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Part 5

Includes Commentaries by the Institute's Health Review Committee

Part 5

Public Health and Air Pollution in Asia (PAPA): A Combined Analysis of Four Studies of Air Pollution and Mortality

C-M. Wong on behalf of the PAPA teams: Bangkok, Hong Kong, Shanghai, and Wuhan

with an Integrated Discussion by
the HEI Health Review Committee

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Part 5. Public Health and Air Pollution in Asia (PAPA): A Combined Analysis of Four Studies of Air Pollution and Mortality

C-M. Wong on behalf of the PAPA teams: Bangkok, Hong Kong, Shanghai, and Wuhan

Bangkok

N. Vichit-Vadakan, N. Vajanapoom, and B. Ostro

Faculty of Public Health, Thammasat University, Pathumthani, Thailand (N.V-V., N.V.); Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Oakland, California, U.S.A. (B.O.)

Hong Kong

C-M. Wong, T.Q. Thach, P.Y.K. Chau, E.K.P. Chan, R.Y.N. Chung, C.Q. Ou, L. Yang, J.S.M. Peiris, G.N. Thomas, T.H. Lam, T.W. Wong, and A.J. Hedley

Department of Community Medicine, School of Public Health, The University of Hong Kong, Hong Kong S.A.R., China (C.M.W., T.Q.T., P.Y.K.C, E.K.P.C., R.Y.N.C., C.Q.O., L.Y., G.N.T., T.H.L., A.J.H.); Department of Microbiology, University of Hong Kong, Hong Kong S.A.R., China (J.S.M.P.); Department of Community and Family Medicine, The Chinese University of Hong Kong, Hong Kong S.A.R., China (T.W.W.)

Shanghai

H. Kan, B. Chen, N. Zhao, S.J. London, G. Song, G. Chen, Y. Zhang, and L. Jiang

Department of Environmental Health, School of Public Health, Fudan University, Shanghai, China (H.K., B.C., Y.Z.); Epidemiology Branch, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina, U.S.A. (H.K., S.J.L.); Department of Biostatistics and Social Medicine, School of Public Health, Fudan University, Shanghai, China (N.Z.); Shanghai Municipal Center of Disease Control and Prevention, Shanghai, China (G.S., L.J.); Shanghai Environmental Monitoring Center, Shanghai, China (G.C.)

Wuhan

Z. Qian, Q. He, H-M. Lin, L. Kong, D. Zhou, S. Liang, Z. Zhu, D. Liao, W. Liu, C.M. Bentley, J. Dan, B. Wang, N. Yang, S. Xu, J. Gong, H. Wei, H. Sun, and Z. Qin

Pennsylvania State University College of Medicine, Hershey, Pennsylvania, U.S.A. (Z.Q., H-M.L., D.L., C.M.B.); Wuhan Academy of Environmental Science, Wuhan, China (Q.H., L.K., Z.Z.); Wuhan Centres for Disease Prevention and Control, Wuhan, China (D.Z., J.D., N.Y., J.G., H.S.); Wuhan Environmental Monitoring Center, Wuhan, China (S.L., W.L., B.W., S.X., H.W., Z.Q.)

EXECUTIVE SUMMARY

BACKGROUND

In recent years, Asia has experienced rapid economic growth and a deteriorating environment caused by the increasing use of fossil fuels. Although the deleterious effects of air pollution from fossil-fuel combustion have been demonstrated in many Western nations, few comparable studies have been conducted in Asia. Time-series studies of daily mortality in Asian cities can contribute

This Investigators' Report is one part of Health Effects Institute Research Report 154, which also includes an Integrated Discussion by the Health Review Committee. Correspondence concerning the Investigators' Report may be addressed to Dr. C-M. Wong, Department of Community Medicine, The University of Hong Kong, 5/F William MW Mong Block, Li Ka Shing Faculty of Medicine Building, 21 Sassoon Road, Hong Kong.

The PAPA Program was initiated by the Health Effects Institute in part to support the Clean Air Initiative for Asian Cities (CAI-Asia), a partnership of the Asian Development Bank and the World Bank to inform regional decisions about improving air quality in Asia. Additional funding was obtained from the U.S. Agency for International Development and the William and Flora Hewlett Foundation. The contents of this document have not been reviewed by private party institutions, including those that support the Health Effects Institute; therefore, it may not reflect the views or policies of these parties, and no endorsement by them should be inferred.

important new information to the existing body of knowledge about air pollution and health. Not only can these studies verify important health effects of air pollution in local regions in Asia, they can also help determine the relevance of existing air pollution studies to mortality and morbidity for policymaking and environmental controls. In addition, the studies can help identify factors that might modify associations between air pollution and health effects in various populations and environmental conditions. Collaborative multicity studies in Asia — especially when designed, conducted, and analyzed using a common protocol — will provide more robust air pollution effect estimates for the region as well as relevant, supportable estimates of local adverse health effects needed by environmental and public-health policymakers.

SPECIFIC OBJECTIVES

The Public Health and Air Pollution in Asia (PAPA*) project, sponsored by the Health Effects Institute, consisted of four studies designed to assess the effects of air pollution on mortality in four large Asian cities, namely Bangkok, in Thailand, and Hong Kong, Shanghai, and Wuhan, in China. In the PAPA project, a Common Protocol was developed based on methods developed and tested in NMMAPS, APHEA, and time-series studies in the literature to help ensure that the four studies could be compared with each other and with previous studies by following an established protocol. The Common Protocol (found at the end of this volume) is a set of prescriptive instructions developed for the studies and used by the investigators in each city. It is flexible enough to allow for adjustments in methods to optimize the fit of health-effects models to each city's data set. It provides the basis for generating reproducible results in each city and for meta-estimates from combined data. By establishing a common methodology, factors that might influence the differences in results from previous studies can more easily be explored. Administrative support was provided to ensure that the highest quality data were used in the analysis. It is anticipated that the PAPA results will contribute to the international scientific discussion of how to conduct and interpret time-series studies of air pollution and will stimulate the development of high-quality routine systems for recording daily deaths and hospital admissions for time-series analysis.

METHODS

Mortality data were retrieved from routine databases with underlying causes of death coded using the World Health Organization (WHO) *International Classification of Diseases, 9th revision* or *10th revision* (ICD-9, ICD-10). Air quality measurements included nitrogen dioxide (NO_2), sulfur dioxide (SO_2), particulate matter with aerodynamic diameter ≤ 10 µm (PM_{10}), and ozone (O_3) and were obtained from several fixed-site air monitoring stations that were located throughout the metropolitan areas of the four cities and that met the standards of procedures for quality assurance and quality control carried out by local government units in each city.

Using the Common Protocol, an optimized core model was established for each city to assess the effects of each of the four air pollutants on daily mortality using generalized linear modeling with adjustments for time trend, seasonality, and other time-varying covariates by means of a natural-spline smoothing function. The models were adjusted to suit local situations by correcting for influenza activity, autocorrelation, and special weather conditions. Researchers in Hong Kong, for example, used influenza activity based on frequency of respiratory mortality; researchers in Hong Kong and Shanghai used autoregressive terms for daily outcomes at lag days; and researchers in Wuhan used additional smoothing for periods with extreme weather conditions.

RESULTS AND DISCUSSION

For mortality due to all natural (nonaccidental) causes at all ages, the effects of air pollutants per 10-µg/m^3 increase in concentration was found to be higher in Bangkok than in the three Chinese cities, with the exception of the effect of NO_2 in Wuhan. The magnitude of the effects for cardiovascular and respiratory mortality were generally higher than for all natural mortality at all ages. In addition, the effects associated with PM_{10} and O_3 in all natural, cardiovascular, and respiratory mortality were found to be higher in Bangkok than in the three Chinese cities. The explanation for these three findings might be related to consistently higher daily mean temperatures in Bangkok, variations in average time spent outdoors by the susceptible populations, and the fact that less air conditioning is available and used in Bangkok than in the other cities. However, when pollutant concentrations were incorporated into the excess risk estimates through the use of interquartile range (IQR), the excess risk was more comparable across the four cities.

We found that the increases in effects among older age groups were greater in Bangkok than in the other three cities. After excluding data on extremely high concentrations of PM_{10} in Bangkok, the effect estimate associated with PM_{10} concentrations decreased in Bangkok (suggesting a convex relationship between risk and PM_{10}, where risk levels off

*A list of abbreviations and other terms appears at the end of the Investigators' Report.

at high concentrations) instead of increasing, as it did in the other cities. This leveling off of effect estimates at high concentrations might be related to differences in vulnerability and exposure of the population to air pollution as well as to the sources of the air pollutant.

IMPLICATIONS OF THE STUDY

The PAPA project is the first coordinated Asian multicity air pollution study ever published; this signifies the beginning of an era of cooperation and collaboration in Asia, with the development of a common protocol for coordination, data management, and analysis. The results of the study demonstrated that air pollution in Asia is a significant public health burden, especially given the high concentrations of pollutants and high-density populations in major cities. When compared with the effect estimates reported in the research literature of North America and Western Europe, the study's effect estimates for PM_{10} were generally similar and the effect estimates for gaseous pollutants were relatively higher. In Bangkok, however, a tropical city where total exposures to outdoor pollution might be higher than in most other cities, the observed effects were greater than those reported in the previous (i.e., Western) studies. In general, the results suggested that, even though social and environmental conditions across Asia might vary, it is still generally appropriate to apply to Asia the effect estimates for other health outcomes from previous studies in the West. The results also strongly support the adoption of the global air quality guidelines recently announced by WHO.

INTRODUCTION

Time-series studies of daily mortality in Asian cities can contribute significantly to the world's literature on the health effects of air pollution. They can help determine the appropriateness of extrapolating from North America and Western Europe to regions where few if any studies have been conducted. In addition, because they involve various exposure conditions and populations, they can shed light on factors that might modify the effects of air pollution on health. Multicity collaborative studies conducted in Asia, especially when analyzed using a common protocol, can generate more robust air pollution effect estimates for the region and provide decision makers with relevant and supportable estimates of the local adverse health effects. If findings in Asia turn out to be similar to those reported in North America and Western Europe, additional support is provided for applying the findings of other North American and Western European studies.

Recent reviews (Anderson et al. 2004; Ostro 2004) suggested that proportional increases in daily mortality per 10-µg/m^3 increase in PM_{10} are generally similar among regions of North America and of Western Europe as well as in the few developing countries where studies have been undertaken. However, there are relatively few studies conducted to date in Asia, and these were not geographically representative and used different methodologies. It is thus difficult to compare results from one Asian city with those of another or with those of the broader literature. In addition, the worldwide data have not been appropriately analyzed to determine whether there are real differences in the magnitude of the effects of short-term exposure or to determine the possible reasons for such differences, such as sources of air pollution or population characteristics.

Efforts to utilize data on air quality and health from various regions are underway with funding from HEI by way of the PAPA project as well as from the European Commission by way of the Air Pollution and Health: a European and North American Approach (APHENA) project. (The APHENA project was concluded in October 2009 [Katsouyanni et al. 2009].) These efforts can provide important insights for the time-series literature because of the variability in air pollution, climate, population, and city characteristics in cities across Asia, North America, and the European Union.

In the PAPA project, a Common Protocol for the design and analysis of data from multiple Asian cities and a management framework to conduct a coordinated analysis were established. The Common Protocol (found at the end of this volume) provided a basis for meta-estimates and for isolating important independent factors using a similar methodology across studies that might explain effect modifications in city-specific estimates. It is anticipated that the results will contribute to the international scientific discussion on how to conduct and interpret time-series studies of the health effects of air pollution and will stimulate the development of routine systems for recording daily deaths and hospital admissions for time-series analysis.

PARTICIPANTS

This study is a collaboration of researchers in four Asian cities: Bangkok, Hong Kong, Shanghai, and Wuhan. These cities are located in South and East Asia (Figure 1), and each has its own specific characteristics with differences in terms of climate, demographics, and socioeconomic status (Appendix A).

Bangkok

Bangkok, Thailand, is a fast-growing and economically and culturally dynamic city, with a population of 6.8 million

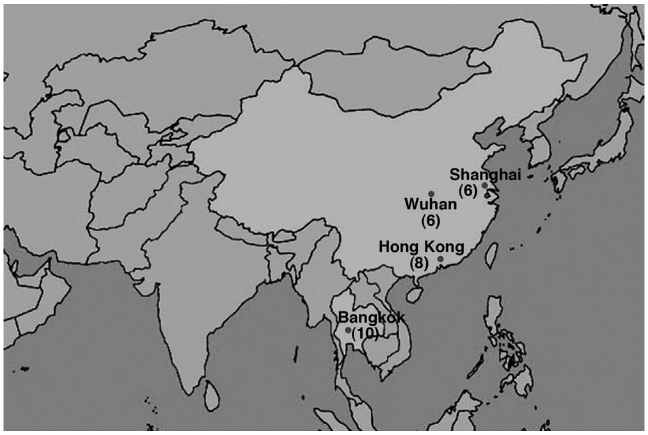


Figure 1. Map of Asia, showing Bangkok, Hong Kong, Shanghai, and Wuhan. The numbers in parentheses indicate the number of monitoring stations used in each city.

in an area of 1569 km^2. The gross national product (GNP) is equivalent to U.S. $2495 per capita. Bangkok's topology features a low, flat plain crisscrossed with canals and rivers. Its climate is tropical monsoon, with a rainy season from May to October, a cool season from November to January, and a hot season from February to April.

The country's health-care services comprise self-care and self-medication (21.2%), rural health centers (19.2%), private clinics (19.0%), district hospitals (14.9%), provincial hospitals (15.6%), private hospitals (4.8%), and others (5.3%). The five leading causes of death at all ages are neoplasms (17.7%), circulatory diseases (15.1%), infectious and parasitic diseases (14.9%), other causes of deaths (8.9%), and respiratory diseases (8.2%).

Hong Kong

Hong Kong, China, is a densely populated city, with 6.7 million inhabitants in an area of 1092 km^2. The GNP is equivalent to U.S. $24,995 per capita. Hong Kong's topology is dominated by hills and mountains, with a flat peninsula, a main island, and many outlying islands. It is in a subtropical region, with abundant rainfall and tropical cyclones in the summer months.

Hospital services are mainly provided by the public sector (95%); primary-care services are mainly provided by the private sector (85%). The five leading causes of death at all ages are malignant neoplasm (34.2%), heart diseases (14.1%), cerebrovascular disease (9.4%), pneumonia (9.1%), and other causes of deaths (5.5%).

Shanghai

Shanghai, China, comprises urban and suburban districts as well as counties, with a total area of 6341 km^2 and a population of 13.2 million (at the end of 2000), representing about 1% of China's total population. The study area was limited to the traditional nine urban districts of Shanghai — Huangpu, Jing'an, Luwan, Xuhui, Changning, Yangpu, Hongkou, Putuo, and Zhabei. The study population of 7 million (in 2004) includes all permanent residents living in the nine districts (289 km^2). The GNP of the study population is equivalent to U.S. $6,660 per capita. The city's topology features a broad, low-altitude alluvial plain that is crisscrossed by waterways. The city has a moderate subtropical climate, with four distinct seasons and abundant rainfall. The average annual rainfall is 1594 millimeters.

Almost all primary-care and hospital services are provided by the public sector. The five leading causes of death at all ages are circulatory diseases (32.9%), neoplasms (30.4%), respiratory diseases (12.4%), injury and poisoning (6.4%), and endocrine, immune, and metabolic diseases (4.0%).

Wuhan

Wuhan is the most populous city in central China, with 7.8 million permanent residents. The GNP is equivalent to U.S. $3,493 per capita. The city's topography features a large plain with hills and a great number of lakes and ponds. The city has a subtropical monsoon climate, with abundant rainfall and four distinct seasons.

There are 1278 public-health organizations in the city, including 308 hospitals. In the suburban areas 90% of the residents are covered by the public medical-care system; in the urban areas 100% of the residents are covered. The five leading causes of death are cerebrovascular diseases (30.4%), neoplasms (17.6%), cardiovascular diseases (13.1%), respiratory diseases (11.8%), and injury and poisoning (6.9%).

SPECIFIC OBJECTIVES

The specific objectives of our coordinated analyses of these four Asian cities were the following:

1. To develop a protocol for the design and analysis of data from several Asian cities;
2. To develop a management framework to conduct the coordinated analyses;
3. To conduct coordinated analyses of common exposures and health endpoints according to the Common Protocol, including meta-analyses to the extent possible;
4. To contribute to the international scientific discussion of how to conduct and interpret time-series studies of the effects of short-term exposure;

5. To report the results of the coordinated analyses in an HEI final report and in papers in the broader peer-reviewed literature; and
6. To stimulate the development of routine systems for recording daily deaths and admissions for the purpose of time-series analysis.

MATERIALS AND METHODS

DESIGN OF DATA COLLECTION

Study Period

The study covered the periods from 1999 to 2003 for Bangkok; from 1996 to 2002 for Hong Kong; and from 2001 to 2004 for both Shanghai and Wuhan (Figure 2).

Mortality Data

In this study, we focused on mortality for all natural causes in all ages, in ages 65 years or older (≥ 65 years), and in ages 75 years or older (≥ 75 years); mortality for cardiovascular disease in all ages; and mortality for respiratory disease in all ages. Mortality from accidental causes and non-cardiopulmonary causes, defined as all natural causes minus cardiovascular and respiratory diseases, were treated as control health outcomes. The ICD-9 and ICD-10 codes for the health outcomes were: all natural causes, ICD-9 001–799 or ICD-10 A00–R99; diseases of the cardiovascular system, ICD-9 390–459 or ICD-10 I00–I99; and diseases of the respiratory system, ICD-9 460–519 or ICD-10 J00–J98.

Data for Bangkok mortality for 1999–2003 were obtained from the Ministry of Public Health. The underlying causes of death were coded using ICD-10.

Data for Hong Kong mortality were obtained from the Census and Statistics Department, Hong Kong Special Administration Region. The underlying causes of death were coded using ICD-9 for 1996–2000 and ICD-10 for 2001–2002.

Data for Shanghai mortality were obtained from the Shanghai Municipal Center of Disease Control and Prevention (SMCDCP). Daily mortality data (excluding accidents and injuries) for residents of the nine urban districts of Shanghai in 2001–2004 were obtained from an SMCDCP database. The underlying causes of death were coded using ICD-9 for 2001 and ICD-10 for 2002–2004.

Data for Wuhan mortality were obtained from the Wuhan Centre for Disease Control and Prevention. The underlying causes of death were coded using ICD-9 for 2000–2002 and ICD-10 for 2003–2004.

The daily mortality counts for all natural causes in all ages for each city showed that there were stronger seasonal variations in the three Chinese cities (which are north of Bangkok and do not have a tropical climate) (Figure 2). Shanghai (mean daily deaths, 119; population, 7.0 million) and Bangkok (mean daily deaths, 95; population, 6.8 million) had more daily deaths than did Hong Kong (mean daily deaths, 84; population, 6.7 million) or Wuhan (mean daily deaths, 61; population, 4.2 million). The ratios of deaths caused by cardiovascular diseases to deaths caused by respiratory diseases were 4:1 in Wuhan, 3:1 in Shanghai, close to 2:1 in Bangkok, and 1.5:1 in Hong Kong. The percentage of combined cardiovascular and respiratory mortality was also highest in Wuhan, at 57%, compared with 49% in Shanghai, 48% in Hong Kong, and 23% in Bangkok (derived from data in Table 1). Deaths occurring at age ≥ 65 years were less frequent in Bangkok (36%) than in the three Chinese cities (72%–84%).

