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AIR POLLUTION AND HOSPITAL ADMISSIONS FOR MYOCARDIAL INFARCTION: ARE THERE POTENTIALLY SENSITIVE GROUPS?

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Recent studies showed that air pollution is a risk factor for hospitalization for myocardial infarction (MI). However, there is limited evidence to suggest which subpopulations are at higher risk for MI arising from air pollution. This study was undertaken to examine the modifying effects of specific secondary cardiovascular diagnosis (including hypertension, diabetes, congestive heart failure, and arrhythmias) on the relationship between hospital admissions for MI and exposure to ambient air pollutants. Hospital admissions for MI and ambient air pollution data for Taipei were obtained for the period 1999–2009. The relative risk of hospital admissions for MI was estimated using a case-crossover approach. None of the secondary diagnosis examined showed significant evidence of effect modification. It would appear that the correlation between air pollutant exposure and MI occurrence is not affected by predisposing factors present in other cardiovascular diseases.

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

Epidemiologic studies showed that individuals with preexisting chronic obstructive pulmonary disease (COPD) (Peel et al. 2007; Sunyer et al. 2000; Zanobetti and Schwartz 2005), congestive heart failure (CHF) (Goldberg et al. 2001a; Kwon et al. 2001; Mann et al. 2002), diabetes (Bateson and Schwartz 2004; Goldberg et al. 2001b; Peel et al. 2007; Zanobetti et al. 2000; Zanobetti and Schwartz 2001; 2002), hypertension (Peel et al. 2007), arrhythmias (Mann et al. 2002), pneumonia (Zanobetti and Schwartz 2005), or myocardial

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infarction (MI) (Peters et al. 2001; Bateson and Schwartz 2004) are at increased risk for adverse health events associated with exposure to air pollution. However, little is known of the personal characteristics that make some individuals especially sensitive to the adverse effects of air pollutants (Bateson 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 adverse health effects associated with short-term increases in exposure to air pollutants are relatively small (Schwartz 1991). There is some consensus that only individuals in poor health experience severe and acute effects (more frequent hospital admissions or death) when levels of air pollutants rise (Bates 1992; Goldberg 1996; Seaton et al. 1995). Thus, the identification of susceptible subpopulations is critically important for scientific and public health purposes, as it may (1) provide information regarding underlying mechanisms and (2) target certain subpopulations 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 MI (D'Ippoliti et al. 2003; Lanki et al. 2006; Peters et al. 2001; 2004; Ruidavets et al. 2005; Sullivan et al. 2005; Zanobetti and Schwartz 2005; 2006). However, relatively little is known regarding the populations particularly susceptible to these exposures (D'ippoliti et al. 2003; Peel et al. 2007; Zanobetti and Schwartz 2005). This study was undertaken to examine the potential modifying effects of specific secondary cardiovascular diagnosis (including hypertension, diabetes, CHF, arrhythmias) on the correlation between hospital admissions for MI and exposure to ambient air pollutants among individuals residing in Taipei city, the largest city in Taiwan, over an 11-year period, 1999–2009, using a case-crossover analysis.

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).

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 fewer health services. More than 98% of the population who are covered by NHI use health services at least once 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 for each admission. Therefore, the information from the NHI database appears to be sufficiently complete for use in epidemiological studies.

Data on all hospital admissions were obtained 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 myocardial infarction (MI) (International Classification of Diseases, 9th revision [ICD-9] code 410). The comorbid health conditions for each admission were defined with the use of all secondary ICD diagnosis codes listed on the index admission (up to four diagnoses). The comorbid health conditions that were examined were defined as follows: hypertension (codes 401–405), diabetes (code 250), dysrhythmia (code 427), congestive heart failure (CHF) (code 428), chronic

obstructive pulmonary disease (COPD) (codes 490–496, excluding 493), pneumonia (codes 480-486), upper respiratory infections (URI) (codes 460–466), and asthma (code 493).

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 (Figure 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 humidity was provided by the Taipei Observatory of the Central Weather Bureau.

