0.5200	0.643313
PM ₁₀ (lag 0-3)	1.0012	0.9951 -1.0073	0.7059	0.37738

RR = relative risk (The warm season was used as the reference)

95% CI = 95% confidence interval

* p <0.05