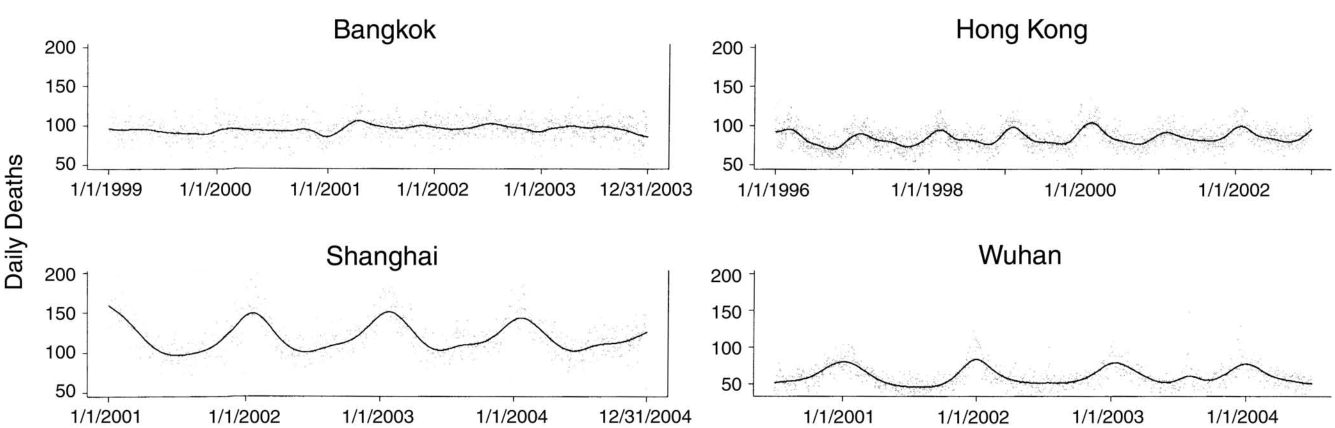


Figure 2. Time series for daily mortality from all natural causes at all ages.

Table 1. Summary Statistics of Daily Mortality Counts

Mortality Class	Minimum				1st Quartile				Median				3rd Quartile			
	Bangkok	Hong Kong	Shanghai	Wuhan	Bangkok	Hong Kong	Shanghai	Wuhan	Bangkok	Hong Kong	Shanghai	Wuhan	Bangkok	Hong Kong	Shanghai	Wuhan
All natural causes																
All ages	29	48	51	25	87	75	103	51	95	83	115	59	103	92	133	69
≥ 65 yr	13	34	46	18	30	57	84	35	34	64	96	41	39	72	112	50
≥ 75 yr	6	17	33	6	18	37	59	19	21	43	70	24	25	49	81	30
Cardiovascular causes	1	6	11	8	10	19	36	22	13	23	43	27	16	28	51	33
Respiratory causes	1	3	3	0	6	12	10	4	8	16	13	6	10	19	17	9

Mortality Class	Maximum				Mean				SD[a]			
	Bangkok	Hong Kong	Shanghai	Wuhan	Bangkok	Hong Kong	Shanghai	Wuhan	Bangkok	Hong Kong	Shanghai	Wuhan
All natural causes												
All ages	147	135	198	213	94.8	84.2	119.0	61.0	12.1	12.8	22.5	15.8
≥ 65 yr	63	113	175	159	34.3	65.4	99.6	43.8	6.7	11.6	20.6	13.4
≥ 75 yr	50	82	129	106	21.3	43.6	71.5	25.7	5.2	9.5	16.7	9.5
Cardiovascular causes	28	54	85	94	13.4	23.8	44.2	27.8	4.3	6.5	11.0	8.8
Respiratory causes	20	34	45	125	8.1	16.2	14.3	7.0	3.1	5.2	6.4	5.8

[a] SD indicates standard deviation.

The most common causes of death were not the same in the four cities. Cancer, for example, was the most common cause of death in Bangkok and Hong Kong; cardiovascular disease and stroke were the most common causes in Shanghai and Wuhan, respectively. These were the underlying causes of death, however, and did not necessarily lead directly to the death. It can be argued that an individual's reserve capacity to resist the health effects of air pollution would decline to a certain critical stage through exposure to environmental and personal risk factors, with the result that he or she could die from short-term exposure to air pollution (Rabl 2006). Thus, the estimates of short-term effects of air pollution on mortality reflect the magnitude of the effects of air pollution on susceptible subjects. Inevitably, there are heterogeneities in the susceptibility of city populations caused by differences in health status as reflected by differences in morbidities and in causes of death. The estimates of health effects on all natural causes are thus average effects for a population. In this study, we assessed the effects of short-term air pollution exposure on mortality from all natural causes as well as from cardiovascular and respiratory causes. Further studies are needed to assess the effects on various vulnerable subgroups.

Data on Air Pollutants and Weather

The pollutants measured in each of the four cities were NO_2, SO_2, PM_{10}, and O_3. All four cities met our criteria for including data from air pollution monitoring stations (see Common Protocol at the end of this volume). NO_2, SO_2, and PM_{10} daily data were 24-hour average concentrations; O_3 daily data were 8-hour average concentrations (10 a.m. to 6 p.m.). Each city maintained several fixed-site air monitoring stations throughout the metropolitan areas that satisfied the measures of quality assurance and quality control carried out by local government units. The locations, manufacturers, and models of the air pollution monitoring equipment for each pollutant in the four PAPA cities are shown in Appendix B. In Bangkok, air pollutant concentrations were measured by the Ministry of Natural Resources and Environment's Pollution Control Department (using 10 air monitoring stations); in Hong Kong, by the Environmental Protection Department (using 8 air monitoring stations); in Shanghai, by the Shanghai Environmental Monitoring Center (using 6 air monitoring stations); and in Wuhan, by the Wuhan Environmental Monitoring Center (using 6 air monitoring stations). The measurement methods for NO_2, SO_2, and O_3 (i.e., chemiluminescence, fluorescence, and ultraviolet absorption, respectively) were similar in all four cities. However, a tapered element microbalance (TEOM) was used in the three Chinese cities to measure PM_{10}, whereas beta-gauge monitors were used to measure PM_{10} in Bangkok.

For the calculation of 24-hour average concentrations of NO_2, SO_2, and PM_{10}, at least 75% of the 1-hour values on that particular day were required. If more than 25% of a station's values for a particular pollutant were missing for the entire period of analysis, the data from that station were not included for that pollutant. For all four cities, there were practically no missing data for the daily concentrations of air pollutants; the small number of missing data were not imputed.

Table 2 shows summary statistics for daily average temperature and relative humidity included in the study. Bangkok is a tropical city with a monsoon climate that is rainy in May through October, cool in November through January, and hot in February through April (average temperature, 29°C; relative humidity, 73%). Hong Kong is a subtropical city that is rainy and has tropical cyclones in the summer (average temperature, 24°C; relative humidity, 78%). Both Shanghai (average temperature, 18°C; relative humidity, 73%) and Wuhan (average temperature, 18°C; relative humidity, 74%) are temperate cities with four distinct seasons and abundant rainfall in the summer. Calendar variables, such as the day of the week, and special events, such as extreme weather in Wuhan and public holidays in Hong Kong, were also included in the analyses and are presented below.

METHODS

In this study, we applied state-of-the-art time-series methods to assess the short-term effects of air pollution on mortality from all natural causes and mortality from cardiovascular and respiratory causes combined. We divided the analysis into two stages: single-city analysis (first stage) and multicity meta-analysis (second stage).

First Stage: Single-City Analysis

The single-city analytic method was developed and then adopted by the four teams of investigators in the four cities and is described in the Common Protocol (found at the end of this volume). The Common Protocol comprised

Table 2. Summary Statistics of Air Pollutant Concentrations and Weather Conditions[a]

	Minimum				1st Quartile				Median				3rd Quartile			
	Bangkok	Hong Kong	Shanghai	Wuhan	Bangkok	Hong Kong	Shanghai	Wuhan	Bangkok	Hong Kong	Shanghai	Wuhan	Bangkok	Hong Kong	Shanghai	Wuhan
NO_2	15.8	10.3	13.6	19.2	31.7	45.2	50.2	38.0	39.7	56.4	62.5	47.2	54.8	69.6	79.2	62.0
SO_2	1.5	1.4	8.4	5.3	10.1	9.6	27.5	21.0	12.5	14.7	40.0	32.5	15.6	22.2	56.2	51.8
PM_{10}	21.3	13.7	14.0	24.8	38.9	31.8	56.3	94.8	46.8	45.5	84.0	130.2	59.8	66.7	128.3	175.0
O_3	8.2	0.7	5.3	1.0	39.1	19.0	37.6	51.1	54.4	31.5	56.1	81.8	75.3	50.6	82.7	118.5
Temperature (°C)	18.7	6.9	−2.4	−2.5	28.1	19.8	10.3	9.7	29.1	24.7	18.3	18.5	29.9	27.8	24.7	26.0
Relative humidity (%)	41.0	27.0	33.0	35.0	68.0	74.0	65.5	65.0	73.0	79.0	73.5	74.0	78.8	84.0	81.0	84.0

	Maximum				Mean				SD[b]				IQR[c]			
	Bangkok	Hong Kong	Shanghai	Wuhan	Bangkok	Hong Kong	Shanghai	Wuhan	Bangkok	Hong Kong	Shanghai	Wuhan	Bangkok	Hong Kong	Shanghai	Wuhan
NO_2	139.6	167.5	253.7	127.4	44.7	58.7	66.6	51.8	17.3	20.1	24.9	18.8	23.1	24.4	29.0	24.0
SO_2	61.2	109.3	183.3	187.8	13.2	17.8	44.7	39.2	4.8	12.1	24.2	25.3	5.5	12.6	28.7	30.8
PM_{10}	169.2	189.0	566.8	477.8	52.0	51.6	102.0	141.8	20.1	25.3	64.8	63.7	20.9	34.9	72.0	80.2
O_3	180.6	195.0	251.3	258.5	59.4	36.7	63.4	85.7	26.4	22.9	36.7	47.0	36.2	31.6	45.1	67.4
Temperature (°C)	33.6	33.8	34.0	35.8	28.9	23.7	17.7	17.9	1.7	4.92	8.5	9.2	1.8	8.0	14.4	16.3
Relative humidity (%)	95.0	97.0	97.0	99.0	72.8	77.9	72.9	74.0	8.3	10.0	11.4	12.5	10.8	10.0	15.5	19.0

[a] Values are μg/m^3 unless otherwise indicated.
[b] SD indicates standard deviation.
[c] IQR indicates interquartile range.

(1) a communication network between the teams and the HEI International Scientific Oversight Committee (ISOC) (Appendix B), (2) criteria for the inclusion of monitoring stations, (3) quality assurance for the data collection, and (4) the health outcomes and air pollutants to be included in the analysis. The Common Protocol also described the development of methods to standardize data management, including compilation of daily data. The statistical methods, including a sensitivity analysis, were also adopted and modified from previous coordinated air-pollution time-series projects, including APHENA, Air Pollution and Health: a European Approach (APHEA), and The National Morbidity, Mortality, and Air Pollution Study (NMMAPS) (Samet et al. 2000). The methods were tailored to suit local situations, such as adjustment for influenza activity, autocorrelation, and special weather conditions. Generalized linear modeling was used to model daily health outcomes, with natural-spline smoothers (Burnett et al. 2004; Wood 2006) for filtering out seasonal patterns and long-term trends in daily mortality as well as temperature and relative humidity. We also included an adjustment for the day of the week and dichotomous variables relevant to individual cities if available, such as public holidays (in Hong Kong) and extreme weather conditions (in Wuhan). In an attempt to minimize autocorrelation, which would have biased the standard errors, a goal for the core models was for plots of the partial autocorrelation functions (PACFs) (Touloumi et al. 2006) to have coefficients in absolute values less than 0.1 for the first two lag days. Randomness of residuals was also considered in selecting the most appropriate models. If these criteria were not met, other methods were used to reduce autocorrelation, including inclusion of additional explanatory variables (e.g., to model influenza epidemics) and the addition of autoregression terms. Air pollutant concentrations were entered into the core models to assess the health effects of specific pollutants. Exposure at the current day (lag 0), a two-day average of lag 0 and 1 days (lag 0–1 [average]), and a five-day average of lags 0 to 4 (lag 0–4 [average]) days were examined. For each pollutant, the excess risk of mortality (with 95% confidence interval [CI]) per 10-µg/m^3 increase in average air pollutant concentration at lag 0–1 day (average) is presented in tables and figures. In the text, however, point estimates with *P* values are used to describe sets of effects.

Because several differences in effect estimates among cities were observed, we conducted additional sensitivity analyses to attempt to explain these differences and to determine the robustness of the initial findings. We focused on PM_{10}, given the wealth of worldwide findings of effects from this pollutant, and used the average concentration of lag 0–1 day (average). In these analyses, we sought to explore several possibilities: that higher concentrations of PM_{10} might be dominated by the coarse fraction and therefore have a different toxicity compared with PM_{10} dominated by the finer particles, that monitors might be overly affected by proximity to traffic, that the seasons might have different effects in different cities, that there might be differences in controls for temperature, that missing values might have an effect, and that there might be differences in spline models. Specifically, the sensitivity analyses for PM_{10} included the following:

1. Exclusion of data from days when the daily concentration of PM_{10} was > 95th percentile;
2. Exclusion of data from days when the daily concentration of PM_{10} was > 75th percentile;
3. Exclusion of data from days when the daily concentration of PM_{10} was > 180 µg/m^3;
4. Exclusion of monitoring stations overly affected by proximity to traffic (as indicated by high ratios of nitric oxide to nitrogen oxides);
5. Assessment of effects of exposure in the warm season (defined approximately from April to October in the four cities) with adjustment for time trends using indicator variables for each year in the core model;
6. Addition of temperature at lag 1–2 days (average), smoothed by natural splines with 3 degrees of freedom (df), to the original core model;
7. Addition of temperature at lag 3–7 days (average), smoothed by natural splines with 3 df, to the original core model;
8. Use of centered daily concentrations of PM_{10} (Wong et al. 2002);
9. Use of natural splines with degrees of freedom of time trend per year, temperature, and relative humidity fixed at df = 8, df = 4, and df = 4, respectively, in the original core model;
10. Use of penalized splines instead of natural splines; and
11. Use of a Common Approach (a model based on the Common Protocol but restricted to a fixed set of procedures and degrees of freedom, treating the data for all four cities identically), using natural splines with degrees of freedom of time trend per year, temperature, and relative humidity fixed at df = 6, df = 3, and df = 3, respectively, and day of the week adjusted into the core model.

A change of excess risk greater than 20% from that of the analyses was regarded as an indication of sensitive results.

The sensitivity analyses for NO_2 included the following:

1. Addition of temperature at lag 1–2 days (average), smoothed by natural splines with 3 df, to the original core model;

2. Addition of temperature at lag 3–7 days (average), smoothed by natural splines with 3 df, to the original core model;
3. Use of centered daily concentrations of NO_2;
4. Use of natural splines with degrees of freedom of time trend per year, temperature, and relative humidity fixed at df = 8, df = 4, and df = 4, respectively, in the original core model;
5. Use of penalized splines instead of natural splines; and
6. Use of a Common Approach, using natural splines with degrees of freedom of time trend per year, temperature, and relative humidity fixed at df = 6, df = 3, and df = 3, respectively, and day of the week adjusted into the core model.

Table 3 shows a summary of model fits and a comparison of the core models (reflecting individual data for each city) and the Common Approach (a model based on the Common Protocol but restricted to a fixed set of procedures and degrees of freedom, treating the data for all four cities identically) as defined in the sensitivity analysis.

The sensitivity of excess risk estimates for each pollutant at lag 0–1 days (average) was assessed by various degrees of freedom per year of the time smoothers.

Concentration–response curves for the effect of each pollutant on each mortality outcome in the four cities were plotted. We applied a natural-spline smoother with 3 df on the pollutant term. Non-linearity was assessed by testing the change of deviance between a non-linear pollutant (smoothed) model with 3 df and a linear pollutant (unsmoothed) model with 1 df.

Second Stage: Multicity Meta-analysis

Individual effect estimates were first expressed in terms of percentage change in mortality (i.e., excess risk per 10-μg/m^3 increase in air pollutant concentration) and per IQR (μg/m^3) increase in air pollutant concentrations. Combined estimates of excess risk of mortality and their standard errors were then calculated using a random-effects model for which estimates were weighted by the inverse of the sum of within- and between-study variances. Homogeneity tests were performed by means of chi-square tests for the differences in the sum of squares between individual and weighted averages of the estimates.

The first-stage main analyses for the individual cities and the second-stage meta-analysis for the combined cities were performed using the statistical program R, version 2.5.1 (R Project for Statistical Computing, Vienna, Austria).

Cross-checking of Results

Cross-checking of results between teams was performed by pairing the Hong Kong and Wuhan teams and the Bangkok and Shanghai teams. Each team ran the models again and used the data and model specifications of the other team in the pair. The results were checked for accuracy against the ones originally given by the other team in the pair. The two sets of results, one for mortality from all natural causes in all ages and PM_{10} concentrations and the

Table 3. Summary of Model Fits and Comparison of Main Model and the Common Approach[a]

	Bangkok		Hong Kong		Shanghai		Wuhan	
Model Characteristics	Main Model	Common Approach	Main Model	Common Approach	Main Model	Common Approach	Main Model	Common Approach
Degree of freedom (per year) in the time smooth	6	6	4	6	4	6	6	6
Use of public holiday indicator	Yes	No	Yes	No	No	No	No	No
Use of local smoothing in special period	No	No	No	No	No	No	Yes	No
Use of autoregressive terms in the core model	No	No	Yes	No	Yes	No	No	No
Dispersion	1.29	1.29	1.16	1.15	1.39	1.46	1.34	1.72
Percentage of deviance explained	19.17	18.48	41.53	42.08	66.52	64.68	65.50	57.61
First-order PACF	0.0859	0.0911	−0.0023	0.0722	0.0673	0.1321	0.0936	0.3200
Sum of first 20 PACFs	0.0859	0.0840	0.1863	0.0121	0.0013	0.1324	0.0971	0.2197

[a] Main models are the base models fitted from the main analysis for each city; the Common Approach is the base model fitted from the Common Protocol but restricted to a fixed set of procedures and degrees of freedom.

other for mortality from all natural causes for the group age ≥ 65 years and NO_2 concentrations, were then cross-checked. The technical details were further checked to ensure that all the analyses were performed in a standardized manner.

The cross-checking results showed no discrepancies between the original estimates and the estimates obtained in the cross-check.

RESULTS

In general, SO_2 and PM_{10} concentrations were similar for Bangkok and Hong Kong and were lower than concentrations in Shanghai and Wuhan, whereas NO_2 concentrations in Hong Kong and Shanghai were higher than those in Bangkok and Wuhan (Figure 3). Compared with those observed in most North American and Western European cities, concentrations of PM_{10} were much higher, NO_2 concentrations were similar, and SO_2 concentrations were higher in Shanghai and Wuhan and similar in Bangkok and Hong Kong (Samet et al. 2000). The Spearman correlations between daily measures of NO_2 and PM_{10} concentrations were consistently high, ranging from 0.6 to 0.8 in the four cities (Appendix C).

MODEL CHARACTERISTICS

The PACF plots of the residuals from the core model for mortality outcomes were within the absolute value of 0.1 in the previous two lag days; there were no discernible patterns recognizable over the various other lag days (Appendix D).

