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Short-Term Effects of Fine Particulate Air Pollution on Ischemic Heart Disease Hospitalizations in Taipei: A Case-Crossover Study

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ABSTRACT

This study was undertaken to determine whether there was a correlation between fine particles ($PM_{2.5}$) levels and hospital admissions for ischemic heart disease (IHD) in Taipei, Taiwan. Hospital admissions for IHD and ambient air pollution data for Taipei were obtained for the period from 2006–2010. The relative risk of hospital admissions was estimated using a case-crossover approach, controlling for weather variables, day of the week, seasonality, and long-term time trends. For the single pollutant model (without adjustment for other pollutants), increased IHD admissions were significantly associated with $PM_{2.5}$ on both warm (> 23°C) and cool days (< 23°C), with an interquartile range increase associated with a 12% (95% CI = 10%–14%) and 4% (95% CI = 2%–6%) increase in IHD admissions, respectively. In the two-pollutant models, $PM_{2.5}$ remained significant after the inclusion of SO_2 or O_3 both on warm and cool days. This study provides evidence that higher levels of $PM_{2.5}$ increase the risk of hospital admissions for IHD.

Keywords: Fine particulate; Air pollution; Ischemic heart disease; Case-crossover; Hospital admissions.

INTRODUCTION

Over the past decade, many epidemiologic studies demonstrated positive associations between ambient levels of airborne particulate matter (PM) (generally measured as PM with an aerodynamic diameter ≤ 10 µm [PM_{10}]) and daily mortality (Levy *et al.*, 2000; Goodman *et al.*, 2004; Pope *et al.*, 2004; Schwartz, 2004; Analitis *et al.*, 2006; WHO, 2006) and hospital admissions or emergency room (ER) visits for cardiovascular and respiratory morbidity (Zanobetti *et al.*, 2000; Le Tertre *et al.*, 2002; Samet and Krewski, 2007). The evidence on adverse effects of particulate air pollution on public health has led to more stringent standards for levels of PM in outdoor air in the USA and in other countries (Dominici *et al.*, 2006).

While previous studies have primarily used PM_{10} as an exposure indicator, fine particles (defined as PM with an aerodynamic diameter less than 2.5 µm; $PM_{2.5}$) have become a greater health and regulatory concern due to epidemiologic studies suggesting that $PM_{2.5}$ might have greater toxicity than larger particles (Schwartz *et al.*, 1996; Cifuentes *et al.*, 2000; Zanobetti *et al.*, 2009). It is now generally accepted that fine particles are more harmful to health effect than larger particles (PM_{10}) because fine particles offer a larger surface area and hence potentially larger concentrations of adsorbed or condensed toxic air pollutants per unit mass (Pope and Dockery, 2006). Indeed, this is why the World Health Organization (WHO) recommends using $PM_{2.5}$ rather than PM_{10} concentrations as air quality indicators (WHO, 2006).

Relatively few epidemiologic studies have been undertaken which address specifically the health effects of $PM_{2.5}$ because only few cities have monitored $PM_{2.5}$ recently (Host *et al.*, 2008). Several studies have investigated the relationship between fine particles and hospital admissions (or ER visits) for ischemic heart disease (IHD) (Dominici *et al.*, 2006; Host *et al.*, 2008; Haley *et al.*, 2009; Halonen *et al.*, 2009; Zanobetti *et al.*, 2009). Because these studies were conducted primarily in America and some European cities, the findings may not be applicable to Taiwan, which possibly has different air pollutant mixtures.

While many epidemiological studies in Taiwan have reported associations of mortality and morbidity with ambient PM_{10} (Yang *et al.*, 2004; Chang *et al.*, 2005; Yang *et al.*, 2007; Chiu *et al.*, 2008; Yang, 2008; Hsieh *et al.*, 2010), fewer studies have evaluated associations with $PM_{2.5}$, which is due to the lack of monitoring data (Hung *et al.*, 2012a, b).