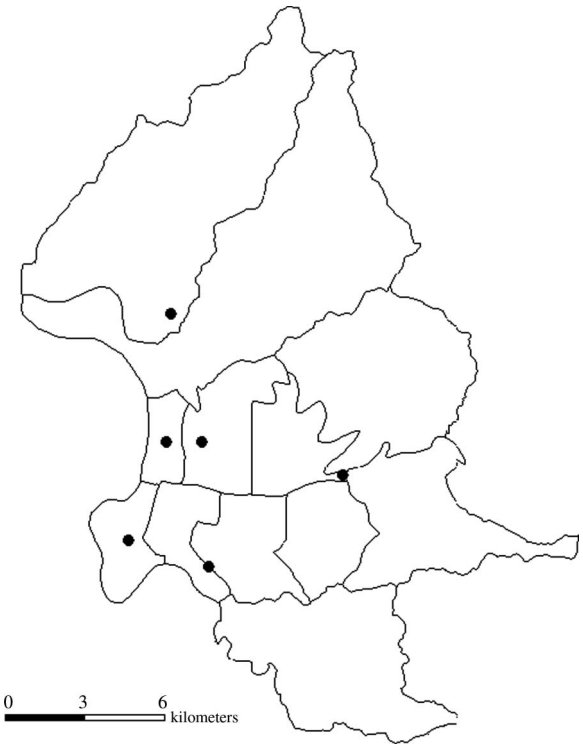

FIGURE 1. Map of Taipei city, showing locations of the air quality monitoring stations.

Statistics

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 adverse effects attributed to air pollutants (Levy et al. 2001). In general, the case-crossover design and the time-series approach yielded almost identical results (Lee and Schwartz 1999; Lu and Zeger 2007; Neas et al. 1999).

A 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 period examined were compared with exposures occurring on all referent days. This time-stratified referent selection scheme minimizes bias due to nonstationary air pollution time-series data (Janes et al. 2005; Lumley and Levy 2000; Mittleman 2005). The results of previous studies indicated that the increased incidence of hospital admissions was associated with higher 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 up to two previous days (i.e., the average air pollutant levels of the same and previous two days) was used. Because ambient air pollutants vary considerably by season, especially O_3 and PM, seasonal interactions between air pollutants levels and frequency of hospital admissions have thus been reported (D'Ippoliti et al. 2003; Katsouyanni et al. 1997). However, previous studies were conducted predominantly in countries where the climates are substantially different from that in Taipei (Chang et al. 2005; Yang 2008; Yang et al. 2004, 2006), which has a subtropical climate with no apparent four-season cycle. Hence, in this study the possible interaction of seasonality on the influence of exposure to 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 frequency of hospital admissions and the levels of air contaminants were estimated using the odds ratios (OR) and their 95% confidence intervals (CI), which were attained 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) that 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 MI, analyses stratified by the presence or absence of a secondary diagnosis were also conducted. Chi-squared statistic and corresponding two-sided p values were calculated to assess the heterogeneity of the pollution regression coefficients from the two strata.

RESULTS

During the 11 yr of the study, there were in total 27,563 hospital admissions for MI for the 47 hospitals in Taipei city. There was a daily average of 6.86 MI hospital admissions in the city over the study period.

The descriptive statistics for the daily air pollutant levels (Table 1), as well as absolute difference between air pollutant levels on study days and average concentrations on control days (Kunzli and Schindler 2005) are shown in Table 2.

The Pearson's correlation coefficients among the air pollutants are presented in Table 3. There was a certain degree of correlation among the pollutants, especially between NO_2 and PM_{10} ($r = .48$), between NO_2 and CO ($r = .77$), and between SO_2 and both PM_{10} ($r = .52$) and NO_2 ($r = .45$). The correlation coefficients among the 6 monitoring stations ranged from for 0.67 to 0.93 for PM_{10}, 0.42 to

TABLE 1. Distribution of MI Admissions and Environmental Variables in Taipei, Taiwan, 1999–2009

Parameter	Minimum value	25%	50%	75%	Maximum value	Mean
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 (°C)	8.1	19.43	24	28.12	33	23.55
Humidity (%)	31.37	68	74.18	81	98	74.29
Number of hospital admissions for MI	0	5	7	9	20	6.86

TABLE 2. Distribution of the Absolute Differences in Ambient Air Pollutants Between the Average Level on Examined Days and the Average Level on Referent Days

Parameter	Minimum value	25%	50%	75%	Maximum value	Mean
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

TABLE 3. Correlation Coefficients Among Air Pollutants

Parameter	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 4. Distribution of MI Hospital Admissions by Age, Gender, and Secondary Disease Diagnosis

Parameter	Number of events (%)
AMI admission	27,563
Age	
<65 yr	11,501 (41.7%)
≥65 yr	16,062 (58.3%)
Gender	
Male	20,508 (74.4%)
Female	7,055 (25.6%)
Secondary disease diagnosis	
Hypertension	10,989 (39.9%)
Diabetes	8,163 (29.6%)
CHF	4,183 (15.2%)
Arrhythmia	3,109 (11.3%)
COPD	1,215 (4.4%)
Pneumonia	1,836 (6.7%)
URI	240 (0.9%)
Asthma	245 (0.9%)

Note. CHF: congestive heart failure; COPD: chronic obstructive pulmonary disease; URI: upper respiratory infections.

0.83 for SO_2, 0.49 to 0.89 for NO_2, 0.38 to 0.9 for CO, and 0.76 to 0.93 for O_3.