Using the Common Approach for all cities, with 6 df and common model specifications, there were no marked changes in model characteristics (see Table 3). There were some differences in the terms of the core models among individual cities, as shown in Main Model columns (the Main Model is the core model with a term added for air pollutant concentrations). In mortality for all natural causes at all ages, the degrees of freedom varied from 4 to 6 per year. Localized smoothing was used only in Wuhan,

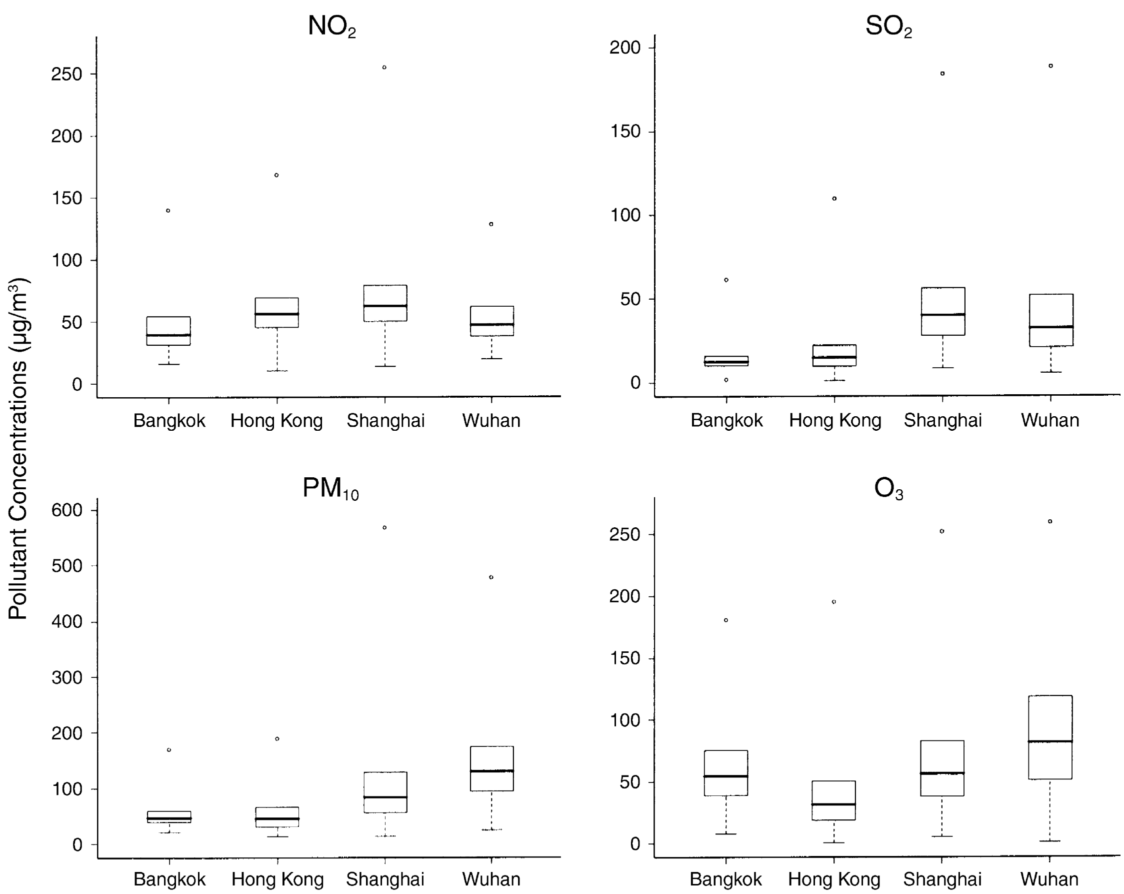


Figure 3. Distribution of the concentrations of the four air pollutants in the four cities.

autoregressive terms were used in Hong Kong and Shanghai, and public holidays indicators were used in Bangkok and Hong Kong. The first-order PACF was relatively closer to zero in Hong Kong than in the other cities, although they were all less than 0.1. The percentage of deviance explained was smaller in Bangkok than in the three Chinese cities, but the dispersion was smaller in Hong Kong and larger in Shanghai and Wuhan.

SINGLE-POLLUTANT ESTIMATES FOR INDIVIDUAL CITIES

For mortality from all natural causes at all ages (Table 4), the excess risk percentage ranged from 0.90% to 1.97% (all $P \leq 0.001$) per 10-μg/m^3 increase in NO_2 concentrations; from 0.87% to 1.61% (all $P \leq 0.05$) per 10-μg/m^3 increase in SO_2 concentrations; from 0.26% to 1.25% (all $P \leq 0.001$) per 10-μg/m^3 increase in PM_{10} concentrations; and from 0.31% to 0.63% (in all cities except Wuhan, where its effect was not statistically significant [i.e., $P > 0.05$]) per 10-μg/m^3 increase in O_3 concentrations. The excess risk showed trends of increasing risk with increase in age groups from all ages to ≥ 65 years and then ≥ 75 years for all four pollutants. The trends were strongest in Bangkok and less strong in Hong Kong and Wuhan; they were not obvious in Shanghai (Figure 4). For all four pollutants, the excess risk in Bangkok was higher than in the three Chinese cities. When the excess risks were calculated using the exposure IQR category from each city (Figure 5), Bangkok and Wuhan had the higher excess risks, except in the case of SO_2, for which Wuhan had the highest excess risk.

We found effects on mortality from non-cardiopulmonary causes — a control health outcome — in which excess risk per 10-μg/m^3 increase in pollutant concentrations ranged from 0.80% to 1.66% for NO_2, 0.68% to 1.75% for SO_2, and 0.17% to 0.30% for PM_{10} in the four cities. For O_3, the excess risk was 0.56% (95% CI 0.20%, 0.91%) in Bangkok and 0.35% (95% CI 0.01%, 0.69%) in Shanghai (data not shown).

In the combined analysis of the four cities, there was heterogeneity in effect estimates, as determined through homogeneity tests for NO_2 and PM_{10} on mortality from all natural causes and for PM_{10} on cardiovascular mortality (Table 4). For all natural mortality, the combined random-effects risk estimates were 1.23% (95% CI 0.84%, 1.62%) for NO_2, 1.00% (95% CI 0.75%, 1.24%) for SO_2, 0.55% (95% CI 0.26%, 0.85%) for PM_{10}, and 0.38% (95% CI 0.23%, 0.53%) for O_3. The results for cardiovascular mortality (Table 4) followed a generally similar pattern to that of

Table 4. Main Mortality Effect Estimates for Individual Cities and Combined Random Effects[a]

Mortality Class / Pollutant	Bangkok	Hong Kong	Shanghai	Wuhan	Random Effect (4 Cities)	Random Effect (3 Chinese Cities)
All Natural Causes, All Ages						
NO_2	1.41 (0.89, 1.95)	0.90 (0.58, 1.23)	0.97 (0.66, 1.27)	1.97 (1.31, 2.63)	1.23 (0.84, 1.62)[b]	1.19 (0.71, 1.66)[b]
SO_2	1.61 (0.08, 3.16)	0.87 (0.38, 1.36)	0.95 (0.62, 1.28)	1.19 (0.65, 1.74)	1.00 (0.75, 1.24)	0.98 (0.74, 1.23)
PM_{10}	1.25 (0.82, 1.69)	0.53 (0.26, 0.81)	0.26 (0.14, 0.37)	0.43 (0.24, 0.62)	0.55 (0.26, 0.85)[c]	0.37 (0.21, 0.54)
O_3	0.63 (0.30, 0.95)	0.32 (0.01, 0.62)	0.31 (0.04, 0.58)	0.29 (−0.05, 0.63)	0.38 (0.23, 0.53)	0.31 (0.13, 0.48)
Cardiovascular Causes						
NO_2	1.78 (0.47, 3.10)	1.23 (0.64, 1.82)	1.01 (0.55, 1.47)	2.12 (1.18, 3.06)	1.36 (0.89, 1.82)	1.32 (0.79, 1.86)
SO_2	0.77 (−2.98, 4.67)	1.19 (0.29, 2.10)	0.91 (0.42, 1.41)	1.47 (0.70, 2.25)	1.09 (0.71, 1.47)	1.09 (0.72, 1.47)
PM_{10}	1.90 (0.80, 3.01)	0.61 (0.11, 1.10)	0.27 (0.10, 0.44)	0.57 (0.31, 0.84)	0.58 (0.22, 0.93)[d]	0.44 (0.19, 0.68)
O_3	0.82 (0.03, 1.63)	0.62 (0.06, 1.19)	0.38 (−0.03, 0.80)	−0.07 (−0.53, 0.39)	0.37 (0.01, 0.73)	0.29 (−0.09, 0.68)
Respiratory Causes						
NO_2	1.05 (−0.60, 2.72)	1.15 (0.42, 1.88)	1.22 (0.42, 2.01)	3.68 (1.77, 5.63)	1.48 (0.68, 2.28)	1.63 (0.62, 2.64)[b]
SO_2	1.66 (−3.09, 6.64)	1.28 (0.19, 2.39)	1.37 (0.51, 2.23)	2.11 (0.60, 3.65)	1.47 (0.85, 2.08)	1.46 (0.84, 2.08)
PM_{10}	1.01 (−0.36, 2.40)	0.83 (0.23, 1.44)	0.27 (−0.01, 0.56)	0.87 (0.34, 1.41)	0.62 (0.22, 1.02)	0.60 (0.16, 1.04)
O_3	0.89 (−0.10, 1.90)	0.22 (−0.46, 0.91)	0.29 (−0.44, 1.03)	0.12 (−0.89, 1.15)	0.34 (−0.07, 0.75)	0.23 (−0.22, 0.68)

[a] Data are presented as excess risk of mortality in % (95% CI) per 10-μg/m^3 increase in average concentration of lag 0–1 day (average).
[b] Significant at $0.01 < P \leq 0.05$ by homogeneity test.
[c] Significant at $P \leq 0.001$ by homogeneity test.
[d] Significant at $0.001 < P \leq 0.01$ by homogeneity test.

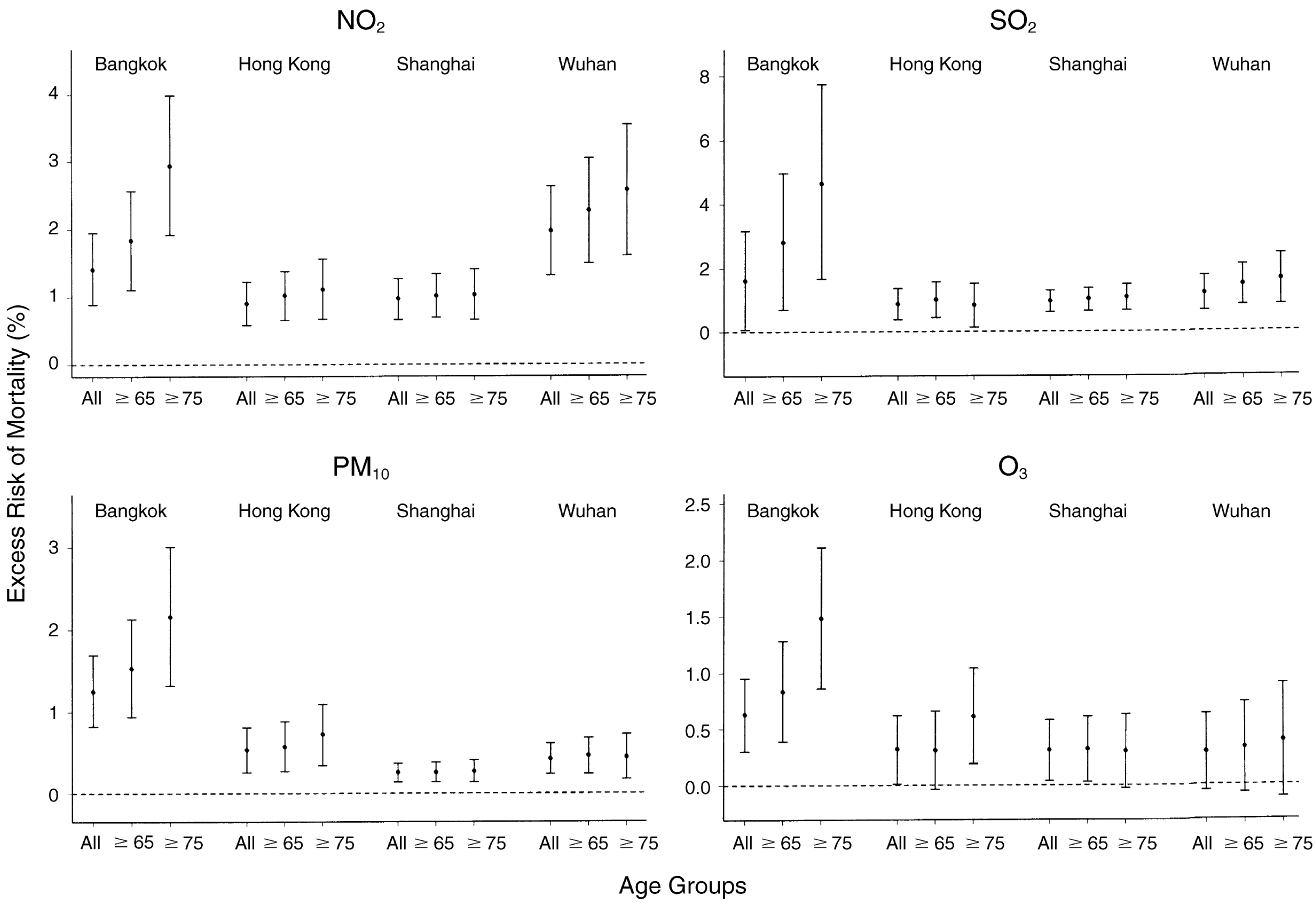


Figure 4. Percentage of excess risk of mortality per 10-μg/m^3 increase in average concentration of each air pollutant for lag 0–1 day (average) for three age groups (all ages, ≥ 65 years, and ≥ 75 years). Error bars indicate 95% CI. The dashed lines at 0 on the *y*-axes indicate the points at which air pollution had no effect on mortality.

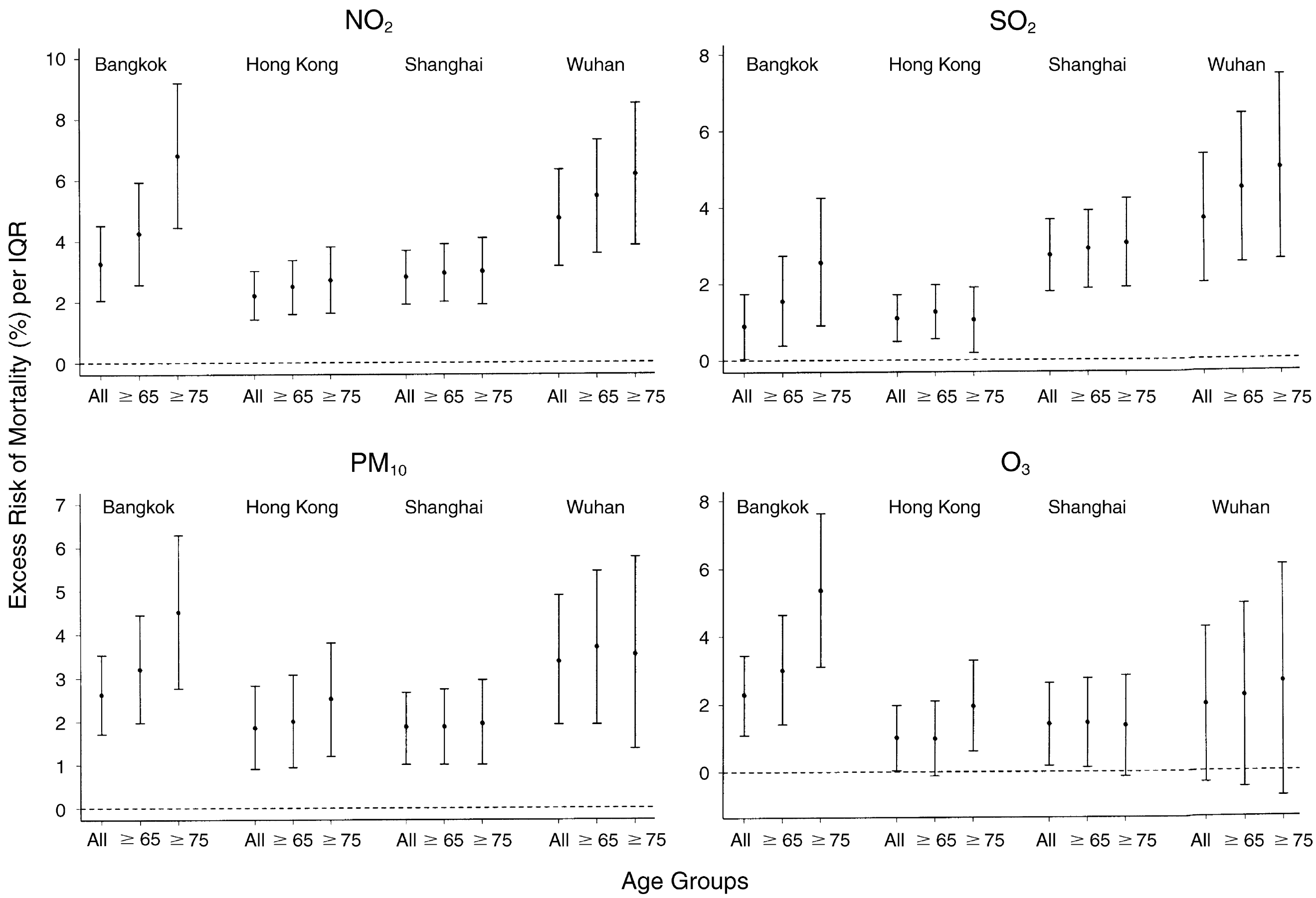


Figure 5. Percentage of excess risk of mortality per IQR increase in average concentration of each air pollutant for lag 0–1 day (average) for three age groups (all ages, ≥ 65 years, and ≥ 75 years). Error bars indicate 95% CI. The dashed lines at 0 on the *y*-axes indicate the points at which air pollution had no effect on mortality.

