Air pollution and hospital admissions for chronic obstructive pulmonary disease: are their potentially sensitive groups?

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Abstract. Recent studies showed that air pollution is a risk factor for hospitalization for chronic obstructive pulmonary disease (COPD). However, there is limited evidence to suggest which subpopulations are at higher risk from air pollution. This study was undertaken to examine the modifying effect of specific secondary diagnosis (including hypertension, diabetes, pneumonia, congestive heart failure) on the relationship between hospital admissions for COPD and ambient air pollutants concentrations. Hospital admissions for COPD and ambient air pollution data for Taipei were obtained for the period from 1999-2009. The relative risk of hospital admissions for COPD was estimated using a case-crossover approach. None of the secondary diagnosis we examined showed much evidence of effect modification.

Keywords: air pollution; COPD; sensitive population; case-crossover; hospital admissions

1. Introduction

Over the past decade, many epidemiologic studies demonstrated associations between high concentrations of air pollutants and daily mortality, hospital admissions, and emergency room (ER) visits (Schwartz 1994, Katsouyanni *et al.* 1997, Brunekreef and Forsberg 2005, Dominici *et al.* 2005, 2006, Zanobetti and Schwartz 2005). Although the correlation is clear, the mechanisms underlying these associations are not fully understood (Zanobetti and Schwartz 2005).

Recent epidemiologic studies showed that individuals with preexisting chronic obstructive pulmonary disease (COPD) (Sunyer *et al*. 2000, Zanobetti and Schwartz 2005, Peel *et al*. 2007),

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congestive heart failure (CHF) (Goldberg *et al*. 2001a, Kwon *et al*. 2001, Mann *et al.* 2002), diabetes (Zanobetti *et al*. 2000, Zanobetti and Schwartz 2001, 2002, Goldberg *et al.* 2001b, Bateson and Schwartz 2004, Peel *et al.* 2007), hypertension (Peel *et al.* 2007), arrhythmias (Mann *et al*. 2002), pneumonia (Zanobetti and Schwartz 2005), myocardial infarction (MI) (Peters *et al.* 2001, Bates and Schwartz 2004) or upper respiratory infections (URI) (Cheng *et al.* 2009) are at increased risk for adverse health events associated with air pollution. However, little is known of the personal characteristics that make some individuals especially sensitive to the adverse effects of air pollution (Bates and Schwartz 2004). This was identified as a key research need (National Research Council 1998). The most recent report by the National Research Council emphasized the need for continued examination of the most sensitive subgroups, including subjects with underlying cardiovascular and respiratory diseases (National Research Council 2004).

The relative risks associated with acute air pollution exposure are relatively small (Schwartz 1991). There is some consensus that only persons in poor health experience severe and acute effects (hospital admission or death) when levels of air pollutants increase (Bates 1992, Goldberg 1996, Seaton *et al*. 1995). Thus, the identification of susceptible subgroups is critically important for scientific and public health purposes, as it may provide information regarding underlying mechanisms and may target certain subgroups who need to reduce exposure during episodes of high levels of air pollution (Goldberg *et al*. 2001a).

Previous studies provided evidence of an association between higher air pollutant levels and hospital admissions or ER visits for COPD (Sunyer *et al*. 1993, Anderson *et al*. 1997, Burnett *et al.* 1995, Chen *et al.* 2000, 2004, Moolgavkar *et al.* 1997, Morgan *et al.* 1998, Dominici *et al.* 2006, Yang and Chen 2007, Lee *et al.* 2007, Sauerzapf *et al*. 2009, Halonen *et al.* 2008, 2009). However, relatively little is known regarding the populations particularly susceptible to these exposures (Zanobetti and Schwartz 2001, Zanobetti *et al.* 2000). This study was undertaken to explore the modifying effect of specific secondary diagnosis (including hypertension, diabetes, pneumonia, and CHF) on the relationship between hospital admissions for COPD and ambient air pollutants among individuals residing in Taipei city, the largest city in Taiwan, over a 11 year period from 1999-2009, using a case-crossover analysis.

2. Materials and methods

Taipei city, situated in the northern part of Taiwan, is the largest metropolitan city in Taiwan. It has a total area of approximately 271.80 km^2 with a population of about 2.64 million. The major source of air pollution is emissions generated from automobile exhaust (Chang *et al*. 2005).