Table 4 shows the numbers and percentages of hospital admissions for MI in the presence of the secondary disease diagnosis, as well as by age and gender. Of the total number of hospital admissions for MI, 74.4% were male and 58.3% were among subjects 65 yr of age and older. In 39.9% (n = 10,989) and 29.6% (n = 8163) of hospital admissions for MI, there was a secondary disease diagnosis of hypertension and diabetes, respectively.

Table 5 shows the results of the stratified analysis to examine effect modification by secondary disease diagnosis. There were small numbers of hospital admissions for MI with comorbid asthma, pneumonia, URI, and COPD, yielding unstable models; consequently, the results for these comorbid conditions are not presented.

The OR were numerically less in patients with hypertension compared to patients without hypertension for all air pollutants on warm days, but this difference did not reach statistical significance. However, the OR were quantitatively higher in patients with hypertension compared to patients without hypertension for all pollutants except for O_3 on cool days. This difference in OR did not reach statistical significance.

Associations of hospital admissions for MI in relation to air pollutants were similar among patients with comorbid diabetes and patients without diabetes on both warm and cool days. Similarly, correlation of hospital admissions for MI with respect to air pollutants and presence or absence of CHF and dysrhythmia on both warm and cold days was not significant.

DISCUSSION

Numerous studies demonstrated an association between air pollutants exposure and increased incidence of hospital and emergency-department admissions for MI (D'Ippoliti et al. 2003; Lanki et al. 2006; Peters et al. 2001; 2004; Ruidavets et al. 2005;Sullivan et al. 2005; Zanobetti and Schwartz 2005, 2006). Few studies examined susceptible subpopulations that might be at greater risk for hospital admissions for MI (D'Ippoliti et al. 2003; Peel et al. 2007; Zanobetti and Schwartz 2005). This study focused on the effect of exposure to air pollutants and higher risk of hospital admissions for MI depending on the presence of comorbidities. None of the secondary disease diagnoses examined, including hypertension, diabetes, CHF, and arrhythmias, showed evidence of significant effect modification.

To our knowledge, only two studies determined the modifying effect of secondary disease diagnosis hypertension on the correlation between air pollutant levels and MI admissions (D'Ippoliti et al. 2003; Peel et al. 2007). Consistent with previous reports (D'Ippoliti et al. 2003; Peel et al. 2007), our study did not show evidence of marked effect modification

TABLE 5. Odds Ratios and Confidence Limits for Hospital Admissions for MI

Comorbid disease	Ambient air pollutant									
	PM_{10}		SO_2		NO_2		CO		O_3	
Warm days ($n = 2231$)										
Hypertension										
With	1.07	(1.0–1.14)	1.02	(0.97–1.08)	1.12	(1.06–1.18)	1.21	(1.11–1.33)	1.11	(1.05–1.18)
Without	1.10	(1.05–1.15)	1.04	(0.996–1.09)	1.14	(1.09–1.19)	1.24	(1.15–1.33)	1.11	(1.06–1.16)
Diabetes										
With	1.10	(1.02–1.18)	1.05	(0.98–1.12)	1.14	(1.07–1.22)	1.25	(1.12–1.39)	1.12	(1.05–1.19)
Without	1.08	(1.04–1.13)	1.04	(0.99–1.08)	1.13	(1.08–1.18)	1.21	(1.14–1.30)	1.11	(1.07–1.16)
CHF										
With	1.11	(0.998–1.23)	1.02	(0.91–1.13)	1.14	(1.03–1.27)	1.26	(1.07–1.49)	1.09	(0.98–1.21)
Without	1.08	(1.04–1.12)	1.04	(1.00–1.08)	1.13	(1.09–1.18)	1.22	(1.15–1.30)	1.12	(1.08–1.16)
Arrhythmia										
With	1.06	(0.94–1.19)	1.04	(0.92–1.18)	1.15	(1.02–1.30)	1.21	(0.995–1.47)	1.11	(0.99–1.26)
Without	1.09	(1.05–1.13)	1.04	(1.00–1.08)	1.13	(1.09–1.18)	1.23	(1.16–1.30)	1.11	(1.07–1.15)
Cool days ($n = 1787$)										
Hypertension										
With	1.08	(1.03–1.13)	0.998	(0.94–1.06)	1.14	(1.08–1.21)	1.15	(1.07–1.25)	1.13	(1.04–1.21)
Without	1.06	(1.02–1.09)	0.97	(0.92–1.01)	1.12	(1.07–1.17)	1.12	(1.05–1.19)	1.16	(1.09–1.23)
Diabetes										
With	1.05	(0.997–1.11)	0.97	(0.91–1.04)	1.12	(1.05–1.19)	1.11	(1.02–1.22)	1.14	(1.04–1.25)
Without	1.07	(1.04–1.11)	0.98	(0.94–1.02)	1.13	(1.09–1.18)	1.14	(1.08–1.21)	1.15	(1.09–1.22)
CHF										
With	1.05	(0.97–1.13)	0.99	(0.90–1.08)	1.12	(1.02–1.23)	1.12	(0.98–1.28)	1.15	(1.01–1.30)
Without	1.07	(1.04–1.10)	0.98	(0.94–1.01)	1.13	(1.09–1.17)	1.14	(1.08–1.20)	1.15	(1.09–1.21)
Arrhythmia										
With	1.08	(0.99–1.18)	0.97	(0.87–1.09)	1.10	(0.98–1.23)	1.12	(0.95–1.31)	1.18	(1.01–1.38)
Without	1.06	(1.03–1.10)	0.98	(0.94–1.01)	1.13	(1.09–1.17)	1.13	(1.08–1.19)	1.15	(1.09–1.21)