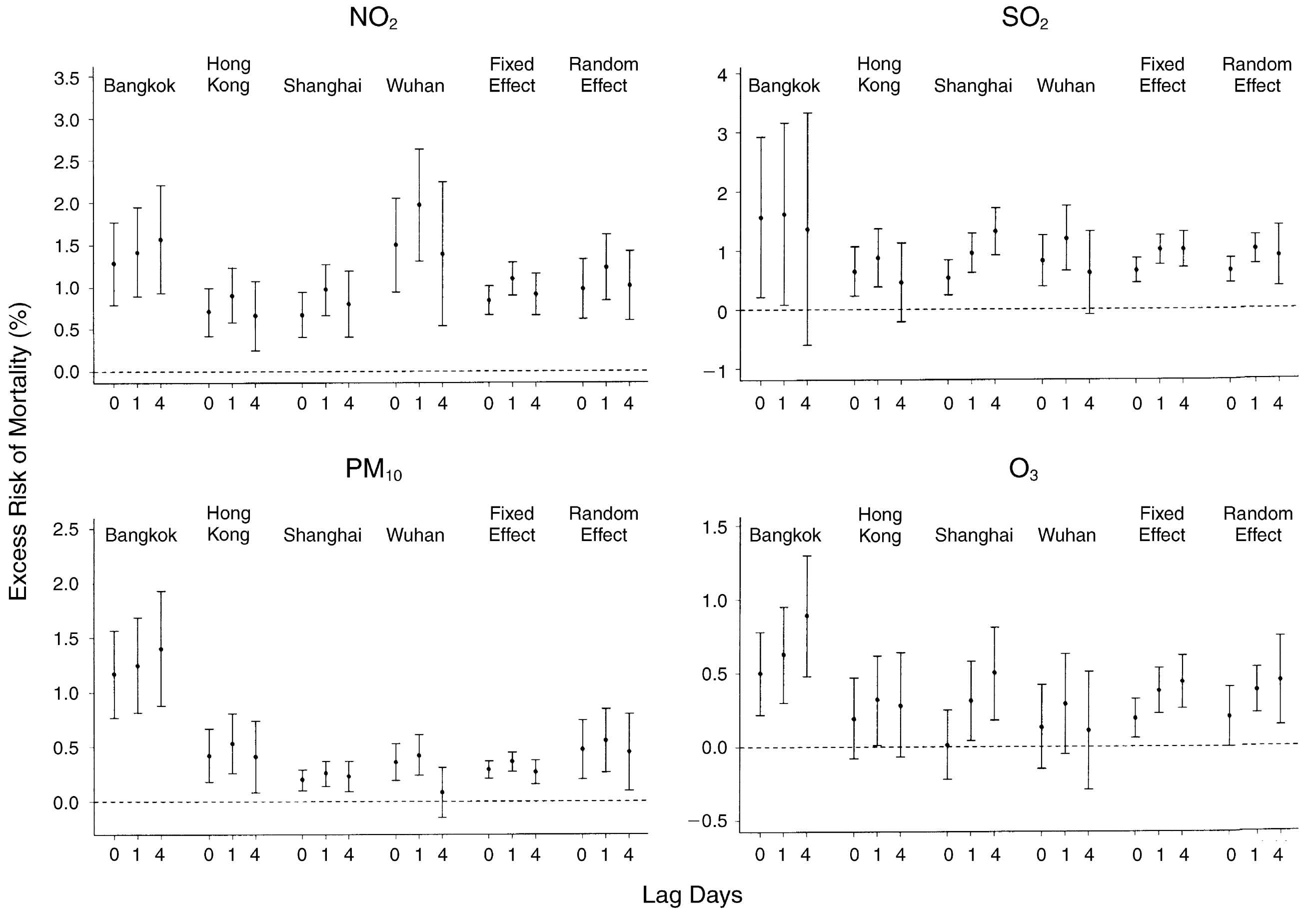


Figure 6. Percentage of excess risk of mortality per 10-µg/m^3 increase in each pollutant concentration for the current day ("0"), lag 0–1 day (average) ("1"), and lag 0–4 days (average) ("4"). Individual (city by city) and combined (all cities) fixed and random effects are also shown. Error bars indicate 95% CI. The dashed lines at 0 on the *y*-axes indicate the points at which air pollution had no effect on mortality. Note varying scales of *y*-axes.

Bangkok, exhibiting the highest excess risk per 10-µg/m^3 increase in concentration for all of the pollutants except SO_2. All of the cities demonstrated associations for each pollutant except SO_2 in Bangkok. Again, there was heterogeneity in the PM_{10} estimate because of the high excess risk exhibited in Bangkok, and all of the meta-analysis estimates were statistically significant. A different pattern emerged for respiratory mortality, for which the highest estimates were found in Wuhan for NO_2 and SO_2 and in Bangkok for PM_{10} and O_3. All of the random-effects estimates were statistically significant at the 5% level except for O_3.

LAG EFFECTS

The results for the effects of alternative lags on all natural mortality are summarized in Figure 6. For the three Chinese cities, with a few exceptions, the lag 0–1 day (average) (indicated by "1" in the figure) usually generated the highest excess risk. For Bangkok, however, the longer cumulative average of lag 0–4 days (average) (indicated by "4" in the figure) generated the highest excess risk, except for SO_2. In the meta-analysis results (see Random Effects in the figure), the lag 0–1 days (average) showed the highest excess risk, except in the case of O_3, for which the excess risk for

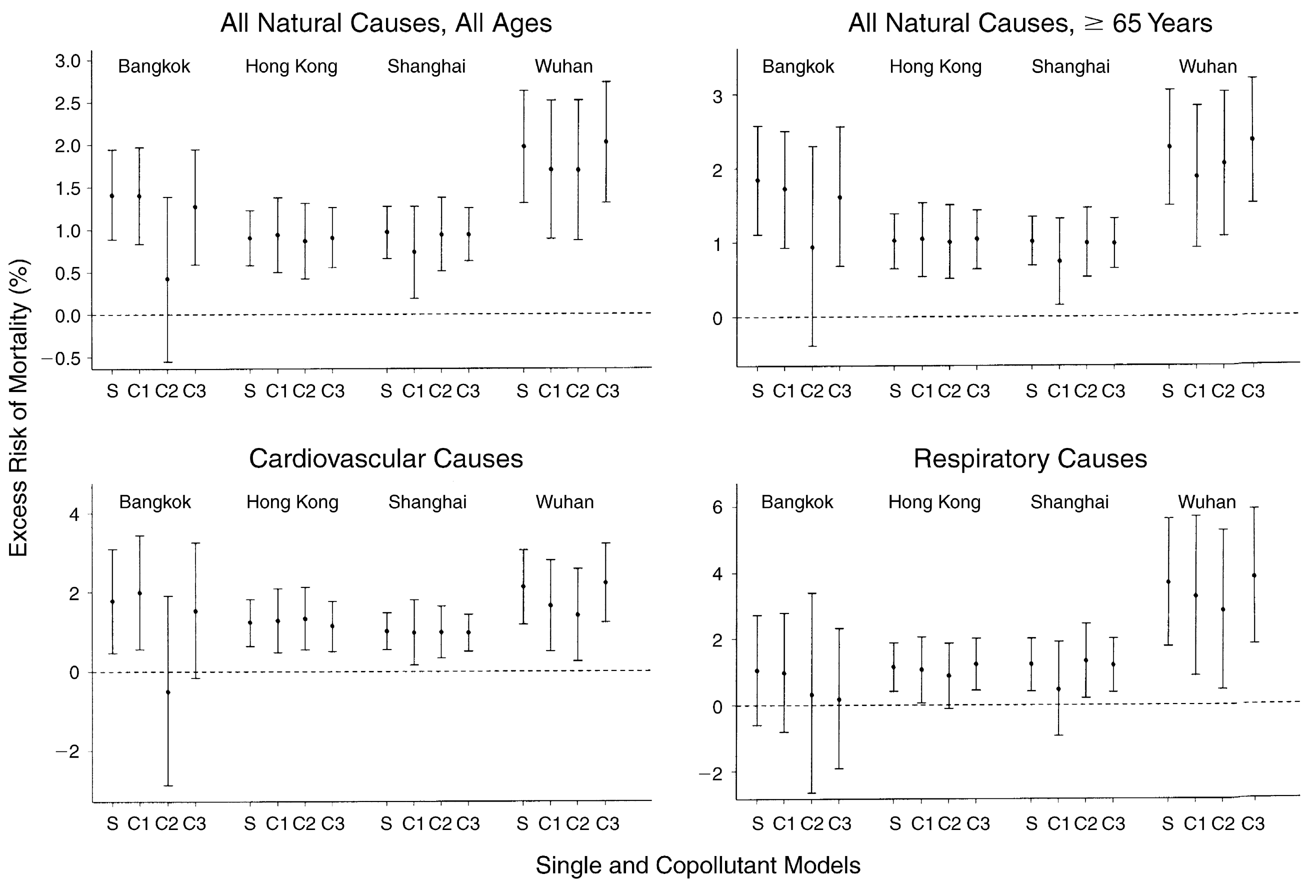


Figure 7. Sensitivity of copollutant on NO_2 effect estimates expressed as percentage of excess risk of mortality per 10-µg/m^3 increase in average concentration of each air pollutant for lag 0–1 day (average). S indicates single-pollutant (NO_2) model. C1 indicates copollutant model using NO_2 and SO_2. C2 indicates copollutant model using NO_2 and PM_{10}. C3 indicates copollutant model using NO_2 and O_3. Error bars indicate 95% CI. The dashed lines at 0 on the *y*-axes indicate the points at which air pollution had no effect on mortality. Note varying scales of *y*-axes.

lag 0–4 days (average) was greatest (because of the strong effects observed in Bangkok and Shanghai).

EFFECTS WITH COPOLLUTANTS

For NO_2, the effects on mortality from all natural causes were robust to adjustment for the other pollutants, except in Bangkok, where the effect was highly attenuated such that the 95% CI overlapped zero after adjustment for PM_{10} (Figure 7). For SO_2, the effects on mortality from all natural causes were attenuated with adjustment for NO_2 in all four cities; but attenuation of the effects on cardiovascular and respiratory mortality were only seen in the three Chinese cities (because the effects of SO_2 were not statistically significant in Bangkok) (Figure 8). For PM_{10}, the effects in the three Chinese cities were attenuated and the 95% CI overlapped zero after adjustment for NO_2; in Bangkok the effects were robust to adjustment for NO_2 (Figure 9). For O_3, attenuations of effects on mortality from all natural causes and on cardiovascular mortality were only observed in Bangkok and Hong Kong; clear copollutant effects were only observed in Shanghai and Wuhan (Figure 10).

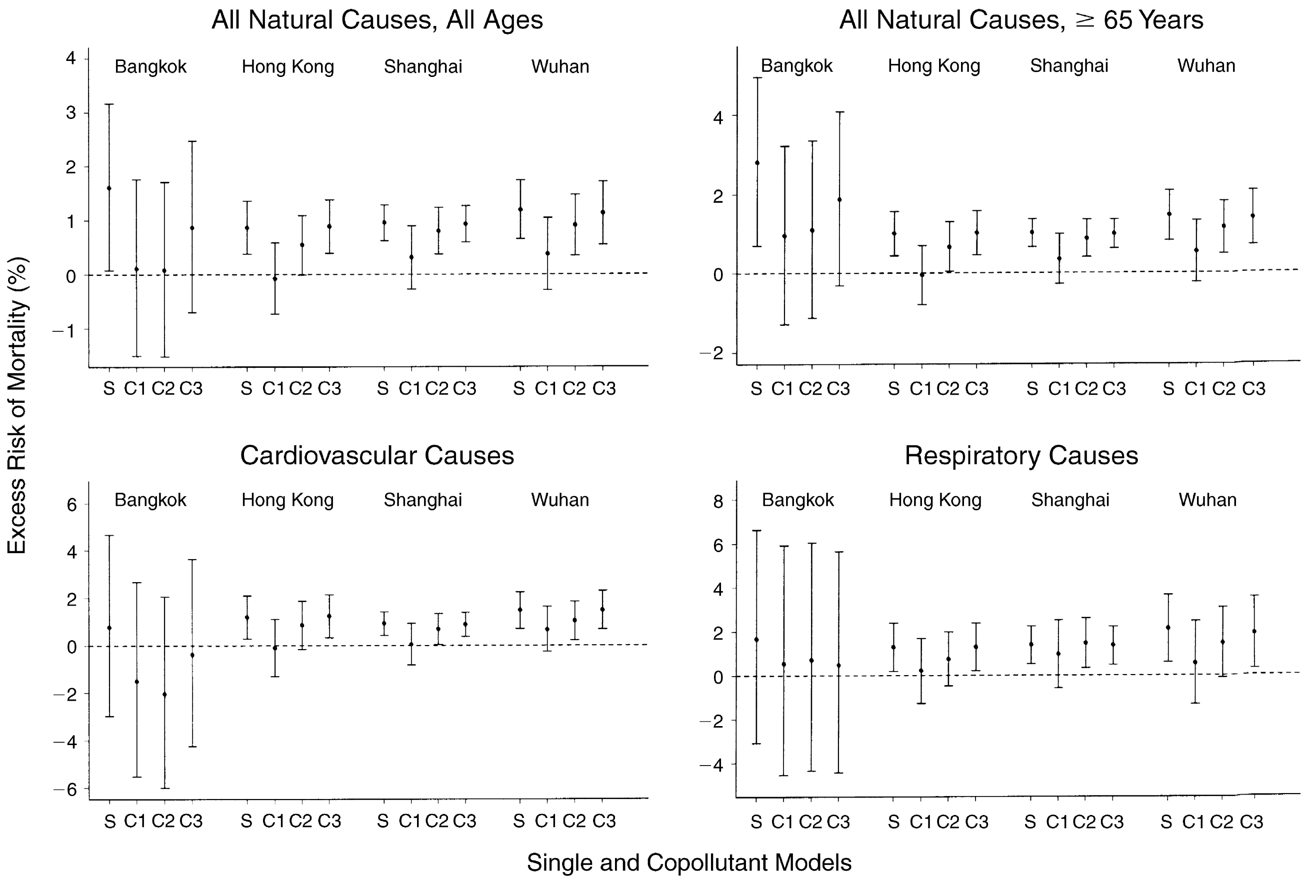


Figure 8. Sensitivity of copollutant on SO_2 effect estimates expressed as percentage of excess risk of mortality for a 10-µg/m^3 increase in average concentration of each air pollutant for lag 0–1 day (average). S indicates single-pollutant (SO_2) model. C1 indicates copollutant model using SO_2 and NO_2. C2 indicates copollutant model using SO_2 and PM_{10}. C3 indicates copollutant model using SO_2 and O_3. Error bars indicate 95% CI. The dashed lines at 0 on the *y*-axes indicate the points at which air pollution had no effect on mortality. Note varying scales of *y*-axes.

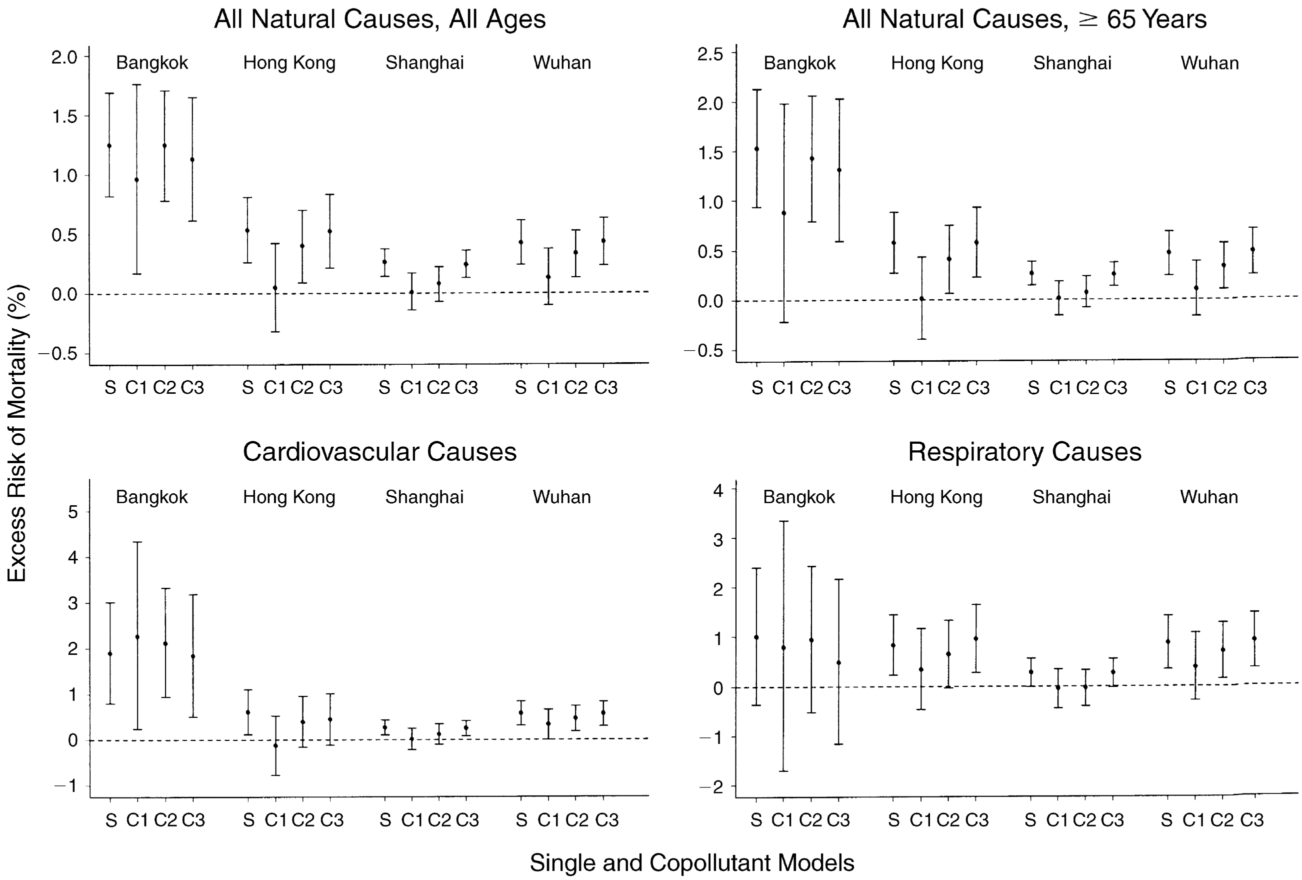


Figure 9. Sensitivity of copollutant on PM_{10} effect estimates expressed as percentage of excess risk of mortality per 10-µg/m^3 increase in average concentration of each air pollutant for lag 0–1 day (average). S indicates single-pollutant (PM_{10}) model. C1 indicates copollutant model using PM_{10} and NO_2. C2 indicates copollutant model using PM_{10} and SO_2. C3 indicates copollutant model using PM_{10} and O_3. Error bars indicate 95% CI. The dashed lines at 0 on the *y*-axes indicate the points at which air pollution had no effect on mortality. Note varying scales of *y*-axes.

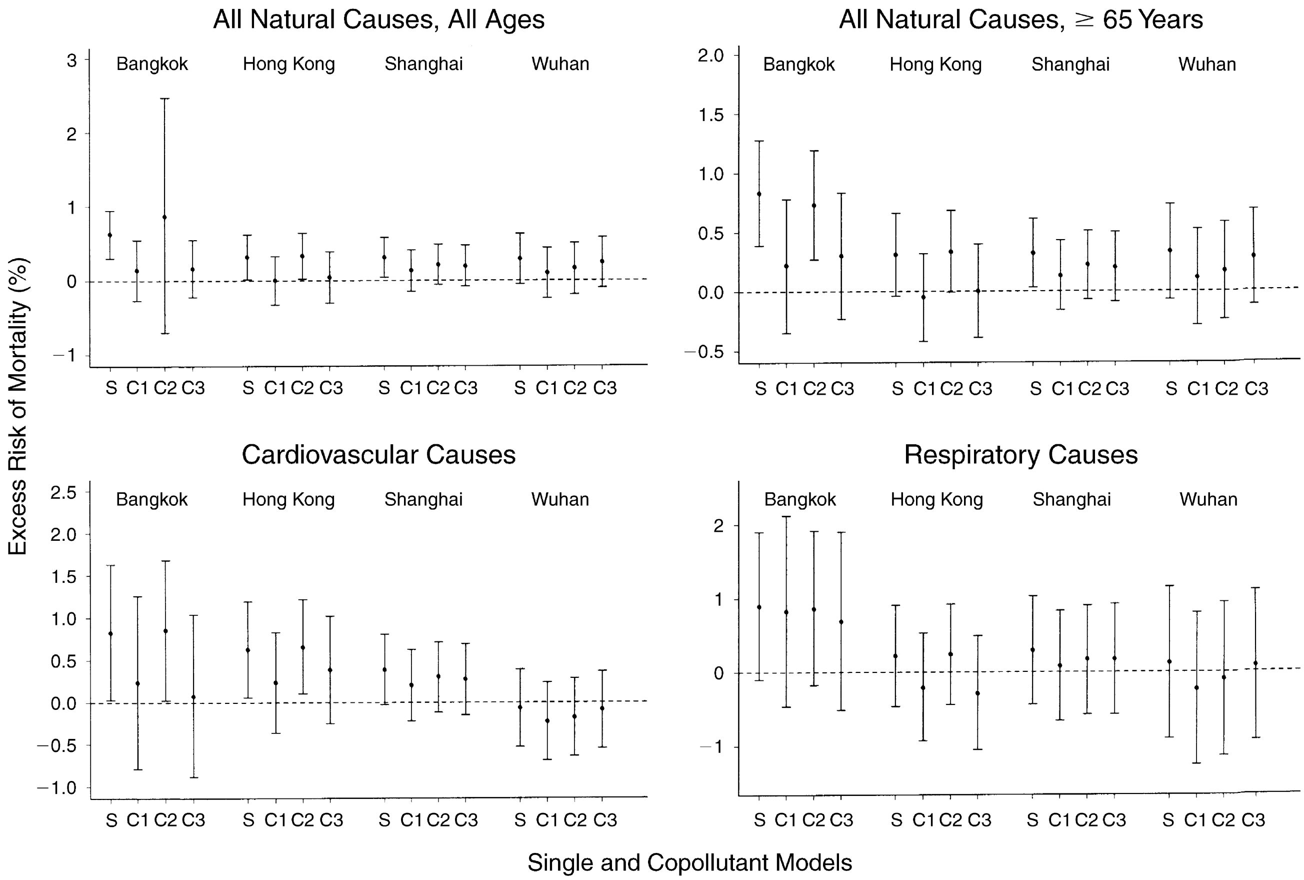


Figure 10. Sensitivity of copollutant on O_3 effect estimates expressed as percentage of excess risk of mortality per 10-µg/m^3 increase in average concentration of each air pollutant for lag 0–1 day (average). S indicates single-pollutant (O_3) model. C1 indicates copollutant model using O_3 and NO_2. C2 indicates copollutant model using O_3 and SO_2. C3 indicates copollutant model using O_3 and PM_{10}. Error bars indicate 95% CI. The dashed lines at 0 on the *y*-axes indicate the points at which air pollution had no effect on mortality. Note varying scales of *y*-axes.