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This study was undertaken to examine the short-term impact of $PM_{2.5}$ on daily hospital admissions for IHD among individuals residing in Taipei city, the largest metropolitan city in Taiwan, over a 5 year period from 2006–2010, using a case-crossover design.

MATERIALS AND METHODS

Taipei City

This study examined daily variations in hospital admissions for IHD in relation to $PM_{2.5}$ levels in Taipei for the 5-year period from 2006 through 2010. Taipei 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 located in northern Taiwan. The major air pollution source is automobile exhaust emission (Chang *et al.*, 2005). Taipei has a subtropical climate, with an annual average temperature of 23°C.

Hospital Admission Data

The National Health Insurance (NHI) Program, which provides compulsory universal health insurance, was implemented in Taiwan on March 1, 1995. Under the NHI, 98% of the island's population receives all forms of health care services including outpatient services, inpatient care, Chinese medicine, dental care, childbirth services, physical therapy, preventive health care, home care, and rehabilitation for chronic mental illness. Most medical institutions (93%) are contracted to the Bureau of NHI (BNHI), and those not contracted provide fewer health services. More than 96% of the population who are covered by NHI used 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 and accurate for use in epidemiological studies. Daily counts of hospital admissions for ischemic heart disease (IHD) (International Classification of Diseases, 9th revision [ICD-9] code 410-414) were extracted from the medical insurance files for the period 2006–2010.

$PM_{2.5}$ and Meteorological Data

Six air quality monitoring stations were established in Taipei city by the Taiwanese Environmental Protection Administration (EPA), a central governmental agency in 1994 (Fig. 1). The monitoring stations were fully automated and routinely monitor 5 "criteria" pollutants including sulfur 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) levels. However, $PM_{2.5}$ was not regularly monitored. $PM_{2.5}$ concentrations in Taiwan have been measured continuously since 2006. The availability

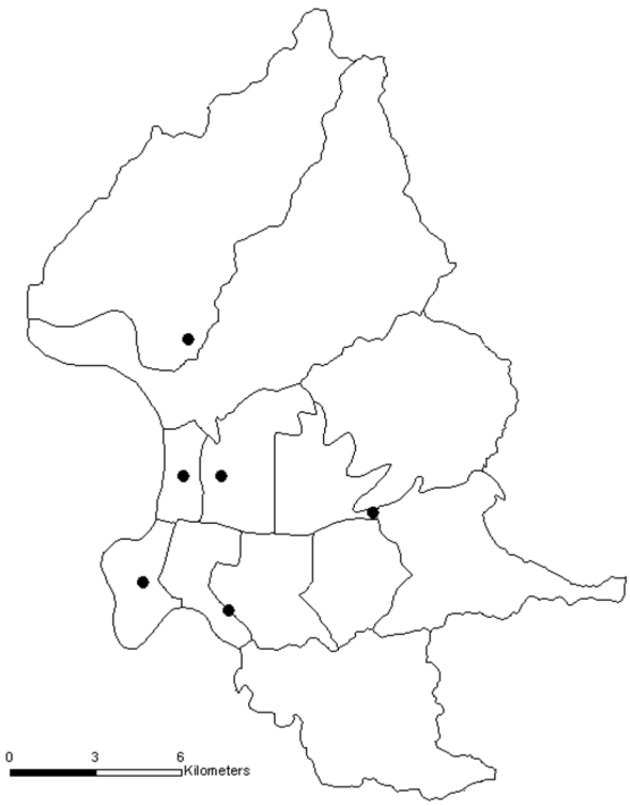

Fig. 1. Map of Taipei city showing location of the air quality monitoring stations.

of the monitoring network for $PM_{2.5}$ provided an opportunity to investigate the impact of $PM_{2.5}$ on hospital adsmissions for IHD. For each day, hourly air pollution data were obtained for all of the monitoring stations. After calculating the hourly mean of each pollutant from the 6 stations, the 24-hr average levels of these pollutants were computed. Daily information on mean temperature and mean humidity was provided by the Taipei Observatory of the Central Weather Bureau.