2.1 Hospital admissions

The National Health Insurance (NHI) Program, which provides compulsory universal health insurance, was implemented in Taiwan on March 1, 1995 and covers most of the population (the coverage rate was 96% in 2000) (BNHI 2001). Most medical institutions (93%) are contracted to the Bureau of NHI (BNHI), and those not contracted provide much fewer health services. More than 98% of the population who are covered by NHI use health services at least one time through contracted medical institutions. Computerized records of daily clinic visits or hospital admissions are available for each contracted medical institution. All medical institutions must submit standard claim

documents for medical expenses on a computerized form which includes the date of admission and discharge, identification number, gender, birthday, and the diagnostic code of each admission. Therefore, the information from the NHI database appears to be sufficiently complete for use in epidemiological studies.

We extracted data on all hospital admissions from the medical insurance file for the period 1999-2009. Cases were defined as those subjects who were admitted to the hospital with a primary diagnosis of COPD (International Classification of Diseases, 9th revision [ICD-9] code 490-496, excluding 493). The co-morbid health conditions for each admission were defined by the use of all secondary ICD-diagnosis codes listed on the index admission (up to 4 diagnoses). The co-morbid health conditions that were examined were defined as follows: hypertension (codes 401-405), diabetes (code 250), dysrhythmia (code 427), ischemic heart disease (IHR) (codes 410-414), CHF (code 428), pneumonia (codes 480-486), upper respiratory infections (URI) (codes 460-466), and asthma (code 493).

2.2 Air pollution and meteorological data

Six air quality monitoring stations were established in Taipei city by the Taiwanese Environmental Protection Administration (EPA), a central governmental agency (Fig. 1). The monitoring stations were fully automated and provided daily readings of levels of sulphur dioxide (SO_2) (by ultraviolet fluorescence), particulate matter (PM_{10}) (by beta-ray absorption), nitrogen dioxide (NO_2) (by ultraviolet fluorescence), carbon monoxide (CO) (by nondispersive infrared photometry), and ozone (O_3) (by ultraviolet photometry). For each day, air pollution data were extracted from all monitoring stations and averaged. Daily information on mean temperature and mean humidity was provided by the Taipei Observatory of the Central Weather Bureau.

2.3 Statistics

The data were analyzed using the case-crossover technique (Maclure 1991, Marshall and Jackson 1993, Mittleman *et al*. 1995). This design is an alternative to Poisson time series regression models for studying the short-term effects attributed to air pollutants (Levy *et al.* 2001). In general, the case-crossover design and the time-series approach yielded almost identical results (Neas *et al*. 1999, Lee and Schwartz 1999, Lu and Zeger 2007).

The time-stratified approach for the case-crossover analysis was used (Levy *et al.* 2001). A stratification of time into separate months was made to select referent days as the days falling on the same day of the week within the same month as the index day. Air pollutant levels during the case period were compared with exposures occurring on all referent days. This time-stratified referent selection scheme minimizes bias due to non-stationary air pollution time-series data (Lumley and Levy 2000, Janes *et al.* 2005, Mittleman 2005). The results of previous studies indicated that the increased hospital admissions were associated with higher air pollutant levels on the same day or the previous 2 days (Katsouyanni *et al.* 1997). Longer lag times have rarely been described. Thus, the cumulative lag up to 2 previous days (i.e., the average air pollution levels of the same and previous 2 days) was used. Because pollutants vary considerably by season, especially O_3 and particles; therefore, seasonal interactions between air pollutants and hospital admissions have often been reported. However, previous studies were conducted mostly in countries (England, USA, Canada, Holland, etc.) where the climates are substantially different from that in Taipei (Yang *et al.*