SENSITIVITY ANALYSES FOR PM_{10}

In general, the effect estimates for PM_{10} were fairly robust to monitors, treatment of missing values, degrees of freedom used in the smoothers, and alternative spline models. All cities showed that the effect estimates for PM_{10} were sensitive to exclusion of the higher concentrations. For the Chinese cities, the exclusion of these concentrations increased the estimated effect of PM_{10}, with excess-risk increases of more than 20%, while in Bangkok the effect estimate decreased, with the excess risk changing from 1.3% to 0.7% per 10-µg/m^3 increase in average concentration at lag 0–1 days (average) (Table 5). Examination of the effects of the warm season, which varied for each city, resulted in significant increases in effect estimates for Bangkok and Wuhan but decreases in Hong Kong and to a lesser extent in Shanghai. Finally, adjusting for temperature through use of longer-term cumulative averages tended to decrease the PM_{10} effect.

SENSITIVITY ANALYSES FOR NO_2

In general, the effect estimates for NO_2 were fairly robust. Analyses altering maximum concentrations, monitors, treatment of missing values, degrees of freedom used in the smoothers, and alternative spline models did not show large changes in the excess risk estimates. Similar to the result of the sensitivity analysis for PM_{10}, adjusting for temperature through use of longer-term cumulative averages tended to decrease the NO_2 effect (Table 6).

SENSITIVITY ANALYSES FOR VARIOUS DEGREES OF FREEDOM IN TIME TREND

Using various degrees of freedom in time trend — up to 12 per year — while controlling for temperature and relative humidity at current lag day, the estimates for PM_{10} were robust in all cities and the estimates for gaseous pollutants were robust except for NO_2 and O_3 in Wuhan and SO_2 in Bangkok (Figure 11).

Table 5. Effect of PM_{10} Exposure in the Warm Season[a,b]

	Bangkok	Hong Kong	Shanghai	Wuhan	Random Effect (4 Cities)	Random Effect (3 Chinese Cities)
Main analysis	1.25	0.53	0.26	0.43	0.55 (0.26, 0.85)[c]	0.37 (0.21, 0.54)[d]
Exclusion of PM_{10} concentration if						
> 95 percentile	**0.82**	**0.75**	0.28	**0.52**	0.53 (0.27, 0.78)[e]	**0.47 (0.21, 0.73)**[e]
> 75 percentile	**0.73**	**0.89**	**0.36**	**0.70**	0.53 (0.29, 0.78)[d]	**0.55 (0.24, 0.85)**[d]
> 180 μg/m^3	1.25	0.54	0.22	**0.73**	0.65 (0.24, 1.06)[c]	**0.46 (0.15, 0.76)**[e]
Exclusion of stations with high traffic sources	1.18	0.54	0.25	0.45	0.55 (0.26, 0.85)[c]	0.38 (0.20, 0.57)[d]
Warm season effect assessed by simple dichotomous variables	**2.16**	**0.37**	0.24	**0.81**	**0.86 (0.11, 1.60)**[c]	0.43 (0.10, 0.76)[d]
Addition of temperature at lag 1–2 days (average) with lag 0 day	1.06	0.43	0.23	0.48	0.51 (0.23, 0.79)[c]	0.36 (0.18, 0.53)[d]
Addition of temperature at lag 3–7 days (average) with lag 0 day	**0.96**	**0.36**	**0.15**	**0.34**	**0.35 (0.14, 0.57)**[f]	**0.25 (0.10, 0.40)**[d]
Daily PM_{10} concentrations defined by centering	1.20	0.53	0.26	0.42	0.54 (0.26, 0.82)[c]	0.37 (0.21, 0.53)[d]
Natural spline[g]	1.23	0.54	0.28	0.38	0.54 (0.26, 0.81)[c]	0.36 (0.23, 0.49)[d]
Penalized spline	1.20	0.48	0.28	0.39	0.52 (0.26, 0.77)[c]	0.34 (0.23, 0.45)[d]
Common approach[h]	1.25	0.60	0.23	0.34	0.55 (0.23, 0.87)[c]	0.36 (0.16, 0.56)[e]

[a] Data are presented as excess risk of mortality in % (95% CI) per 10-μg/m^3 increase in average concentration of lag 0–1 day (average). Bold indicates when excess risk changed > 20% from the main analysis.

[b] "Warm season" defined as extending approximately from April to October in the four cities with adjustment for time trends using indicator variables for each year in the core model.

[c] Significant at $P \le 0.001$ by homogeneity test.

[d] Not significant.

[e] Significant at $0.01 < P \le 0.05$ by homogeneity test.

[f] Significant at $0.001 < P \le 0.01$ by homogeneity test.

[g] Use of natural spline with degrees of freedom of time trend per year, temperature, and relative humidity fixed at df = 8, df = 4, and df = 4, respectively.

[h] Use of natural spline with degrees of freedom of time trend per year, temperature, and relative humidity fixed at df = 6, df = 3, and df = 3, respectively.

Table 6. Sensitivity Analyses of NO_2 Effects for All Natural Causes, All Ages[a]

	Bangkok	Hong Kong	Shanghai	Wuhan	Random Effect (4 Cities)	Random Effect (3 Chinese Cities)
Main analysis	1.41	0.90	0.97	1.97	1.23 (0.84, 1.62)[b]	1.19 (0.71, 1.66)[b]
Addition of temperature at lag 1–2 days (average) with lag 0 day	1.18	**0.59**	**0.70**	**1.14**	**0.80 (0.53, 1.07)**[c]	**0.69 (0.48, 0.91)**[c]
Addition of temperature at lag 3–7 days (average) with lag 0 day	**1.09**	**0.53**	**0.53**	**1.24**	**0.74 (0.43, 1.05)**[c]	**0.64 (0.33, 0.95)**[c]
Daily PM_{10} concentrations defined by centering	1.60	0.93	0.97	1.93	1.27 (0.86, 1.68)[b]	1.18 (0.73, 1.63)[b]
Natural spline[d]	1.41	0.90	1.02	1.85	1.21 (0.86, 1.56)[b]	1.16 (0.74, 1.59)[b]
Penalized spline	1.34	0.79	0.99	1.88	1.17 (0.78, 1.56)[b]	1.13 (0.66, 1.61)[b]
Common approach[e]	1.41	1.11	1.03	1.82	1.22 (0.95, 1.49)[c]	1.19 (0.86, 1.51)[c]

[a] Data are presented as excess risk of mortality in % (95% CI) per 10-μg/m^3 increase in average concentration of lag 0–1 day (average). Bold indicates when excess risk changed > 20% from the main analysis.

[b] Significant at $0.01 < P \le 0.05$ by homogeneity test.

[c] Not significant.

[d] Use of natural spline with degrees of freedom of time trend per year, temperature, and relative humidity fixed at df = 8, df = 4, and df = 4, respectively.

[e] Use of natural spline with degrees of freedom of time trend per year, temperature, and relative humidity fixed at df = 6, df = 3, and df = 3, respectively.

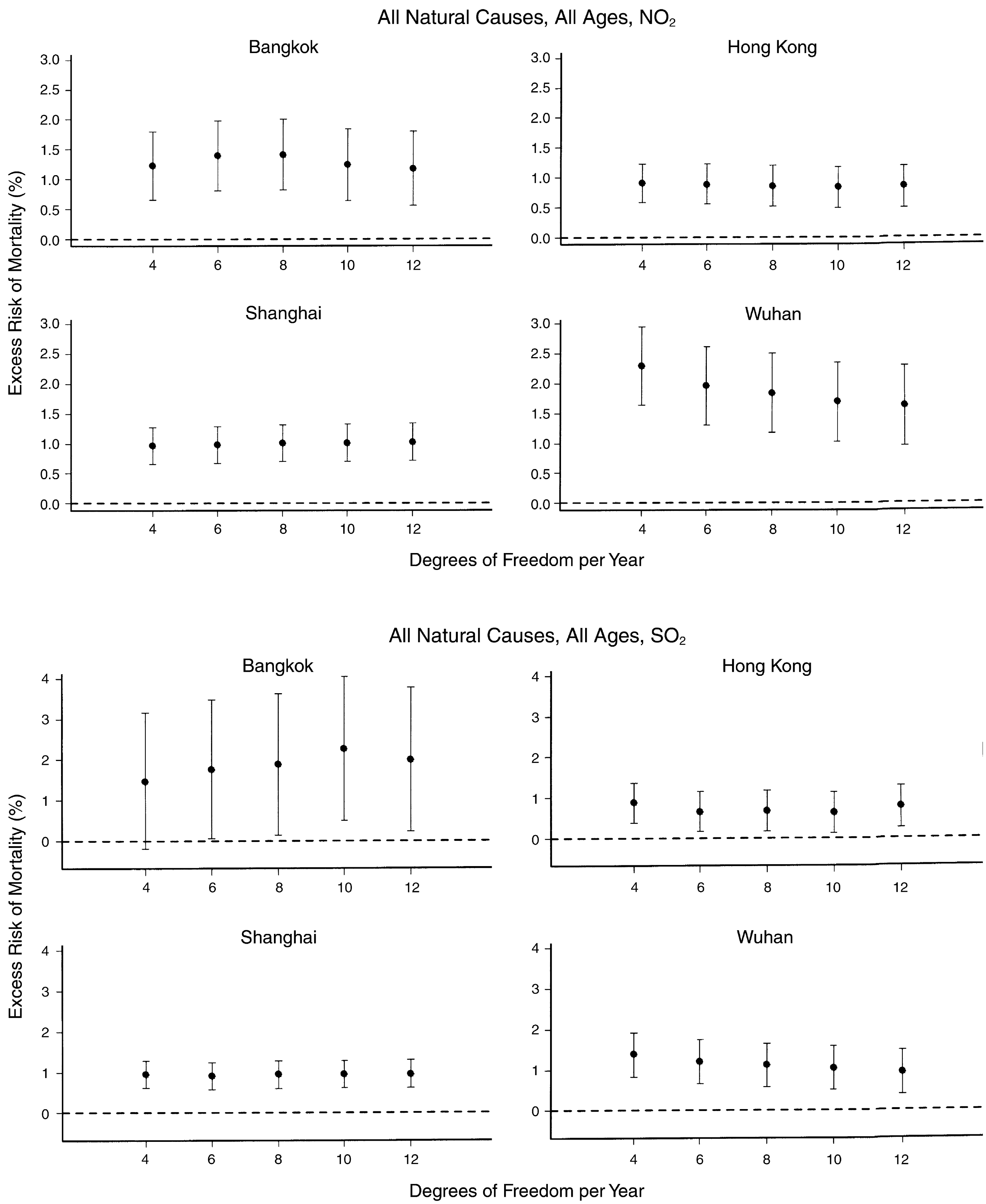
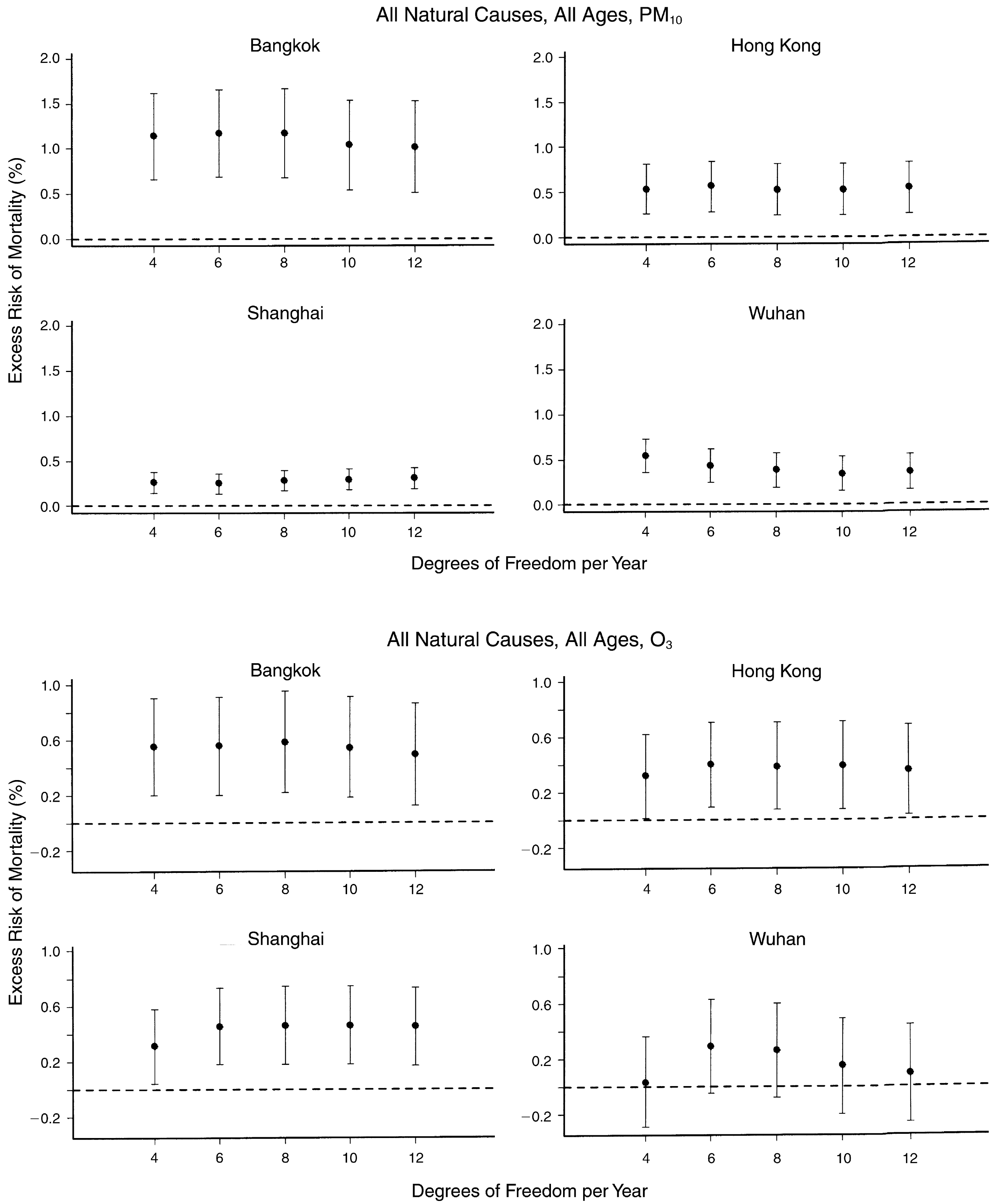


Figure 11. Sensitivity analyses for the effect of different degrees of freedom on estimates of percentage of excess risk of mortality per 10-µg/m^3 increase in NO_2, SO_2, PM_{10}, and O_3 at lag 0–1 day (average). Error bars indicate 95% CI of estimates of excess risk. Note varying scales of *y*-axes.



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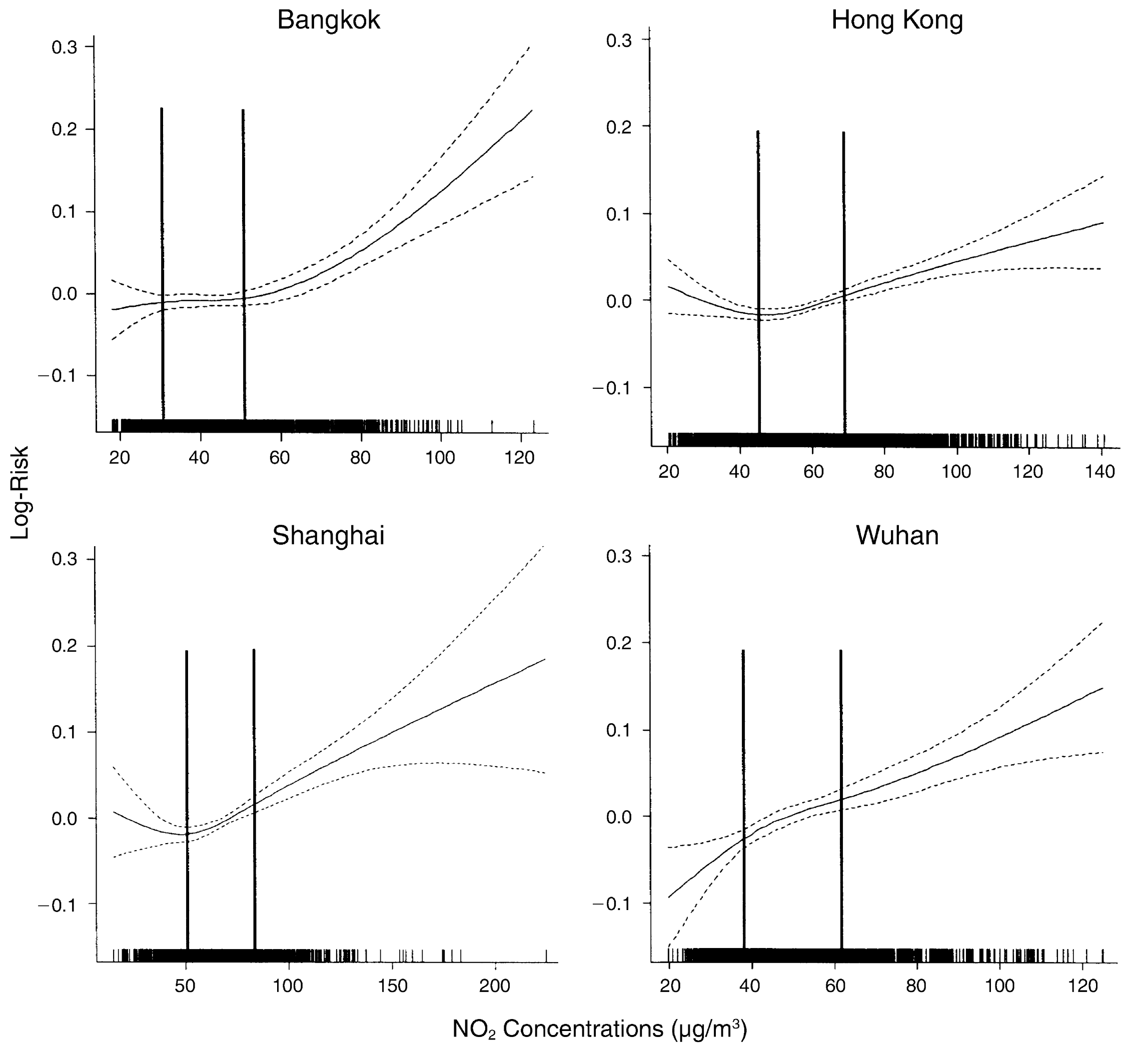

Figure 12. The concentration–response curves for mortality from all natural causes at all ages in all the four cities and the daily average concentration for NO_2, SO_2, PM_{10}, and O_3 at lag 0–1 day (average). Solid line indicates concentration–response curve, dotted lines indicate 95% confidence intervals, the two vertical lines in each panel indicate the IQR of pollutant concentration, and the short lines along the *x*-axes indicate number of observations. Note differences in the scales of the *x*-axes.