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 pollutant (Levy *et al.*, 2001). In general, the case-crossover design and the time-series approach yielded almost identical results (Lee and Schwartz, 1999; Neas *et al.*, 1999; Lu and Zeger, 2007).

The time-stratified approach was used for the case-crossover analysis (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 pollution 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-stationarity of air pollution time-series data (Lumley and Levy, 2000; Janes *et al.*, 2005; Mittleman, 2005). The results of previous studies indicated that increased hospital admissions were associated with high air pollutant levels on the same day or the previous two days (Katsouyanni *et al.*, 1997). Longer lag times have rarely been described. Thus the cumulative lag period up to 2 previous days (i.e., the average air pollutant levels of the same and previous 2 days) was used. Because pollutants vary considerably by season, especially O_3 and particles, seasonal interactions between $PM_{2.5}$ and hospital admissions have often been reported. However, previous studies were conducted mostly in countries where the climates are substantially different from that in Taipei (Yang *et al.*, 2004; Chang *et al.*, 2005), which has a subtropical climate with no apparent 4-season cycle. Hence in this study the potential interactions of seasonality on the effects of $PM_{2.5}$ was not considered; but 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 for IHD and levels of $PM_{2.5}$ 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 9.2; SAS Institute, Inc., Cary, NC). We fitted both single-pollutant models and two-pollutant models with a different combination of pollutants (up to two pollutants per model) to assess the stability of the effect of $PM_{2.5}$. Exposure levels to air pollutants were entered into the models as continuous variables. Meteorologic variables such as daily average temperature and humidity on the same day, which might play a confounding role, were included in the model. Inclusion of barometric pressure did not change the effect estimates and therefore was not considered in the final model. OR were calculated for the interquartile difference (IQR, between the 25th and the 75th percentile) for $PM_{2.5}$, as observed during the study period.

RESULTS

During the 5 years of the study, there were a total of 85,631 IHD hospital admissions for the 47 hospitals in Taipei city. The descriptive statistics for admissions and corresponding environmental data are shown in Table 1. There was an average of 46.9 daily IHD hospital admissions in the city over the study period.

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 PM_{10} and $PM_{2.5}$ (r = 0.78), $PM_{2.5}$ and SO_2 (r = 0.61), $PM_{2.5}$ and NO_2 (r = 0.54), $PM_{2.5}$ and CO (r = 0.54), SO_2 and NO_2 (r = 0.52), SO_2 and CO (r = 0.50), and between NO_2 and CO (r = 0.89). The correlation coefficients among the six monitoring stations ranged from 0.91 to 0.94 for $PM_{2.5}$, 0.96 to 0.98 for PM_{10}, 0.60 to 0.79 for SO_2, 0.78 to 0.92 for NO_2, 0.88 to 0.94 for CO, and 0.79 to 0.94 for O_3.

Table 1. Distribution of daily IHD admissions, weather, and air pollution variables in Taipei, Taiwan, 2006–2010.

Variable[a]	Min	Percentile			Max	Mean
		25%	50%	75%		
PM_{10} (μg/m^3)	14.26	34.89	46.83	62.37	888.02	51.71
$PM_{2.5}$ (μg/m^3)	8.35	19.46	27.06	36.92	140.54	29.99
SO_2 (ppb)	1.00	2.73	3.65	4.91	11.14	3.94
NO_2 (ppb)	3.22	19.97	23.86	28.81	55.59	24.67
CO (ppm)	0.13	0.50	0.63	0.80	1.76	0.68
O_3 (ppb)	4.00	17.95	23.95	30.23	70.89	24.65
Temperature (°C)	9.35	19.50	24.11	28.42	33.18	23.69
Humidity (%)	31.37	66.54	73.11	79.57	94.19	72.82
IHD admissions	0	26	52	63	101	46.9

Abbreviation: Min, minimum value; Max, maximum value

[a] 24-hour average

Table 2. Correlation coefficients among air pollutants.