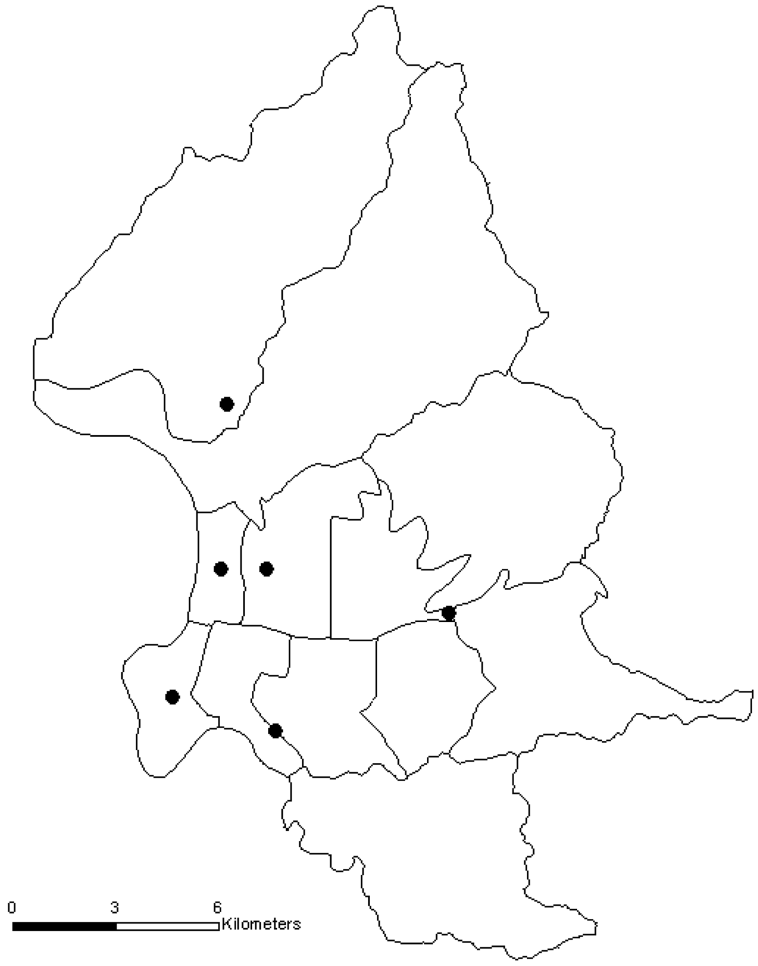

Fig. 1 Map of Taipei city showing location of the air quality monitoring stations

2004, 2006, Chang *et al*. 2005, Yang 2008), which has a subtropical climate with no apparent 4-season cycle. Hence, in this study the possible interaction of seasonality on the effects of air pollutants was not considered; however, temperature was used instead. The adverse health effects of each air pollutant were examined for the "warm" days (days with a mean temperature above 23°C) and "cool" days (days with a mean temperature below 23°C) separately.

The associations between hospital admissions and the levels of air contaminants were estimated using the odds ratio (OR) and their 95% confidence intervals (CI) which were produced using conditional logistic regression with weights equal to the number of hospital admissions on that day. All statistical analyses were performed using the SAS package (version 9.1; SAS Institute, Inc., Cary, NC). Exposure levels to air pollutants were entered into the models as continuous variables. Meteorologic variables (daily average temperature and humidity on the same day) which might play a confounding role were included in the model. OR were calculated for the interquartile (IQR) difference (between the 25th and the 75th percentile) of each pollutant, as observed during the study

period.

To examine potential effect modification of the influence of air pollutants on the risk of hospital admissions for COPD, analyses stratified by the presence or absence of a secondary diagnosis were conducted as described above. Chi-square statistic and corresponding two-sided p values were calculated to assess the heterogeneity of the pollution regression coefficients from the two strata.

3. Results

During the 11 years of the study, there were a total of 58,861 COPD hospital admissions for the 47 hospitals in Taipei city. There was an average of 14.65 daily COPD hospital admissions in the city over the study period.

The descriptive statistics for the daily air pollutant levels, as well as absolute difference between air pollutant levels on case days and average concentrations on control days (Kunzli and Schindler 2005) are shown in Table 1.

The Pearson's correlation coefficients among the air pollutants are presented in Table 2. There was a certain degree of correlation among the pollutants, especially between NO_2 and CO ($r = 0.77$) and between SO_2 and PM_{10} ($r = 0.52$). The correlation coefficients among the six monitoring stations ranged from for 0.67 to 0.93 for PM_{10}, 0.42 to 0.83 for SO_2, 0.49 to 0.89 for NO_2, 0.38 to 0.90 for CO, and 0.76 to 0.93 for O_3.

