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Exposure to air pollutants and mortality in hypertensive patients according to demography: A 10 year case-crossover study

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This study evaluated whether short term exposures to NO_2, O_3, particulate matter <10 mm in diameter (PM_{10}) were associated with higher risk of mortality. A total of 223,287 hypertensive patients attended public health-care services and newly prescribed at least 1 antihypertensive agent were followed-up for up to 5 years. A time-stratified, bi-directional case-crossover design was adopted. For all-cause mortality, significant positive associations were observed for NO_2 and PM_{10} at lag 0–3 days per 10 $\mu g/m^3$ increase in concentration (excess risks 1.187%–2.501%). Significant positive associations were found for O_3 at lag 1 and 2 days and the excess risks were 1.654% and 1.207%, respectively. We found similarly positive associations between these pollutants and respiratory disease mortality. These results were significant among those aged ≥65 years and in cold seasons only. Older hypertensive patients are susceptible to all-cause and respiratory disease-specific deaths from these air pollutants in cold weather.

1. Introduction

Globally, air pollution in indoor and outdoor environment has been a substantial public health issue. The World Health Organization has addressed the health effects of air pollutants, including nitrogen dioxide (NO_2), ozone (O_3), sulfur dioxide (SO_2), and particulate matters (PM) in the Air Quality Guidelines Global Update 2005 (WHO, 2006). Particulate matter with an aerodynamic diameter <10 μm (PM_{10}) is the most frequently used indicator for suspended particles in the air, and the highest concentrations of PM_{10} were reported in Asia (WHO, 2006).

There has been substantial evidence linking air pollution and adverse health outcomes in different countries (Samet et al., 2000; Le Tertre et al., 2002; Katsouyanni et al., 1997; Wong et al., 2002; Pönkä and Virtanen, 1996; Ballester et al., 2001; Neas et al., 1999; Medina et al., 2004; Kan et al., 2003; Ruidavets et al., 2005; Dominici et al., 2006, 2005; Brunekreef and Forsberg, 2005; Zanobetti et al., 2009; Holguín et al., 2003; Koken et al., 2003; Ostro et al., 2011; Anderson et al., 2010; Henrotin et al., 2007; Qian et al., 2013). These studies utilized a variety of modeling methods, including log-linear regression models (Samet et al., 2000), autoregressive Poisson models (Le Tertre et al., 2002; Ballester et al., 2001), analysis of time series data (Katsouyanni et al., 1997), and Poisson regression of ecological data (Wong et al., 2002; Pönkä and Virtanen, 1996). Some studies employed aggregate instead of individual data (Medina et al., 2004; Brunekreef and Forsberg, 2005) by health impact assessment, or analyzed the linkage by generalized addictive models (Dominici et al., 2005). Very few reports studied mortality outcomes using territory-wide individual data by case-crossover analysis, which has been recognized as one of the most robust study designs in evaluating the health effect of short-term exposures to air pollutants.

In a recent meta-analysis conducted by Lai and colleagues (Lai et al., 2013), a total of 48 studies conducted in Chinese populations have been identified. Yet the authors raised the potential caveats of search bias as the literature search is based on one database (PubMed) only, and that for each pollutant some heterogeneity was detected due to several studies (Lai et al., 2013).

The Air Quality Guideline (AQG) of the WHO recommended future research to enable emerging environmental equity data to be incorporated into air pollution guidelines and policy action (WHO,

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2006). Studies that aim to evaluate the heterogeneity of exposure-response function according to age, gender and other demographics are particularly relevant. Most of the studies performed among Chinese subjects reported that the pollutant levels were higher than the WHO annual AQG (WHO, 2006), or the derived annual mean according to the WHO short-term AQG (Lai et al., 2011).

We have recently established a big database consisting of more than 220,000 Chinese hypertensive patients seen in the public sector of the whole territory of Hong Kong. Individual data, instead of aggregate information, are available. According to the WHO recommendation for future research, this study aims to evaluate the association between short-term air pollution and all-cause, cardiovascular, respiratory and injury-specific mortality in this large population-based cohort of Chinese subjects, and identify the subgroups of individuals who are more susceptible of the harms due to exposure to these pollutants.

2. Materials and methods

2.1. Mortality data

The data were from a population-based cohort of hypertensive patients who attended any public health-care sectors in Hong Kong which provide services for more than 90% of all patients with chronic diseases in the whole Hong Kong territory. They were prescribed at least one antihypertensive agent for the first time by the clinics or hospitals between 2001 and 2005. Detailed description of the dataset was presented elsewhere (Wong et al., 2013a,b,c,d, 2011, 2010a,b, 2009a,b, 2008) and the patients were followed-up till 2010 or their death, whichever was earlier. A clinical database which has previously been established and validated was used (Wong et al., 2008). It has a high level of completeness with respect to its socio-demographic details (100%) and prescription records (99.8%) (Wong et al., 2008). This computerized system represents the sole portal of data entry, allowing linkage of physician-entered information at each patient visit in all public clinical settings in all districts of Hong Kong. This study included all people who visited the public healthcare sector and who resided in Hong Kong. The population is more than seven million as of 2012. Hong Kong is divided into three distinct regions, namely Hong Kong Island (most urbanized); Kowloon; and the New Territories (most rural). The ethics clearance of the study was obtained from the Clinical Ethics Research Committee of the Hospital Authority, and the Survey and Behavioral Research Ethics Committee of The Chinese University of Hong Kong. Informed consent was not necessary as all subjects were anonymized with unique identity numbers. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. The cases in this study were defined as the deaths of these patients. Four types of mortality were considered, namely death due to any causes, respiratory diseases (ICD-10: J000-J999), cardiovascular diseases (ICD-10: I000-I999), and injury (ICD-10: S000-T999). Since there has been no biological plausibility between exposure to pollutants and injury, mortality due to any injury was included as an outcome measure (in which its association with pollutant exposure was expected to be zero) to explore if our database and analysis are robust. The vast majority of all mortality in Hong Kong was certified and documented in hospitals, allowing accurate ascertainment of mortality (Sun et al., 2011). Some studies have employed death outcome in hospitals as a valid representation of patient death, since death usually occurs in hospitals for Chinese patients (Sun et al., 2011; Schooling et al., 2006; Lam et al., 2001). The causes of death due to different diseases were defined according to the primary cause of mortality for each patient, as determined by the physicians-in-charge when death was registered in the death certificates. The information on mortality was obtained from a valid public hospital death registry.