CONCENTRATION–RESPONSE RELATIONSHIPS

For mortality from all natural causes, there appeared to be positive concentration–response relationships in most analyses. Between the first and third quartile of a given pollutant concentration, most concentration–response relationships appeared to be linear, except in Shanghai, for which the relationship was mainly non-linear (Figure 12). Tests showed that at all ages there were non-linear relationships between NO_2 and mortality ($P \leq 0.001$) in Bangkok, between NO_2 and all of the mortality causes under study ($P \leq 0.01$) and between SO_2 and mortality from all natural causes ($P \leq 0.05$) in Hong Kong, and between PM_{10} and mortality from all natural causes ($P \leq 0.05$) as well as between NO_2 and SO_2 and respiratory mortality ($P \leq 0.05$) in Shanghai (Table 7). There were no non-linear relationships between any pollutants and the mortality causes under study ($P > 0.05$) in Wuhan (Table 7).

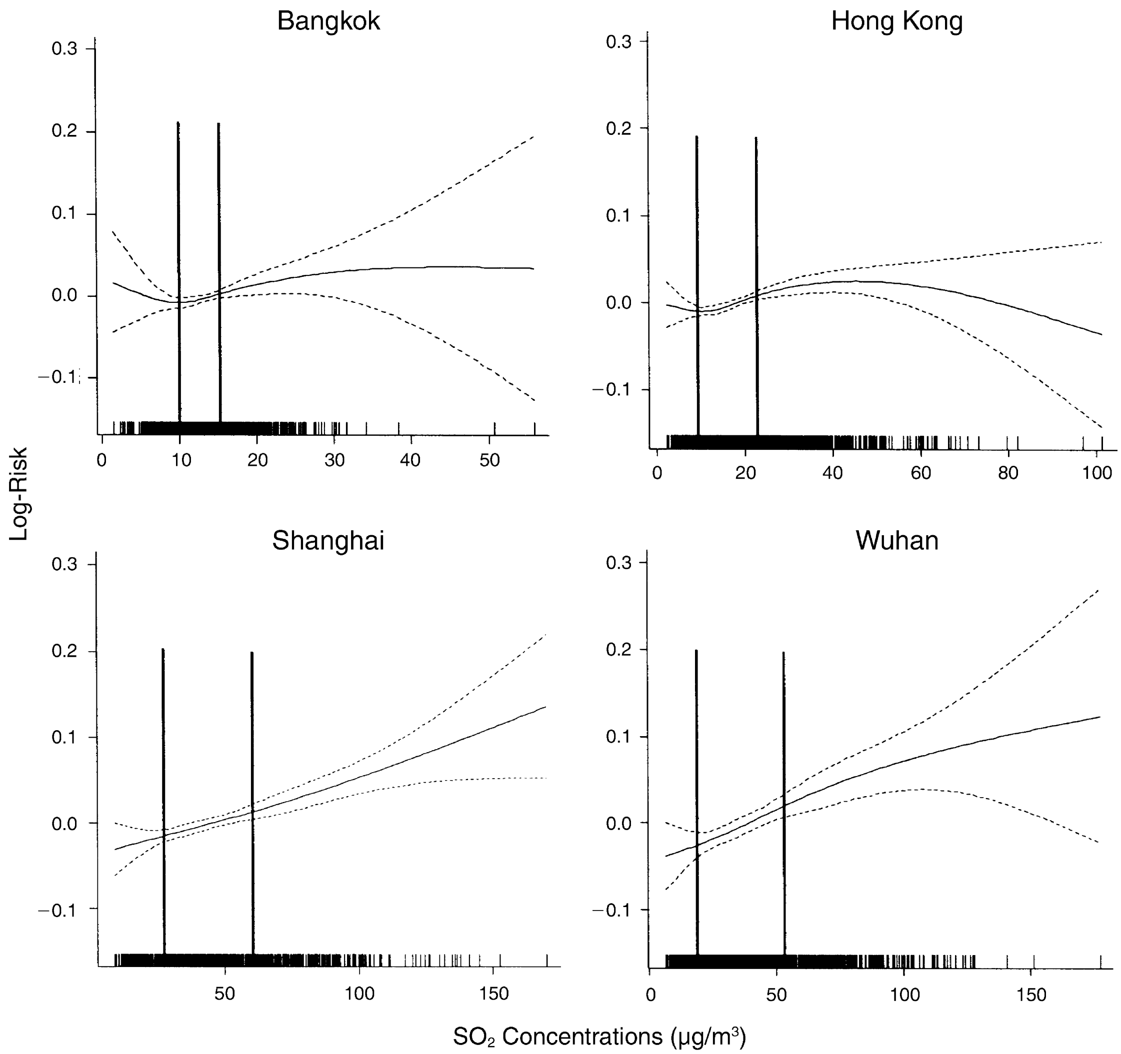

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Figure 12 (*Continued*).

Table 7. Test of Non-Linearity for the Concentration–Response Curve[a]

	All Natural Causes, All Ages				Cardiovascular Causes				Respiratory Causes			
	Bangkok	Hong Kong	Shanghai	Wuhan	Bangkok	Hong Kong	Shanghai	Wuhan	Bangkok	Hong Kong	Shanghai	Wuhan
NO_2	14.94[b]	14.70[b]	3.36[c]	4.64[c]	4.77[c]	12.27[e]	2.41[c]	1.00[c]	0.39[c]	9.97[e]	7.64[d]	2.77[c]
SO_2	2.15[c]	6.20[d]	0.19[c]	3.85[c]	0.13[c]	3.13[c]	1.85[c]	3.36[c]	5.65[c]	1.69[c]	12.53[e]	2.25[c]
PM_{10}	4.39[c]	0.80[c]	6.0[d]	3.58[c]	2.29[c]	0.65[c]	2.33[c]	0.76[c]	0.56[c]	0.73[c]	4.82[c]	3.90[c]
O_3	0.34[c]	0.19[c]	4.95[c]	5.66[c]	0.15[c]	0.98[c]	3.03[c]	2.06[c]	0.18[c]	0.94[c]	0.03[c]	1.32[c]

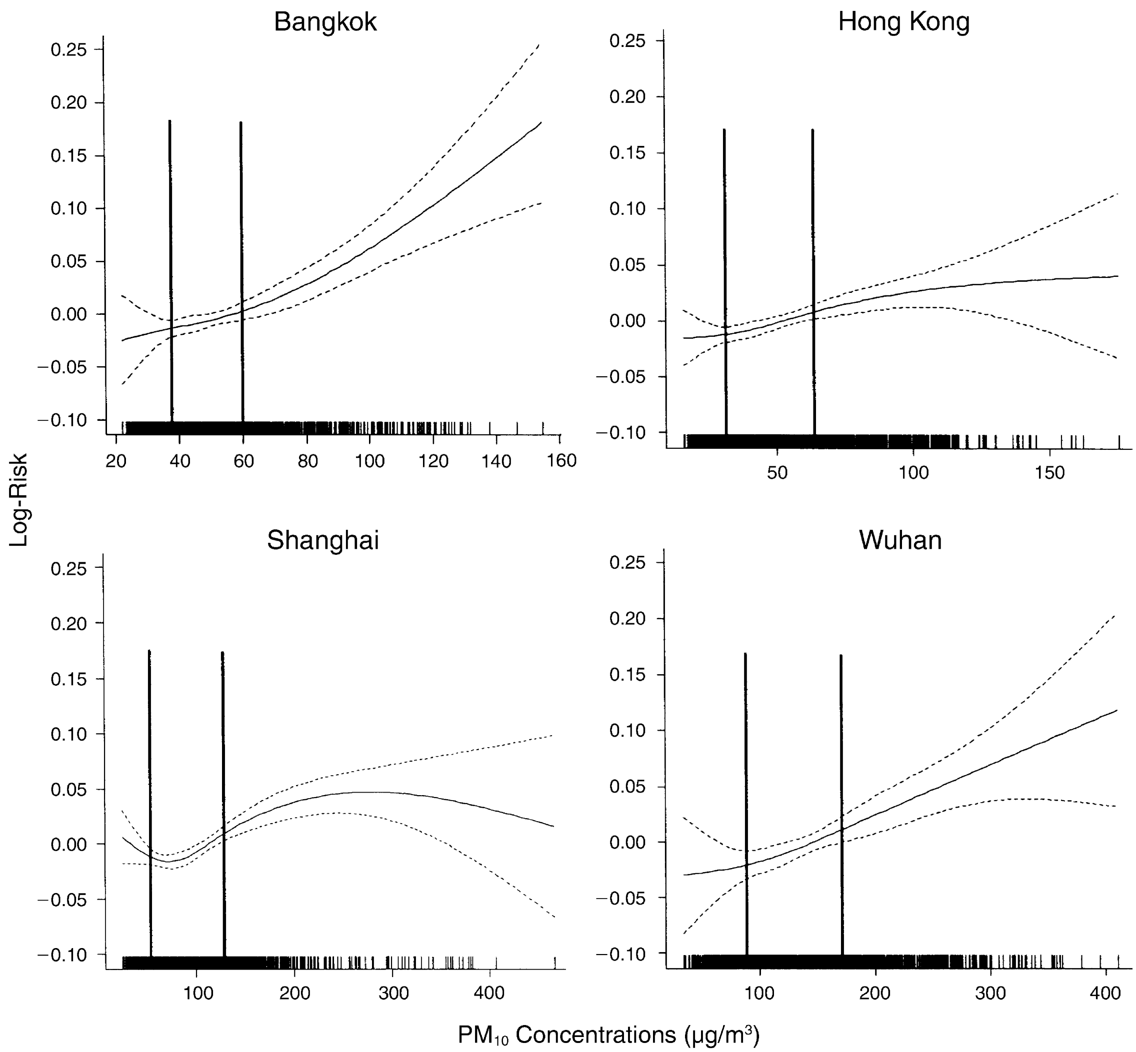
[a] Chi-square distribution with 2 df. *P* values are for the deviance between a non-linear model (with 3 df) and a linear model (with 1 df).

[b] Significant at $P \le 0.001$.

[c] Not significant.

[d] Significant at $0.01 < P \le 0.05$.

[e] Significant at $0.001 < P \le 0.01$.



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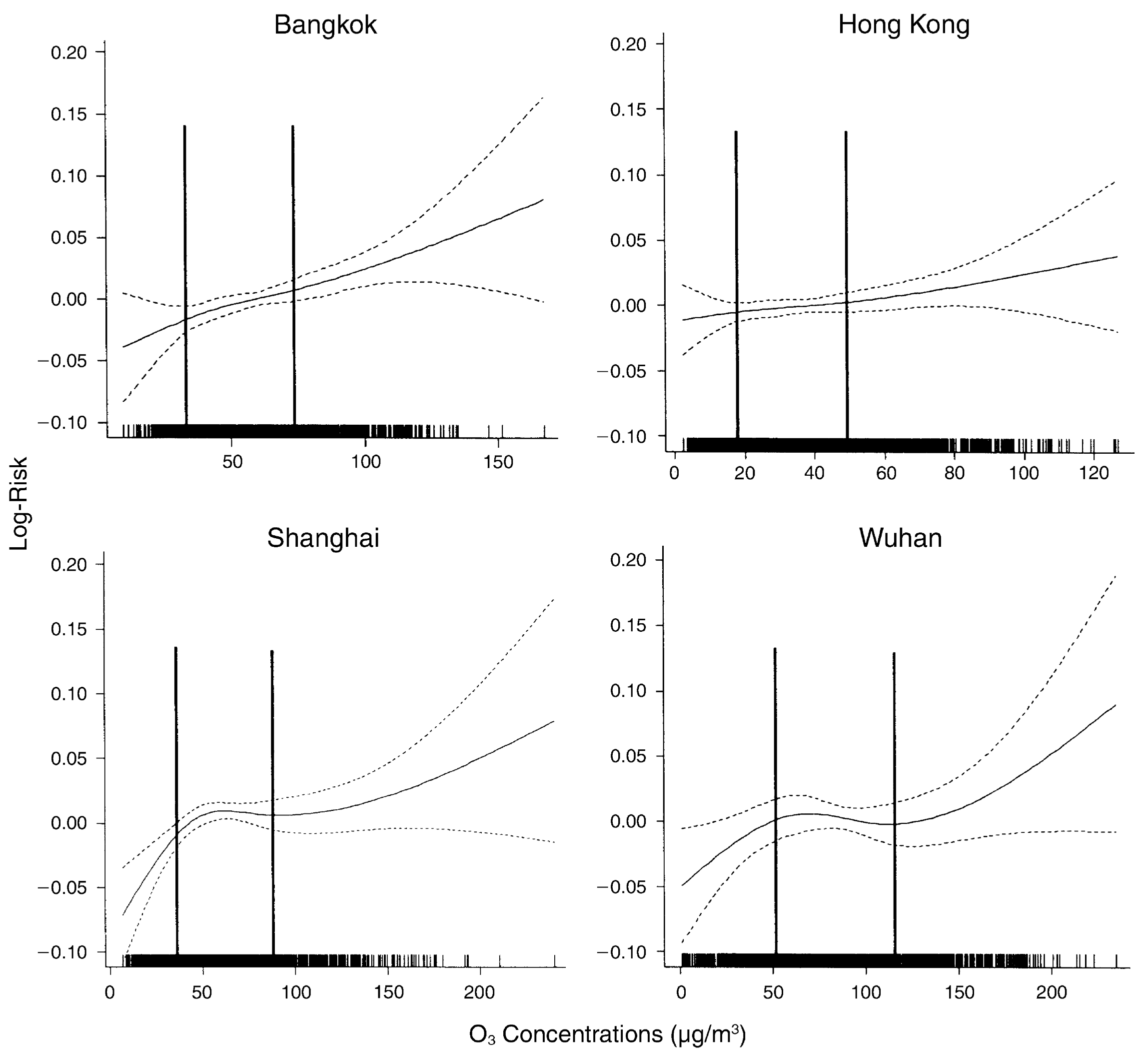

Figure 12 (*Continued*).

DISCUSSION

LITERATURE REVIEW OF RESEARCH ON SHORT-TERM EFFECTS OF FOUR CRITERIA POLLUTANTS IN ASIA

The deterioration of ambient air quality in Asian countries has become a serious problem. Published papers of studies of the effects of pollution on health in China, India, Indonesia, Japan, Malaysia, Singapore, South Korea, Taiwan, and Thailand were found (HEI International Scientific Oversight Committee 2004). Most of the studies focused on the association between outdoor air pollution and mortality in time-series analyses.

For NO_2, very few time-series studies were found. These were mainly from South Korea and Hong Kong (Hong et al. 1999; Wong et al. 2001). The variation of effects was large compared with other pollutants for all natural mortality, respiratory mortality, and cardiovascular mortality. For SO_2, most time-series studies in China showed significant associations with all natural mortality even at concentrations below the current WHO Air Quality Guideline (Chen et al. 2004). A review of Asian studies (HEI International Scientific Oversight Committee 2004) also found that SO_2 was associated with all natural mortality regardless of random-effects or fixed-effects models. For PM_{10}, although fewer time-series studies were published in Asia than in other regions, most studies reported significant associations with all natural mortality but only for respiratory and cardiovascular mortality in Bangkok (Ostro et al. 1999). A meta-analysis of Chinese studies found that each 10-µg/m^3 increase in PM_{10} concentrations was significantly associated with a 0.3% increase in mortality from all natural causes, a 0.4% increase in cardiovascular mortality, and a 0.6% increase in respiratory mortality (Aunan and Pan 2004). However, significant associations with respiratory and cardiovascular mortality were not found in the Seoul or Hong Kong studies (Hong et al. 1999; Wong et al. 2001). For O_3, various time-average concentrations — such as 1 hour, 8 hours, and 24 hours — were used, and the resulting estimates varied greatly among the studies (HEI International Scientific Oversight Committee 2004).

REVIEW OF RESULTS FROM THE PAPA PROJECT

In the combined four-city analysis, the excess risk per 10-µg/m^3 increase in NO_2 concentrations was two to three times greater than those reported in the APHEA project (Samoli et al. 2006) for mortality from all natural causes, cardiovascular disease, and respiratory disease at all ages (1.23% [95% CI 0.84, 1.62] versus 0.3%, 1.36% [95% CI 0.89, 1.62] versus 0.4%, and 1.48% [95% CI 0.68, 2.28] versus 0.38%, respectively) (Appendix E). For SO_2, the PAPA project estimate (based on the random-effects model) for mortality from all natural causes of 1.00% (95% CI 0.75, 1.24) was higher than the estimate of 0.52% previously reported for other Asian cities studied (HEI International Scientific Oversight Committee 2004) and the estimate of 0.40% reported by the APHEA project (Katsouyanni et al. 1997) (Appendix E). For PM_{10}, the PAPA project effect estimate for mortality from all natural causes at all ages of 0.55% (95% CI 0.26, 0.85) was comparable to the estimate of 0.49% for other Asian cities and the estimate of 0.6% reported by the APHEA project (Anderson et al. 2004) but was higher than the estimate of 0.21% reported by the NMMAPS (Health Effects Institute 2003) (Appendix E). A meta-analysis of Chinese studies found that each 10-µg/m^3 increase in PM_{10} concentrations was significantly associated with a 0.3% increase in mortality from all natural causes, a 0.4% increase in cardiovascular mortality, and a 0.6% increase in respiratory mortality (Aunan and Pan 2004). For O_3, the PAPA project estimate of 0.38% (95% CI 0.23, 0.53) was significant and higher than that reported by APHEA (0.20%) (Anderson et al. 2004) and NMMAPS (0.26%) (Bell et al. 2004) for mortality from all natural causes. The estimates reported for cardiovascular mortality were similar in PAPA (0.37%; 95% CI 0.01, 0.73), APHEA (0.4%), and NMMAPS (0.32%). The estimate for respiratory disease for PAPA (0.34%; 95% CI −0.07, 0.75) was similar to that of NMMAPS (0.32%) but negative and not statistically significant for APHEA (−0.1%; $P > 0.05$) (Appendix E).

In the main effects for the major health outcomes under study, there were similarities as well as dissimilarities in effect estimates between cities. For NO_2, similarities were found between Bangkok and Wuhan, and between Hong Kong and Shanghai, in terms of the magnitude and precision of the estimates. The effects for Bangkok and Wuhan were higher but less precise (as reflected by a wider 95% CI) compared with those of Shanghai and Hong Kong. For SO_2, the estimates for Bangkok were relatively higher but less precise compared with those of the three Chinese cities. The lack of precision in the Bangkok estimates might have been caused by a lack of variability in SO_2 (the standard deviation for SO_2 in Bangkok was 5 µg/m^3 compared with 12–25 µg/m^3 in the Chinese cities). However, when the excess risk was expressed as a per-IQR increase, the effect estimates were very similar in the four cities. For PM_{10}, the estimates in the three Chinese cities were very similar, but the estimates in Bangkok were higher and less precise even though the standard deviation for the pollutant concentrations in Bangkok was about the same as in Hong Kong and about one-third that of Shanghai and Wuhan. For O_3, the effect estimates and precision among the four cities were similar, although the estimates for Bangkok were slightly higher.