Table 3 shows the number and percentage of COPD admissions in the presence of the secondary diagnosis and by age and gender groups. Of these cases, 73.1% were male. 83.16% were among subjects 65 years of age and older. Hypertension, diabetes, pneumonia, and CHF were were the

Table 1 Distribution of COPD admissions, weather, and air pollution variables in Taipei, Taiwan, 1999-2009

Variable	Min	25%	50%	75%	Max	Mean
Distribution of daily concentrations						
PM_{10} ($\mu g/m^3$)	14.42	34.57	46.09	61.82	313.34	50.97
SO_2 (ppb)	0.15	2.64	3.71	5.01	12.7	3.94
NO_2 (ppb)	3.22	22.09	27.02	32.48	78.28	27.59
CO (ppm)	0.12	0.63	0.87	1.16	3.98	0.93
O_3 (ppb)	2.69	16.64	22.66	28.97	70.89	23.31
Temperature (^oC)	8.1	19.43	24	28.12	33	23.55
Humidity (%)	31.37	68	74.18	81	98	74.29
COPD admissions	0	10	14	18	42	14.65
Distribution of the absolute differences between the average level on case days and the average level on referent days						
PM_{10} ($\mu g/m^3$)	-118.55	-15.51	-1.41	13.39	265.35	0.39
SO_2 (ppb)	-7.54	-1.22	-0.11	1.14	9.77	0.03
NO_2 (ppb)	-31.8	-5.27	-0.23	5.35	40.08	0.24
CO (ppm)	-2.22	-0.18	-0.01	0.18	2.14	0.01
O_3 (ppb)	-32.43	-6.43	-0.09	6.12	48.23	0.01

Abbreviation: Min, minimum value; Max, maximum value

Table 2 Correlation coefficients among air pollutants

Variable	PM_{10}	SO_2	NO_2	CO	O_3
PM_{10}	1.00	0.52	0.48	0.28	0.35
SO_2	-	1.00	0.45	0.29	0.06
NO_2	-	-	1.00	0.77	-0.01
CO	-	-	-	1.00	-0.25
O_3	-	-	-	-	1.00

Table 3 Distribution of COPD admissions by age, gender, and secondary diagnosis in Taipei, Taiwan, 1999-2009

Variable	No. of events (%)	
COPD admission	58,861	
Age		
< 65	9,913	(16.8%)
≥ 65	48,948	(83.2%)
Gender		
Male	43,015	(73.1%)
Female	15,846	(26.9%)
Secondary diagnosis		
Hypertension	17,290	(29.4%)
Diabetes	9,264	(15.7%)
Pneumonia	7,079	(12.0%)
CHF	5,083	(8.6%)
Dysrhythmia	4,178	(7.1%)
URI	1,008	(1.7%)
Asthma	933	(1.6%)
AMI	212	(0.4%)

secondary diagnosis most frequently reported (29.5%, 15.7%, 12%, and 8.6%, respectively).

Table 4 shows the results of the stratified analysis to examine effect modification by secondary diagnosis. There were small numbers of admissions with co-morbid asthma, URI, AMI, and dysrhythmia, resulting in unstable models; therefore, the results for these co-morbid conditions are not presented.

Associations of admissions in relation to air pollutants were similar among patients with co-morbid hypertension and patients without hypertension both on warm and cool days. The OR for these air pollutants among patients with co-morbid hypertension expressed as a range were 1.04-1.24 per IQR rise of pollutant compared with 1.03-1.21 per IQR increase in patients without co-morbid hypertension on warm days. The ranges were 0.99-1.13 and 0.99-1.14, respectively, on cool days.