2.2. Air pollution and meteorological data

Data regarding hourly concentration of nitrogen dioxide (NO_2), ozone (O_3), and particulates with an aerodynamic diameter less than 10 μm (PM_{10}) were obtained in the study period 2001–2010 from the air monitoring stations of the Environmental Protection Department, Hong Kong Government (Pearl River Delta Regional Air Quality Monitoring Network). The level of SO_2 in Hong Kong was very low, and was therefore not included in the present analysis. To ensure the air quality results attained a high degree of accuracy and precision, the Government developed a quality system and established a set of Standard Operation Procedures on quality assurance and quality control (Pearl River Delta Regional Air Quality Monitoring Network). These include the zero/span checks, dynamic calibration, and precision checks. The methods used in measuring air pollutant concentration are widely recognized, including a combination of UV fluorescence, differential optical absorption spectroscopy, chemiluminescence, UV absorption, oscillating microbalance, and BETA particulate monitoring (Pearl River Delta Regional Air Quality Monitoring Network). The daily mean concentration of each pollutant was computed as the average of the hourly data if more than two-thirds of the hourly data were available for that day; otherwise, the daily mean was deemed as missing. Missing daily concentrations in one station were predicted by a regression of data from that station on the corresponding data from the nearest neighboring station (Duffy, 2006). The daily mean temperatures and relative humidity at different districts were acquired from the Hong Kong Observatory (Hong Kong Observatory).

2.3. Statistical analysis

A bi-directional case-crossover design was used to examine the association between air pollutants, meteorological variables and mortality due to different causes (Neas et al., 1999). This design was developed to study the effects of short-term exposures to air pollutants on the risk of acute events (Jaakkola, 2003; Maclure, 1991). Cases were all subjects who died during the study period. In this study, each subject served as his own control and the covariate levels at the date of death (case day) were compared with levels obtained in a period chosen before and after the death (control days). The control days were selected to represent the usual exposure levels in the source population that lead to death. Moreover, we used a bidirectional control period before and after the day of death. This allowed for individual adjustment for seasonality, longer-term trends and days of the week. In order to adjust for the effects of public holidays and influenza outbreaks, an additional analysis was conducted where patients who died in these periods, respectively, were excluded. The control days were selected 7 and 14 days before and after the case day. Conditional logistic regression analysis was performed to estimate the association between death due to the specific cause and each of the air pollutants/meteorological variables. Thus, odds ratios (OR) and their 95% confidence intervals (95% CI) were computed. The analyses were stratified by season, namely cold season (from December to March) and warm season (from April to November) as a previous study showed that season was a significant factor influencing clinical outcomes (Neas et al., 1999). For each outcome, if significant association with the variables were found from the conditional logistic regression, those variables would be included in the multivariate conditional logistic regression for examination of association with the respective outcome. The ORs of death were computed by an increment of 10 units ($\mu g/m^3$) of pollutant concentration for each pollutant, and an increment of 1 unit for temperature (°C) and humidity (1%). The ORs were then converted to excess risk in percentages. The conditional logistic regression analysis was conducted using the PHREG procedure of SAS (Neas et al., 1999). Stratified analyses according to age (<65 years vs. ≥ 65 years) on the day of mortality and gender were also conducted for those mortality outcomes which have been identified as significantly associated with air pollutant levels. The effect of air pollutants with different lag structures (from lag 0 to lag 3) was examined. Lag 0 represents the current-day pollutant concentration; lag 1 represents the concentration in the previous 1 day, and so on.

Table 1
Characteristics of the 44,104 deaths from the cohort of hypertensive patients.

Characteristics	Frequency (%)
Gender	
Male	22,420 (50.8%)
Female	21,684 (49.2%)
Age (years)	77.8 (13.5)[a]
District	
Hong Kong	7,911 (18.0%)
Kowloon	17,011 (38.6%)
New Territories	19,126 (43.4%)
Service type	
In-/day- patient Clinic	4,584 (10.4%)
Special Outpatient Clinic	3,598 (8.2%)
Accident & Emergency Department	10,524 (23.9%)
General Outpatient Clinic	18,960 (43.0%)
Others	6,315 (14.3%)
Co-morbidity	
0	17,290 (39.3%)
1	19,790 (44.9%)
≥2	6,968 (15.8%)
Public assistance needed	
Yes	13,950 (31.7%)
No	30,098 (68.3%)
Seasons	
Warm	15,879 (36.0%)
Cold	28,225 (64.0%)
Causes of death	
All-cause	44,104
Cardiovascular	8,846 (20.1%)
Respiratory disease	11,554 (26.2%)
Injury	808 (1.8%)
Others	22,896 (51.9%)

[a] Figures refer to mean (SD).