Variable	PM_{10}	$PM_{2.5}$	SO_2	NO_2	CO	O_3
PM_{10}	1.0	0.78	0.43	0.35	0.35	0.26
$PM_{2.5}$	-	1.0	0.61	0.54	0.54	0.31
SO_2	-	-	1.0	0.52	0.50	0.06
NO_2	-	-	-	1.0	0.89	–0.07
CO	-	-	-	-	1.0	–0.23
O_3	-	-	-	-	-	1.0

Table 3 shows the effect estimates of $PM_{2.5}$ on hospital admissions for IHD in single-pollutant models and two-pollutant models. For the single pollutant model (without adjustment for other pollutants), increased IHD admissions were significantly associated with $PM_{2.5}$ both on warm days (> 23°C) and cool days (< 23°C), with an IQR increase associated with a 12% (95% CI = 10%–14%) and 4% (95% CI = 2%–6%) increase in IHD admissions, respectively.

In two-pollutant model, $PM_{2.5}$ remained significant after the inclusion of SO_2 or O_3 both on warm and cool days. It was not possible to examine the joint effect of $PM_{2.5}$ and PM_{10} in a two-pollutant model given their high correlation levels (r = 0.78).

DISCUSSION

This study is one of the few that have investigated the association between exposure to $PM_{2.5}$ and hospital admissions for IHD and is the first Asian study in this topic. Data demonstrated that the levels of $PM_{2.5}$ were positively associated with increases in the daily number of IHD hospitalizations after the inclusion of SO_2 or O_3 both on warm and cool days. The observed effect of $PM_{2.5}$ were not maintained in the presence of NO_2 or CO. This might be due to the collinearity between $PM_{2.5}$ levels and NO_2 or CO levels, which is a common problem in this type of study.

Studies on the effect of fine particles on IHD admissions are rare, and results have been inconsistent. Haley *et al.* (2009) conducted a study in New York State, and found no evidence of an association between IHD admissions and exposure to fine particles. A study in Helsinki by Halonen *et al.* (2009) also reported no evidence of positive associations between IHD admissions and $PM_{2.5}$. In contrast, Dominici *et al.* (2006) reported an association of 0.44% (95% CI = 0.02%–0.86%) increase in risk of IHD admissions per 10 μg/m^3 increase in $PM_{2.5}$ level across 204 US counties. Zanobetti *et al.* (2009) found an increase of 1.89% (95% CI = 1.34%–2.45%) in IHD emergency admissions for a 10 μg/m^3 increase in $PM_{2.5}$ level. A study in six French cities by Host *et al.* (2008) reported a 10μg/m^3 increment in the level of $PM_{2.5}$ was associated with a 4.5% (95% CI = 2.3%–6.8%) increase in IHD admission. In this study, we found a 6.87% (which corresponds to 12% increase per IQR increment) and 2.29% (which corresponds to 4% increase per IQR increment) increase in hospitalization for IHD per 10 μg/m^3 increment in the 3 day moving average (lag 2) concentrations of $PM_{2.5}$ for warm days and cool days, respectively.

In our study, effects were observed on both warm and cool days, but they were larger on warm days. We were able to confirm that particulate matter effects vary by season (Peng *et al.*, 2005; Dominici *et al.*, 2006; Bell *et al.*, 2008; Zanobetti *et al.*, 2009). Furthermore, compared with other studies in developed countries, our study found larger effect estimates per unit increase of $PM_{2.5}$. Variations in seasonal and regional effect estimates may in part result from differences in the chemical composition of $PM_{2.5}$ (Bell *et al.*, 2008). Air pollution has consistently been associated with increased hospital admissions in cities throughout the world. Recent studies suggest that the increase in hospital admissions is due primarily to $PM_{2.5}$ (Schwartz *et al.*, 1996; Suh *et al.*, 2011). Major $PM_{2.5}$ components vary by region and by season, but typically include ammonium sulfate and nitrate, elemental carbon, carbonaceous species, carbonates, metals, and water (Peng *et al.*, 2009; Lee and Hieu, 2011; Suh *et al.*, 2011). Despite considerable research, the relative

Table 3. Association between $PM_{2.5}$ and admissions for IHD in Taipei, Taiwan, 2006–2010.