Associations of admissions in relation to air pollutants were similar among patients with co-morbid diabetes and patients without diabetes both on warm and cool days. The OR for these air pollutants among patients with co-morbid diabetes expressed as a range were 1.04-1.25 per IQR rise of pollutant compared with 1.03-1.22 per IQR increase in patients without co-morbid diabetes on warm

Table 4 OR (95% CI)* of COPD admissions for each nterquartile range increase† by secondary diagnosis in Taipei, Taiwan, 1999-2009

Comorbid	Pollutant				
	PM_{10}	SO_2	NO_2	CO	O_3
Warm days (n=2,231)					
Hypertension					
With	1.09 (1.04-1.14)	1.04 (0.99-1.09)	1.14 (1.09-1.19)	1.24 (1.15-1.33)	1.12 (1.07-1.17)
Without	1.09 (1.06-1.13)	1.03 (1.00-1.06)	1.13 (1.10-1.16)	1.21 (1.16-1.27)	1.12 (1.09-1.15)
Diabetes					
With	1.08 (1.01-1.15)	1.04 (0.98-1.10)	1.16 (1.09-1.23)	1.25 (1.13-1.38)	1.12 (1.05-1.19)
Without	1.09 (1.07-1.12)	1.03 (1.01-1.06)	1.13 (1.10-1.16)	1.22 (1.17-1.27)	1.12 (1.09-1.15)
Pneumonia					
With	1.10 (1.02-1.18)	1.02 (0.95-1.09)	1.12 (1.04-1.20)	1.20 (1.07-1.35)	1.15 (1.07-1.24)
Without	1.09 (1.06-1.12)	1.03 (1.01-1.06)	1.14 (1.11-1.16)	1.22 (1.17-1.27)	1.11 (1.09-1.14)
CHF					
With	1.03 (0.94-1.13)	0.99 (0.90-1.09)	1.11 (1.02-1.21)	1.16 (1.01-1.34)	1.11 (1.02-1.21)
Without	1.10 (1.07-1.13)	1.04 (1.01-1.06)	1.14 (1.11-1.16)	1.23 (1.18-1.27)	1.12 (1.09-1.14)
Cool days (n=1,787)					
Hypertension					
With	1.06 (1.03-1.10)	0.99 (0.95-1.03)	1.10 (1.06-1.15)	1.11 (1.05-1.17)	1.13 (1.07-1.20)
Without	1.07 (1.04-1.09)	0.99 (0.96-1.02)	1.13 (1.10-1.16)	1.14 (1.10-1.18)	1.11 (1.07-1.15)
Diabetes					
With	1.07 (1.02-1.13)	0.99 (0.93-1.05)	1.10 (1.04-1.17)	1.12 (1.04-1.22)	1.12 (1.03-1.21)
Without	1.06 (1.04-1.09)	0.99 (0.96-1.01)	1.12 (1.10-1.15)	1.13 (1.10-1.17)	1.12 (1.08-1.16)
Pneumonia					
With	1.06 (0.99-1.12)	0.99 (0.92-1.06)	1.12 (1.04-1.19)	1.13 (1.03-1.24)	1.13 (1.03-1.25)
Without	1.07 (1.05-1.09)	0.99 (0.97-1.01)	1.12 (1.10-1.15)	1.13 (1.10-1.17)	1.11 (1.08-1.15)
CHF					
With	1.11 (1.03-1.19)	1.02 (0.93-1.12)	1.14 (1.05-1.24)	1.18 (1.05-1.33)	1.13 (1.01-1.27)
Without	1.06 (1.04-1.08)	0.98 (0.96-1.01)	1.12 (1.09-1.14)	1.12 (1.09-1.16)	1.12 (1.08-1.15)

* Adjusted for temperature and humidity
† Calculated for an interquartile range increases of PM_{10} (27.25 μg/m3), SO_2 (2.37 ppb), NO_2 (10.39 ppb), CO (0.53 ppm), and O_3 (12.33 ppb)

days. The ranges were 0.99-1.12 and 0.99-1.13, respectively, on cool days.

Similarly, associations of hospital admissions for COPD with respect to air pollutants and presence or absence of pneumonia and CHF on both warm and cool days was not significant.