For mortality from accidental causes, which was used as a control outcome, no associations with exposure to air pollution were found in Bangkok, Hong Kong, and Shanghai, i.e., the three cities that had the data. However, as the health effects of air pollution are not specific and can be found in persons with a variety of comorbidities, it is not surprising that excess risks with magnitudes similar to those for cardiopulmonary mortality were found for non-cardiopulmonary health outcomes. The significant excess risks of mortality from non-cardiopulmonary causes can be attributed to the use of underlying cause of death in the current study. Persons with an underlying health problem are likely to be more vulnerable to air pollution and are classified as having died from these underlying problems. Identifying persons vulnerable to air pollution deserves greater attention in future studies.

ROBUSTNESS OF THE RESULTS FROM THE PAPA STUDY

In sensitivity analyses for PM_{10} effect estimates, most of the estimates did not change to an extent greater than a predefined 20% from those of the main analyses.

Across the four cities, additional adjustments for the average temperature at 3–7 lag days (average) showed that the effect estimates for PM_{10} were attenuated. We suspect that there might have been residual confounding caused by uncontrolled lag effects of temperature. However, current-day temperature was predefined in the core models and was determined at the beginning of the study to be sufficient to adjust for temperature effects. On the other hand, there were high correlations between temperatures at each of lag days 1 to 7 and at current day, which convinced us not to make further adjustments of this lag-temperature effect in the core models.

BROADER SCIENTIFIC IMPLICATIONS ARISING FROM THE RESULTS OF THE PAPA STUDY

1. PM_{10} Estimate Comparison Among the Four Cities

The effect estimates for PM_{10} for the three Chinese cities were relatively similar when compared with those of Bangkok, but there are also discrepancies among them. The estimates for Shanghai were consistently almost half those of Hong Kong and Wuhan, for both of which the effect estimates were comparable for all three mortality outcomes (all natural causes, 0.52% versus 0.43%; cardiovascular, 0.61% versus 0.57%; and respiratory, 0.83% versus 0.87%). Shanghai had relatively higher PM_{10} concentrations than Hong Kong (102.0 versus 51.6 µg/m^3); the lower effect estimates for Shanghai despite higher concentrations compared with those of Hong Kong (0.26%–0.27% versus 0.53%–0.83%) could thus be explained by the flattening of concentration–response curves at the higher concentrations. However, this pattern of concentration–response curve cannot be used to explain the higher estimate for Wuhan, which had a higher PM_{10} concentration than that of Shanghai (141.8 versus 102.0 µg/m^3). These discrepancies in effect estimates might also be related to differences in the locations of the monitoring stations as well as to differences in the actual ambient levels of exposure of the population compared with concentrations measured at the stations.

Consistent with a previous study (Ostro et al. 1999), Bangkok's PM_{10} concentrations and effect estimates were higher than those of the three Chinese cities (1.25 versus 0.26–0.53; 1.90 versus 0.27–0.61; and 1.01 versus 0.27–0.87) (Table 4). The reasons could be related to consistently higher temperatures, more time spent outdoors by the population, and less air conditioning available and in use in Bangkok than in the other cities (Ostro et al. 1999). It is also likely that, with relatively higher mortality caused by infectious diseases and more deaths at younger ages, the population of Bangkok is more exposed to a larger number of risk factors and might be more susceptible to air pollution. In addition, by design, the monitors in Bangkok tended to be located away from major sources, such as highways, whereas in the Chinese cities most monitors were located closer to major roads. Tsai and colleagues (2000) reported that in Bangkok the exposure levels for both indoor and outdoor PM in shopping areas were underestimated by the ambient monitoring stations, and therefore the excess risk per air pollutant concentration based on underestimates would appear to be larger than it should be based on measurements from well-calibrated stations. $PM_{2.5}$ constitutes a larger percentage of the PM_{10} collected in Bangkok than in the Chinese cities, which suggests that the PM_{10} in Bangkok has a different composition than the PM_{10} in the Chinese cities, is possibly more toxic, and might thus be more strongly related to adverse health effects (Jinsart et al. 2002).

2. Differences in Lag Effects Between Bangkok and the Chinese Cities

In most cases in the three Chinese cities, the maximum effects always occurred at lag 0–1 day (average), except for O_3 in Shanghai, where the maximum effect occurred at the latter lag days. This lag pattern is consistent with those reported in the literature, which supports a maximum at lag 1 day for most pollutants (Samoli et al. 2005, 2006). The pattern for O_3 is also consistent with that of the literature (Goldberg et al. 2001; Wong et al. 2001). The lag patterns for SO_2 and O_3 in Bangkok were consistent with those of the three Chinese cities; however, the lag patterns for NO_2 and PM_{10} with larger effects at longer lag days were different from those of the three Chinese cities. Thus, for the traffic-related pollutants NO_2 and PM_{10}, the effects not only appeared to be stronger but were also more delayed in Bangkok than in the three Chinese cities. This difference deserves further investigation.

3. Stronger Effects for Cardiopulmonary Causes than for All Natural Causes and at Older Ages than at All Ages

In all four cities, the effects of air pollution were stronger for cardiopulmonary mortality than for all natural mortality. This is consistent with the results reported in most studies in Western Europe and North America (Samet et al. 2000; Anderson et al. 2004) and supports the validity of the estimates from the current study. In addition, the effects of the four single pollutants appeared to be stronger at older ages than at younger ages or for all ages. The stronger age effects for the four pollutants in Bangkok support the hypothesis that the population of Bangkok is more susceptible and that the city's higher effect estimates might be attributable to its age effects.

4. Effects on Estimates of Excluding High Concentrations of PM_{10}

As expected, the exclusion of high PM_{10} concentrations from the analysis affected the estimates. Consistent with the literature from Western Europe and North America, the exclusion of PM_{10} concentrations greater than the 75th or 95th percentile led to higher estimates in all three Chinese cities. These results suggest that the concentration–response curve might follow a convex shape, i.e., the relative risk levels off. However, the same exclusion led to lower estimates in Bangkok, for reasons that are not clear but that might be related to the exclusion of readings from one monitor located in a region with both high PM concentrations and a fairly susceptible population. These contradictory results deserve further investigation.

5. Differences Between Cities in Effect Estimates During the Warm Season

Effect estimates during the warm season were higher than those of all seasons combined in both Bangkok (excess risk 2.16% versus 1.25%) and Wuhan (excess risk 0.81% versus 0.43%), whereas those in Hong Kong (excess risk 0.37% versus 0.53%) and Shanghai (excess risk 0.24% versus 0.26%) were lower. These observations support a hypothesis that the population in Bangkok or in Wuhan, being less affluent than those of the other two cities, might be more exposed because of the use of less air conditioning in the warm season; this might also explain the generally higher air pollution effects observed in Bangkok and Wuhan compared with the other two cities (Long et al. 2007). The lower effect estimates in Hong Kong might also be explained by the cleaner southerly winds that prevail in the warm season; in Wuhan (known as "the oven city") the higher effect might be caused by the extremely high temperatures in the warm season. There might also be synergistic effects between PM_{10} and extremely high temperatures on mortality. Nevertheless, further clarification will be needed in order to understand how results obtained in hotter climates can be extrapolated to cooler climates. In view of the seriousness of global warming (Stafoggia et al. 2008), it would be interesting to test for interactions between temperature and air pollution. This would also provide information about the additional benefits of air pollution abatement for the Asian cities, which are affected most by both of these factors because of the density of the populations.

6. Modeling Issues

Temperature effects on morbidity and mortality have been reported in the United States (Schwartz et al. 2004; Medina-Ramon and Schwartz 2007). The studies showed that various cumulative lag days of temperature had effects on both morbidity and mortality. In the PAPA study, the effects of PM_{10} were likely decreased after adjustment for additional temperature at longer lag days for the four cities, suggesting that the temperature at longer lag days would probably be a confounder of the PM_{10} effect. Further investigation of temperature effects should be incorporated into future studies. However, using higher degrees of freedom in the time trend or replacing the smoothing function by the penalized spline did not alter the PM_{10} effect. This showed that the PM_{10} effect estimates were insensitive to the various methods adopted. For the copollutant effect analysis, inconsistent results were found between Bangkok and the three Chinese cities in the effects of NO_2 with adjustment for the other pollutants and also in the effects of PM_{10} with adjustment for NO_2, in that the main effects of both pollutants were attenuated after the adjustments. These discrepancies in results reflect the possibility that the sources of the two pollutants might be different between Bangkok and the three Chinese cities. They also reflect the fact that NO_2 is as important as PM_{10} in Asia. Further investigations are needed to clarify the sources as well as the chemical reactions and interaction effects between pollutants in ambient air.

Under the Common Protocol, a unified approach was adopted by the investigators for the individual cities. It included common terms to be used in the core models, a similar smoothing function to control for seasonality with 4 to 6 df, and common criteria for accepting core models as adequate according to the PACF and patterns of the residuals. However, the investigators for each city were allowed to adopt one of three strategies according to their individual situation, to meet the model acceptance criteria. In this way, the core models were similarly developed with similar criteria for their having been adequately adjusted for confounding. Although different degrees of smoothing were allowed, most of the differences in terms of model fit were in fact very small. This flexible but consistent approach, which was necessary because of the great differences in seasonality and climate conditions among the four cities, has the advantage of being applicable to cities with a variety of weather conditions.

7. Concentration–Response Curves for PM_{10}

Understanding the shapes of concentration–response curves is important for environmental public health policy making, such as the setting of air quality standards. Comparisons across geographic regions are also important in demonstrating causality and how the effects estimated for one location can be generalized to others. The concentration–response curves for PM_{10} effects on all natural mortality reported in this PAPA study suggest a linear relationship without a threshold in most of the cities. An exception was found for Shanghai, where some non-linear relationship appears, which suggests a threshold at around 50 μg/m^3 and a leveling-off effect for concentrations greater than 200 μg/m^3. Thus the estimates from this study are mostly consistent with a linear model without threshold, which has been found in most time-series studies in Western Europe and North America (Daniels et al. 2000; Samoli et al. 2005; Pope and Dockery 2006). On the other hand, we cannot dismiss the possibility that a non-linear relationship, with health effects that cannot be detected below a certain level, might exist in some populations and environments. However, the concentration–response curve for a pollutant would be affected by the analytic methods used, the susceptibility of the population investigated, and the toxicity of the pollutant, as well as the weather and social conditions with which the pollutant might interact. Our concentration–response curves were subject to substantial uncertainty, especially for those above the 75th percentile of air pollutant concentrations. Further research is needed on these issues.

IMPLICATIONS OF THE PAPA STUDY

1. This PAPA project is the first coordinated Asian multi-city air pollution study ever published. It signifies the beginning of an era of cooperation and collaboration among cities in the world's fastest growing region, where air pollution has become one of the most important public health hazards and locally derived health effect estimates are needed to inform decision makers in formulating environmental public health policy.
2. In this study — the first wave of the PAPA project — only four cities were involved, but they included very large populations (about 30 million people in all). As the number of mega-cities in the world increases, the lessons learned from the development of a Common Protocol for the coordination of multi-city research studies in Asia (and other continents) will be instructive.
3. Sound policy decisions about the control of air pollution are urgently needed in these fast-growing cities, with their fast-growing environmental public health problems. Given the high concentrations of pollutants and millions of affected individuals found in less economically developed countries, our study results demonstrate an important public health consequence of pollution exposure. In addition, they suggest the likelihood of even higher effect estimates (based perhaps on total exposure and socioeconomic status) in certain cities than those reported in the North American and Western European literature. With careful training and oversight as well as continued quality assurance, the results of the PAPA project demonstrate that research efforts of this kind are possible in regions of the world that have not previously been investigated.
4. The effect estimates of the project were derived from a wide variety of pollution concentrations among the four cities. The results could thus be relevant to a wide spectrum of cities with varying environmental and social conditions. However, certain caveats should be made clear. Specifically, the location of the monitors and certain city characteristics (e.g., time spent outdoors, use of air conditioning, and socioeconomic status) are likely to have a significant impact on the effect estimates.
5. An important aspect revealed by the project is that similar linear concentration–response relationships were observed in locations with high concentrations of air pollution as well as in other locations where air pollution concentrations were much lower. This result strongly supports the adoption of the global air quality guidelines recently announced by WHO (*www.euro.who.int/air/activities/20050222_2*). Further, our results indicate that the assumption of linearity for the estimation of the benefits of pollution control, even in cities with very high concentrations of PM_{10}, is justified (Ostro 2004).

6. Finally, the importance of gaseous pollutants should be pointed out. They exhibited stronger effects in the PAPA study compared with those reported in previous studies (e.g., the APHEA study). The sources and weather conditions giving rise to higher concentrations and greater health effects of gaseous pollutants warrant further investigation. However, because correlations between pollutants even after adjustment for seasonal variation were higher (data not shown), caution is required in the interpretation of the effect estimates associated with any single pollutant. It might also be the case that the effects of gaseous pollutants observed in this study were caused by traffic in general, which emits a complex mixture of pollutants, making it difficult to isolate a single pollutant responsible for the observed excess risks.

LIMITATIONS

Among the major limitations of our study was the difference in monitor locations from city to city. In densely populated cities such as Hong Kong and Shanghai, the monitors tended to be close to major roadways; in Bangkok and Wuhan, they were located farther from major sources. A 10-$\mu g/m^3$ change in pollutant concentration might therefore represent different magnitudes of exposure for the overall populations in the various cities. It is thus difficult to determine both the "true" effect and to compare our results both within the PAPA cities and with previous studies. In addition, the specific components of PM responsible for the observed health effects have not been elucidated. Such elucidation will aid in targeting and prioritizing future pollution control efforts. There might be slight differences in quality and completeness of the data because of differences in the quality assurance process of the surveillance systems in the four cities. Differences in data quality might lead to differences in measurement errors and to different levels of attenuation in the effect estimates. However, at the beginning of the study a data-quality audit team was employed by HEI to visit the four cities and audit the data. The data quality was declared to be satisfactory, and thus the differences in measurement errors might be minimal.

In addition, information about potential effect modifiers (e.g., time spent outdoors, use of air conditioning, residential distance to roadways, housing construction, comorbidity in the population, etc.) varied in its availability and quality, making it difficult to explain quantitative differences among the PAPA cities.

Owing to the availability of data on mortality and air pollution, various study periods, ranging from 4 to 7 years with various degrees of freedom, were included in the project by the four teams of investigators. This affected the precision of the effect estimates for the four cities; however, adjustment was made to account for these differences in combining the estimates from all four cities. But the effects of using different study periods should be minimal, because the overall time periods all centered around 2001–2002 and no particular social or economic changes occurred that would have affected the cities during the study periods nor have confounded the subsequent comparisons among them.

This is the first time a coordinated research study has ever been performed in Asian cities. The number of cities involved in the current study — the first wave of the PAPA project — was relatively small compared with other coordinated time-series studies of the effects of air pollution, such as the U.S. NMMAPS (Health Effects Institute 2003). However, the estimates of health effects were reasonably precise, showing that the effects of air pollution in Asia are equal to or higher than those found in Western European and North American studies.

CONCLUSION

The risks of mortality associated with particulate pollutants in Asian cities are similar to or greater than those observed in most Western European and North American cities, despite large differences in the ranges of pollutant concentrations, while the mortality risks associated with gaseous pollutants in Asian cities are as high or higher than in Western cities. The methodology adopted and developed in the PAPA study could be used for other countries preparing to conduct local studies of the health effects of their air pollution. The PAPA results can also be used in Asian and other cities for health impact assessments. In the years to come, additional efforts to understand the socioeconomic and demographic factors that might modify the effects of air pollution are warranted.

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APPENDIX A. Specific Characteristics in Each City

	Bangkok	Hong Kong	Shanghai	Wuhan
Study period	1999–2003	1996–2002	2001–2004	2001–2004
Population (millions)	6.8 (2005)	6.7 (2001)	7.0 (in 2004)	7.8 (2002) or 4.2 (2002, core city)
Area (km^2)	1568.7	1092	289 (core city only)	8494 (total) or 210 (core city only)
Geographic coordinates	13°44′ N, 100°31′ E	22°15′ N, 114°10′ E	31°15′ N, 121°28′ E	30°34′ N, 114°17′ E
Climate	Tropical monsoon: rainy season (May–October), cool season (November–January), and hot season (February–April)	Subtropical: rain and tropical cyclones in the summer months	Subtropical: four distinct seasons and abundant rainfall from May to September	Subtropical, monsoon climate: abundant rainfall in summer and four distinct seasons
Mean temperature (°C)	28.9 (SD = 1.7)	23.7 (SD = 4.9)	17.7 (SD = 8.5)	17.9 (SD = 9.2)
Rainfall per year (mm)	1618 (2005)	3092 (2001)	1594	1150–1450
Topography	Low flat plain crisscrossed with canals and rivers, with no mountains	Dominated by hills and mountains, with flat peninsula and many outlying islands	Low-altitude alluvial plain crisscrossed by waterways	Large plain with hills in the south, rivers winding through the city
Health care system	Health care services provided by health centers (44.1%), governmental hospitals (15.7%), private health services (13%), and self-care (10.3%)	Primary care services provided mainly by the private sector (85%); hospital services provided mainly by the public sector (95%)	Almost all primary care and hospital services are provided by the public sector	90% of the suburban residents and 100% of the urban residents are covered by 1278 public health organizations in the city (including 308 hospitals)
GNP equivalent per capita (year)	US$2,495 (2004)	US$24,995 (2001)	US$6,660 (2004)	US$3,493 (2000–2002)
Smoking rates (15 years or older)[b]	Male 37.2% Female 2.1%	Male 22.0% Female 3.5%	Male 50.6% Female 2.3%	Male 75.0% Female < 0.5%
Leading causes of death (for all ages and both sexes)[c]	1. Neoplasms, 17.7% 2. Diseases of circulatory system, 15.1% 3. Certain infectious and parasitic diseases, 14.9% 4. External causes, 8.9% 5. Disease of respiratory system, 8.2%	1. Malignant neoplasms, 34.2% 2. Heart diseases, 14.1% 3. Cerebrovascular disease, 9.4% 4. Pneumonia, 9.1% 5. External causes, 5.5%	1. Circulatory diseases, 32.9% 2. Tumor, 30.4% 3. Respiratory diseases, 12.4% 4. Injury and poisoning, 6.4% 5. Endocrine, immune and metabolic diseases, 4.0%	1. Cerebrovascular diseases, 30.4% 2. Neoplasms, 17.6% 3. Cardiovascular diseases, 13.1% 4. Respiratory diseases, 11.8% 5. Injury and poisoning, 6.9%

[a] All data in this table were quoted or derived from the local government in each city.
[b] Based on data from 2004 for Bangkok, 2000 for Hong Kong, 2005 for Shanghai, and 1996 for Wuhan.
[c] Based on data from 2004 for Bangkok, 2001 for Hong Kong, 2004 for Shanghai, and 2000–2002 for Wuhan.