Temperature		OR (95% CI)[a]
≥ 23°C (1,021 days)	Without adjustment[b]	1.12 (1.10–1.14)
	Adjusted for SO_2	1.14 (1.11–1.16)
	Adjusted for NO_2	1.02 (0.97–1.04)
	Adjusted for CO	1.01 (0.99–1.03)
	Adjusted for O_3	1.12 (1.09–1.14)
< 23°C (805 days)	Without adjustment[b]	1.04 (1.02–1.06)
	Adjusted for SO_2	1.16 (1.13–1.18)
	Adjusted for NO_2	0.99 (0.97–1.01)
	Adjusted for CO	1.03 (1.01–1.05)
	Adjusted for O_3	1.05 (1.03–1.07)

[a] Calculated for an interquartile range increases of $PM_{2.5}$ (17.46 μg/m^3) and adjusted for temperature and humidity.
[b] Single pollutant model.

toxicity of different constituents of $PM_{2.5}$ remains unclear but likely varies (Suh *et al.*, 2011).

Some pathophysiological hypotheses may be inferred to explain the association between short-term effects of $PM_{2.5}$ and IHD occurrence. Fine particles have been suggested as the effective toxic fraction of PM, because PM promote and maintain oxidative stress both at the respiratory level (the entry system) and at the systemic level where oxidative stress produces inflammation (MacNee and Donaldson, 2003; Ghio *et al.*, 2012). Cardiovascular effects may reflect neurogenic and inflammatory processes (Brook *et al.*, 2004). Mechanisms underlying the effects of $PM_{2.5}$ on cardiovascular mortality and morbidity may include changes in blood coagulability (Seaton *et al.*, 1995), increased circulating markers of inflammation (Kodavanti *et al.*, 2002; Ulrich *et al.*, 2002; Brook *et al.*, 2004), and alterations in autonomic nervous system control of the heart (Liao *et al.*, 1999; Gold *et al.*, 2000; Devlin *et al.*, 2003; Pope *et al.*, 2004; Liao *et al.*, 2011).

The origin of chemical pollutants in an urban atmosphere is known to be principally due to road traffic (Linares and Diaz, 2010a; Wang *et al.*, 2012). $PM_{2.5}$ concentrations have a less important natural component than PM_{10} concentrations. This smaller natural component makes $PM_{2.5}$ a more reliable indicator than PM_{10} for measuring anthropic activity in a large city (Linares and Diaz, 2010b; Tiwari *et al.*, 2012).

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, age, underlying chronic disease, or other individual-level characteristics 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). In general, the case-crossover design and the general additive model (GAM) approach, which has been the analytic method of choice for studying the short-term adverse effects of air pollution since 1990 (Schwartz and Marcus, 1990), produced almost identical results (Lee and Schwartz, 1999; Neas *et al.*, 1999; Lu and Zeger, 2007).

For a factor to confound the relationship between $PM_{2.5}$ levels and IHD admissions it needs to be correlated with both variables. It is unlikely that smoking and other indoor pollutants confound the present association since day to day variations in indoor emissions, including smoking need not be correlated with fine particulate air pollution.

Exposure measurement error is a common concern in environmental epidemiology. $PM_{2.5}$ levels were assigned from fixed, outdoor monitoring stations to individuals to estimate exposure (assuming that exposure was homogeneous all over the studied area). Exposure measurement errors resulting from the differences between the population-average exposure and ambient $PM_{2.5}$ levels are not avoidable. However, the potential for misclassification of exposure due to the lack of personal measurements of $PM_{2.5}$ 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).

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 might affect the magnitude of the observed associations in comparison with other geographic locations.

In summary, this study provides evidence of associations between short-term exposure to fine particles and increased hospital admissions for IHD. The ecological design of the study precludes the inference of cause and effect. However, these findings reinforce the possible role of fine particles on hospital admissions for IHD.

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