4. Conclusions

Numerous studies have found an association between air pollutants and hospital and emergency department admissions for COPD (Sunyer *et al*. 1993, Anderson *et al.* 1997, Burnett *et al.* 1995,

Chen *et al.* 2000, 2004, Moolgavkar *et al.* 1997, Morgan *et al.* 1998, Dominici *et al*. 2006, Yang and Chen 2007, Lee *et al.* 2007, Sauerzapf *et al.* 2009, Halonen *et al.* 2008, 2009). In this study, we examined whether the effect of air pollutants on the risk of hospital admissions for COPD depending on the presence of co-morbidities. None of the secondary diagnosis that we examined (hypertension, diabetes, pneumonia, CHF) showed much evidence of effect modification. To our knowledge, only two previous studies have examined the modifying effect of secondary diagnosis on the association between air pollution and COPD admissions. Zanobetti *et al.* (2000) found that the association between PM_{10} and the rate of admission for COPD was nearly twofold greater among patients with comorbid CHF than those without. Zanobetti and Schwartz (2001) did not find effect modification for COPD due to diabetes in all ages, but when analyzed by age, they found that diabetes is an effect modifier in the old age group (> 75 years). Our finding is not consistent with previous reports (Zanobetti and Schwartz 2001, Zanobetti *et al*. 2000). There is a need for further research on this topic.

Previous studies suggest that COPD patients are more susceptible to PM-related hospital admissions for cardiovascular disease (Peel *et al.* 2007, Zanobetti *et al.* 2000) and nonaccidental mortality (Sunyer *et al.* 2000). Bateson and Schwartz (2004), however, reported no increased risk of mortality in relation to PM_{10} in persons with existing COPD. Epidemiologic panel studies that examined the effect of PM on lung function demonstrated greater declines in forced expiratory volume 1 second and forced vital capacity in persons with COPD versus those without in response to PM exposure (Lagorio *et al.* 2006, Trenga *et al*. 2006, Sacks *et al.* 2011).

The case-crossover study design was proposed by Maclure (1991) to study the effects of transient, intermittent exposures on the subsequent risk of rare acute-onset events in close temporal proximity to exposure. This design offers the ability to control many confounders by design rather than by statistical modelling. This design is an adaptation of the case-control study in which each case serves as his or her own referent. Therefore time-invariant subject-specific variables such as gender and age do not act as confounders. In addition, time-stratified approach (Levy *et al.* 2001) was found to be effective in controlling for seasonality, time trends, and chronic and slowly varying potential confounders (Lumley and Levy 2000, Janes *et al.* 2005, Mittleman 2005).

Exposure measurement error is a common concern in environmental epidemiology. Air pollutant levels were assigned from fixed, outdoor monitoring stations to individuals to estimate exposure. Exposure measurement errors resulting from the differences between the population-average exposure and ambient contaminant levels are not avoidable. However, the potential for misclassification of exposure due to the lack of personal measurements of air pollutant exposure in this study is of the Berkson type and known to produce a bias toward the null and an underestimate of the association (Katsouyanni *et al.* 1997, Zeger *et al.* 2000).

Misclassification of co-morbid diseases due to diagnostic or coding errors is possible. However, these errors are unlikely to be related to air pollutant levels. Nonetheless, this non-differential misclassification is expected to reduce the precision of our estimates and potentially bias the relative risk estimates toward the null.

Our study population is homogenous in terms of race compared with populations in other cities. This study was conducted in a subtropical city. These facts may restrict somewhat the generalizability of these findings to other locations with different meteorological and racial characteristics. Furthermore, behavior such as air conditioning use or time spent outdoors may affect personal exposures. This could affect the magnitude of the observed associations in comparison with other geographic locations. Further, the admission dates may have differed from the dates of symptom onset in some cases,

resulting in non-differential exposure misclassification and causing a bias toward the null and an underestimate of association.

Our results do not support effect modification by the presence of comorbidities, especially for diabetes and CHF, which have been found to modify the association between air pollution and COPD in previous studies (Zanobetti and Schwartz 2001, Zanobetti *et al.* 2000). The reasons are unknown. Taiwan is a small island with a convenient communication network. As many as 96% of the people in Taiwan have joined the NHI since 1996. Logically, it is feasible that all of study population had access to medical care and the comorbid diseases are better controlled in our study population compared to the population in other studies. This could be a reason for not seeing stronger results in those patients with the comorbid diseases. Another explanation may be that comorbid disease status are too insensitive to produce effect modification.

In summary, this study did not observe evidence of effect modification by presence of hypertension, diabetes, pneumonia, and CHF of the association of air pollution and COPD admissions. Because this study is one of the few of its kind, this findings need to be replicated in additional cities. Further epidemiologic studies are required to confirm or refute these findings.

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