Note. Data were adjusted for temperature and humidity. Data were 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).

by hypertension for the association of exposure to air pollution and increased risk for hospital admissions for MI.

Our study did not find evidence of effect modification by presence of diabetes on enhanced risk for hospital admissions for MI. This finding is consistent with studies of D'Ippoliti et al. (2003) and Zanobetti and Schwartz (2005). However, previous studies suggested that the presence of diabetes may modify the relationship between air pollutant exposure and higher frequency of adverse cardiovascular outcomes (Bateson and Schwartz 2004; Goldberg et al. 2001b; Peel et al. 2007; Zanobetti et al. 2000; Zanobetti and Schwartz 2001; 2002). There is a need for further research on this topic.

Previous studies suggested that CHF patients are more susceptible to pollution-related hospital admissions for ischemic heart disease (Mann et al. 2002) and nonaccidental mortality (Goldberg et al. 2001a; Kwon et al. 2001). Our study, however, found no elevated risk of hospital admissions for MI in relation to exposure to air pollution in subjects with preexisting CHF. This finding is generally consistent with other studies (D'Ippoliti et al. 2003; Zanobetti and Schwartz 2005).

Our study results did not demonstrate evidence of significant effect modification in presence of arrhythmias. These results are similar to those reported previously (D'Ippoliti et al. 2003; Peel et al. 2007). The number of hospital admissions for MI in our data set with a secondary disease diagnosis of pneumonia, URI, or COPD was low, and this stratification was not determined. Zanobetti and Schwartz (2005) reported an increased risk of ER visits for MI in relation to PM_{10} among patients with a secondary diagnosis of pneumonia or a previous admission for COPD. Zanobetti et al. (2000) found that a secondary disease diagnosis

for URI, pneumonia, and COPD modified the risk of admissions for heart disease. Peel et al. (2007), however, showed no increased risk of ER visits for ischemic heart disease in relation to air pollution exposures in persons with a comorbidity for COPD.

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, a 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 (Janes et al. 2005; Lumley and Levy 2000; 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 comorbid diseases due to diagnostic or coding errors is possible. However, these errors are unlikely to be related to air pollutant levels. Nonetheless, this nondifferential misclassification is expected to reduce the precision of our estimates and potentially bias the RR estimates toward the null.

Our study population is homogeneous 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 compared to other geographic locations.

Our results do not support significant effect modification by the presence of comorbidities of other diseases, especially diabetes, which was found to modify the association between exposure to air pollutants and increased frequency of hospital admissions for MI as reported by Peel et al. (2007). Different sources of information for comorbid conditions (emergency-department billing records in other studies vs. medical records in our study) may have different amounts of measurement errors in assessing secondary disease diagnoses. The characterization of the individual comorbidities from the secondary disease diagnoses was not optimal, given that the sensitivity of the hospital discharge records for secondary disease diagnoses is generally low (Romano and Mark 1993). The low sensitivity might have precluded us from finding significant effect modification. Taiwan is a small island with a convenient communication network. As many as 96% of individuals in Taiwan have joined the NHI since 1996. Logically, it is feasible that all of the study population had access to medical care and that the comorbid diseases are better controlled in our population compared to populations in other studies. This could also be a reason for not seeing significant results in those patients with the comorbid diseases. Another explanation may be that comorbid disease status is too insensitive to produce marked effect modification. Heart-rate variability, circulating eosinophils, and serum triglycerides measures may be more sensitive measures of effect modification (Yeatts et al. 2007).

In summary, this study did not demonstrate evidence of significant effect modification in presence of hypertension, diabetes, CHF, and arrhythmias with respect to the association between exposure to air pollutants and higher incidence of hospital admissions for MI. Hypertension is a highly prevalent chronic disease. Although the relative increase in risk was

small, given the larger number of hospitalizations for MI, even a small relative risk can account for a large number of admissions for MI, which may be of significant public health interest (Zanobetti and Schwartz 2002).

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