APPENDIX B. Monitoring Sites, Base Model, and Average Number of Observations in Each City

		Manufacturer/Model Number of the Monitors			
City/Monitoring Stations[a]	Geographic Coordinates[b]	NO_2	SO_2	PM_{10}	O_3
Bangkok (n = 1541)[c]		API Monitor Lab Philips	API Dasibi Monitor Lab Philips	R&P Environmental S.A. Greasby Kimoto Metone Wedding	API Dasibi Monitor Lab Philips
Office of Environmental Planning and Policy	x 666866; y 1523660				
Bansomdat jao praya	x 662223; y 1518376				
Ratburana	x 664394; y 1511337				
Meteorological dept.	x 674047; y 1510821				
Junkasame	x 670924; y 1526288				
Ramkhamhaeng	x 676743; y 1521453				
National housing authority	x 678600; y 1523822				
Huai Khwang	x 669233; y 1524606				
None Tree Vitaya	x 667906; y 1514015				
Singharatpitayakom	x 657401; y 1512713				
Hong Kong (n = 2293)[c]		API (model 200A)	TECO (model 43A)	Rupprecht & Patashnick TEOM Series 1400a-AB	API (model 400 or 400A)
Central/western	22°18.5′N; 114°07.7′E				
Kwai Chung	22°21.7′N; 114°07.5′E				
Kwun Tong	22°20.0′N; 114°11.7′E				
Sham Shui Po	22°20.0′N; 114°00.9′E				
Sha Tin	22°24.0′N; 114°09.5′E				
Tai Po	22°27.1′N; 114°09.7′E				
Tsuen Wan	22°23.5′N; 114°06.3′E				
Yuen Long	22°26.8′N; 114°01.2′E				
Shanghai (n = 1361)[c]		API	TE	R&P	API
Yangpu	31.27°N; 121.54°E				
Hongkou	31.26°N; 121.48°E				
Putuo	32.40°N; 121.40°E				
Jing'an	31.23°N; 121.42°E				
Luwan	31.20°N; 121.48°E				
Xuhui	31.16°N; 121.41°E				
Wuhan (n = 1383)[c]		Dasibi (model 2108)	Dasibi (model 4108)	Dasibi (model 7001)	Dasibi (model 1008)
Jiangan	30°37.133′N; 114°16.917′E				
Hanyang	30°33.412′N; 114°15.233′E				
Nanzhan	30°31.973′N; 114°18.154′E				
Wugang	30°36.703′N; 114°25.817′E				
Donghu	30°34.403′N; 114°22.206′E				
Kifa/Jiantan	30°29.574′N; 114°13.254′E				

[a] All monitoring stations are non-roadside general type.

[b] Geographic coordinates for all monitoring stations are presented. Coordinates for monitors in Bangkok are x and y coordinates for map from Air Quality and Noise Management Bureau, Ministry of National Resources and Environment Monitoring Stations, Bangkok (*www.aqnis.pcd.go.th/station/allstation.htm*). Coordinates for monitors in Hong Kong and Wuhan are listed as latitude and longitude in degrees, minutes, and seconds. Coordinates for Shanghai are listed as latitude and longitude in decimal degrees.

[c] n indicates average number of days for which the air pollutant data were available.

APPENDIX C. Spearman Correlations Between Measured Daily Levels of Four Pollutants in Each City

	SO_2				PM_{10}				O_3			
	Bangkok	Hong Kong	Shanghai	Wuhan	Bangkok	Hong Kong	Shanghai	Wuhan	Bangkok	Hong Kong	Shanghai	Wuhan
NO_2	0.27	0.37	0.64	0.76	0.71	0.80	0.75	0.75	0.61	0.45	−0.04	0.11
SO_2	—	—	—	—	0.24	0.24	0.67	0.65	0.18	−0.13	0.19	0.09
PM_{10}	—	—	—	—	—	—	—	—	0.55	0.58	0.26	0.17

APPENDIX D. PACF Plots of the Residuals from PACF Models

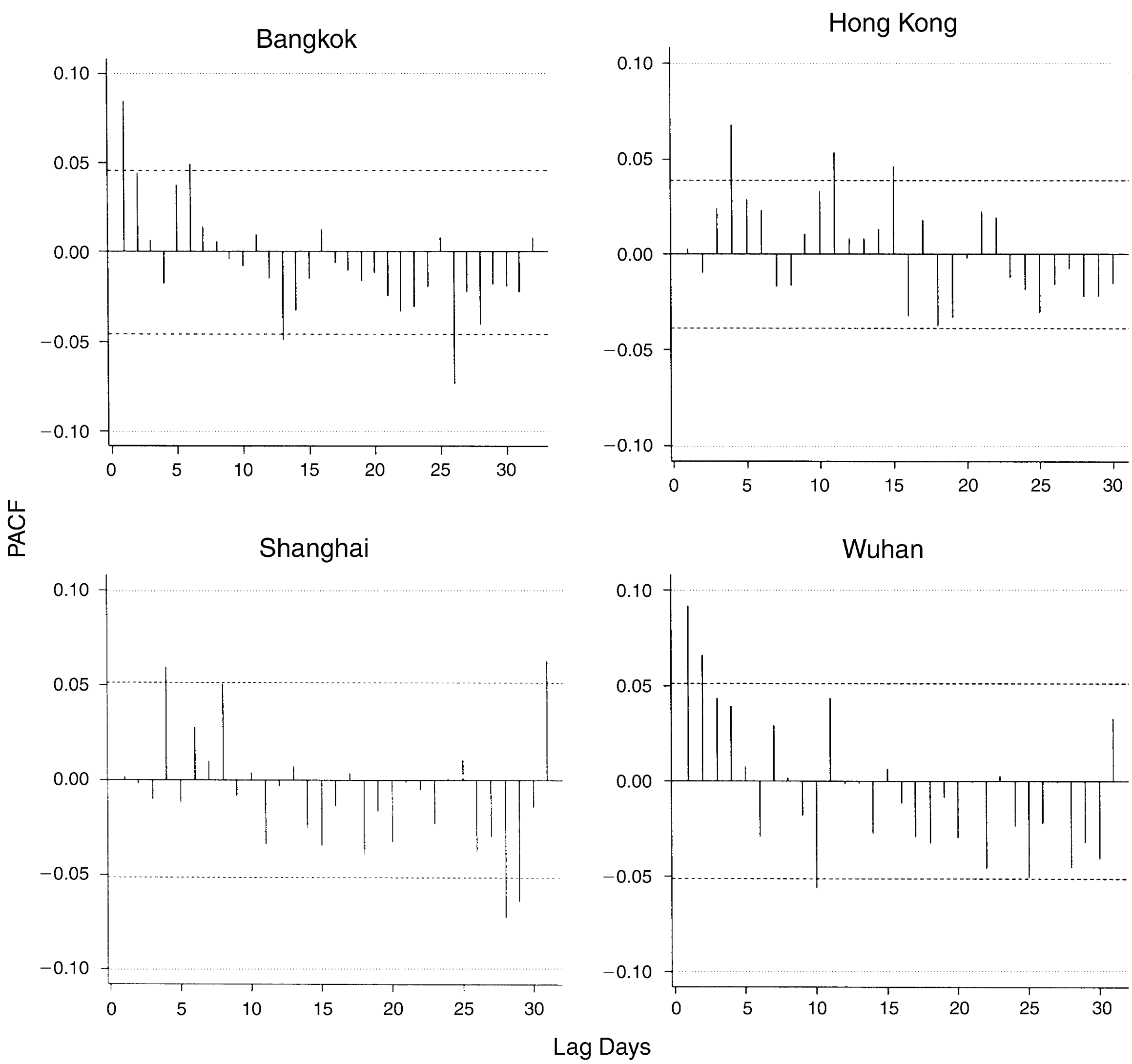


Figure D.1. PACF plot of the residuals from the core model for all natural causes and all ages. Dotted lines at ± 0.10 indicate the acceptable range of PACF for acceptance of a core model according to the PAPA Common Protocol. Dashed lines at approximately ± 0.05 indicate the 95% CI for the observed PACF plots.

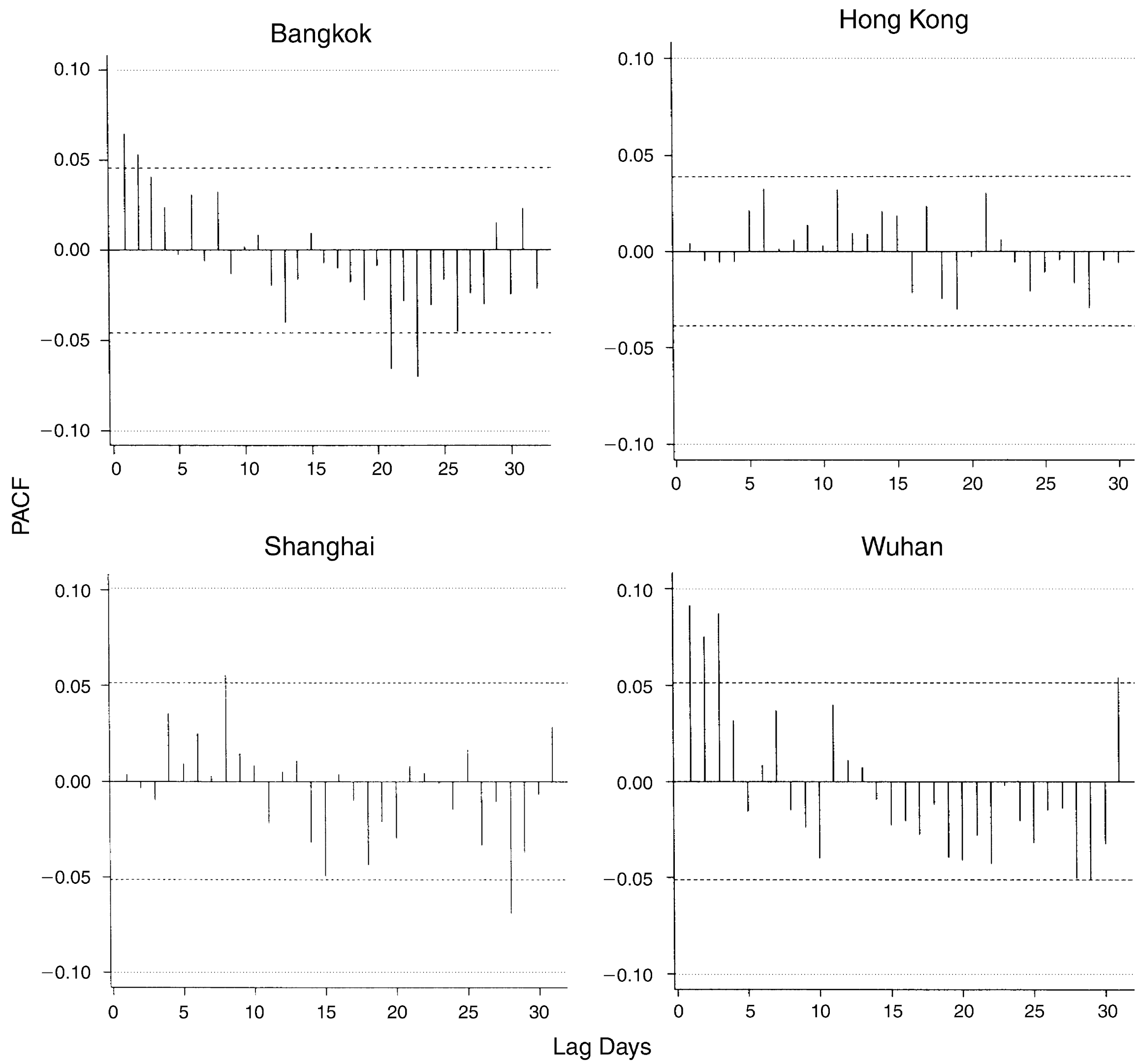


Figure D.2. PACF plot of the residuals from the core model for all natural causes and ages ≥ 65 years. Dotted lines at ± 0.10 indicate the acceptable range of PACF for acceptance of a core model according to the PAPA Common Protocol. Dashed lines at approximately ± 0.05 indicate the 95% CI for the observed PACF plots.

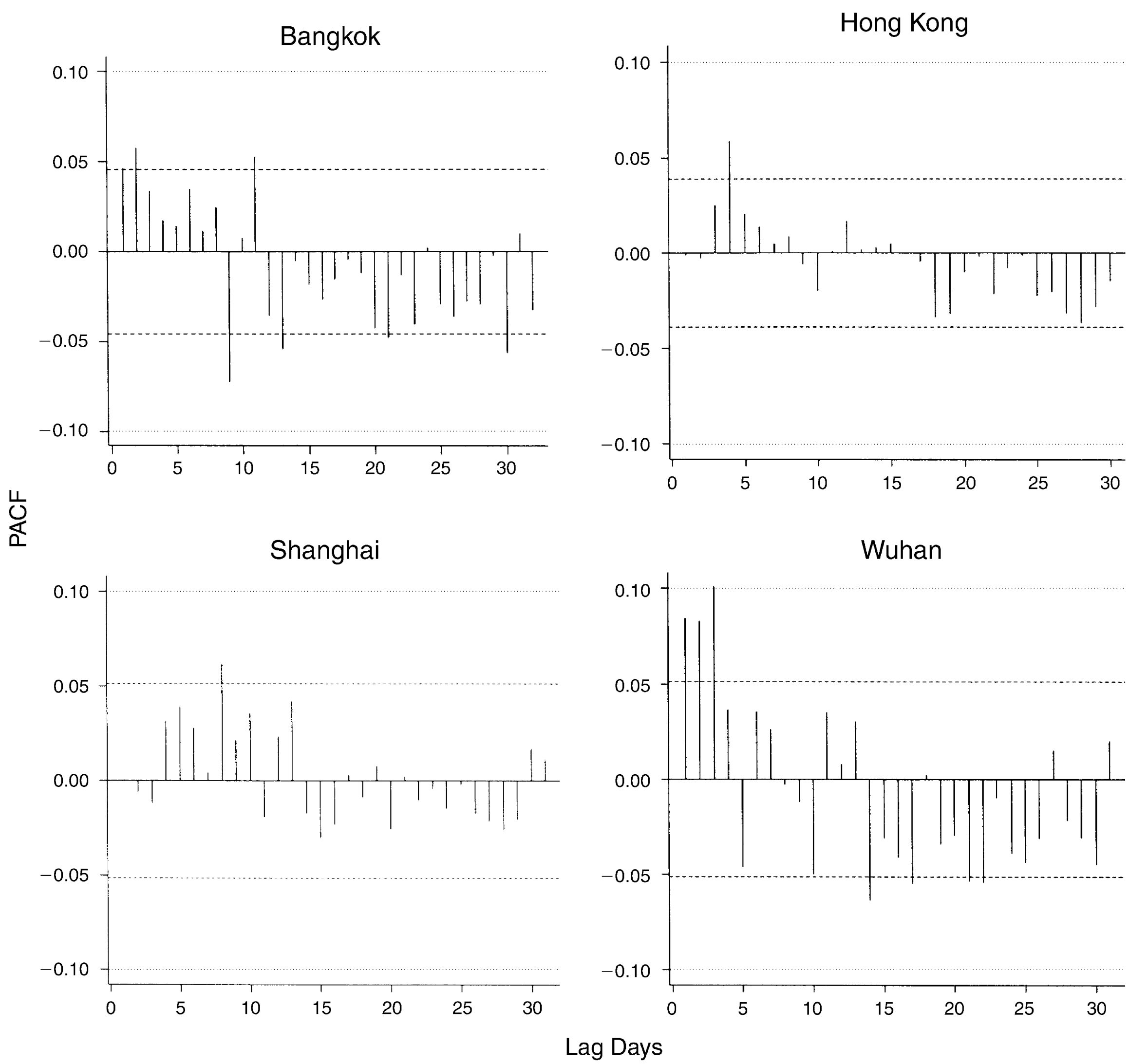


Figure D.3. PACF plot of the residuals from the core model for all natural causes and ages ≥ 75 years. Dotted lines at ± 0.10 indicate the acceptable range of PACF for acceptance of a core model according to the PAPA Common Protocol. Dashed lines at approximately ± 0.05 indicate the 95% CI for the observed PACF plots.

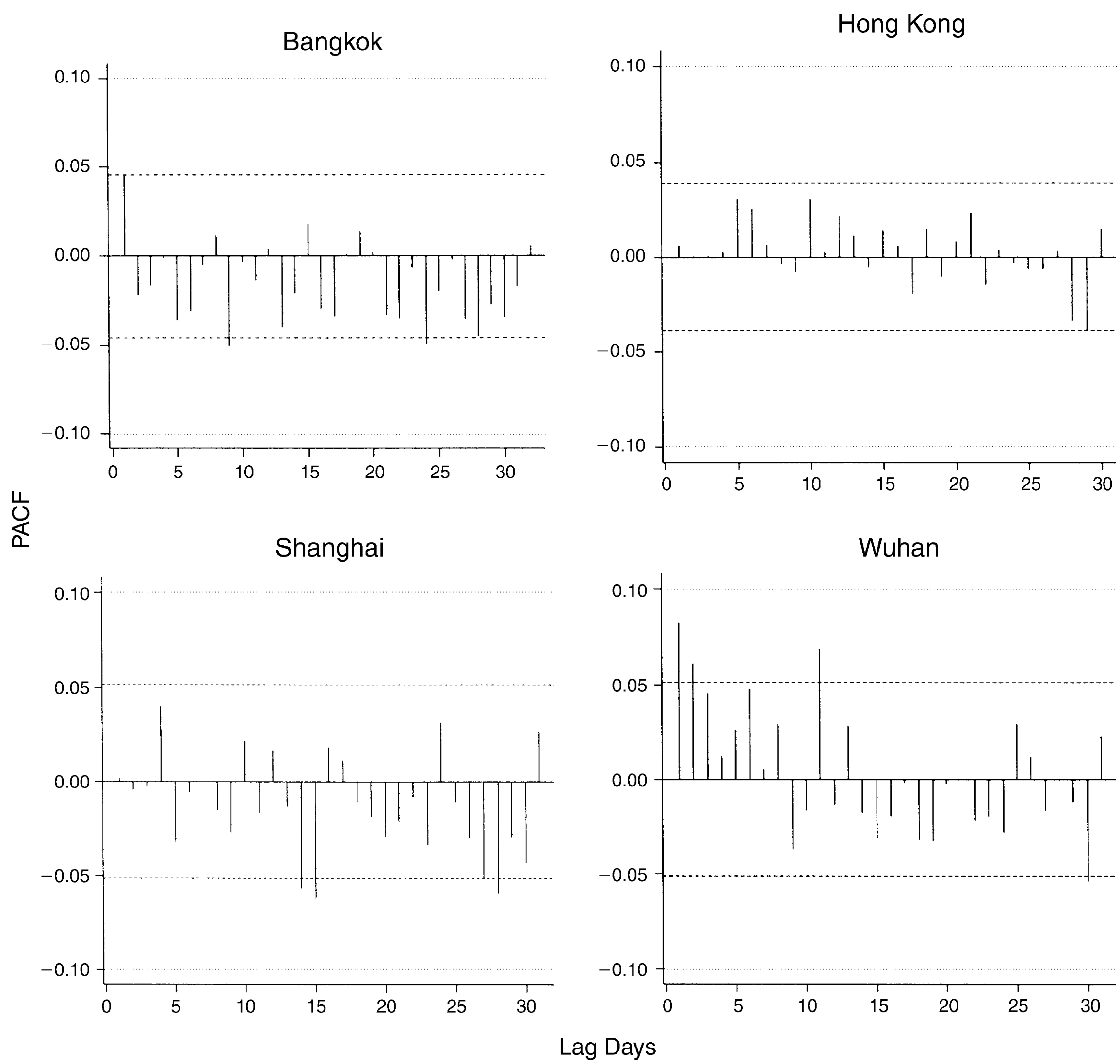


Figure D.4. PACF plot of the residuals from the core model for cardiovascular disease. Dotted lines at ± 0.10 indicate the acceptable range of PACF for acceptance of a core model according to the PAPA Common Protocol. Dashed lines at approximately ± 0.05 indicate the 95% CI for the observed PACF plots.

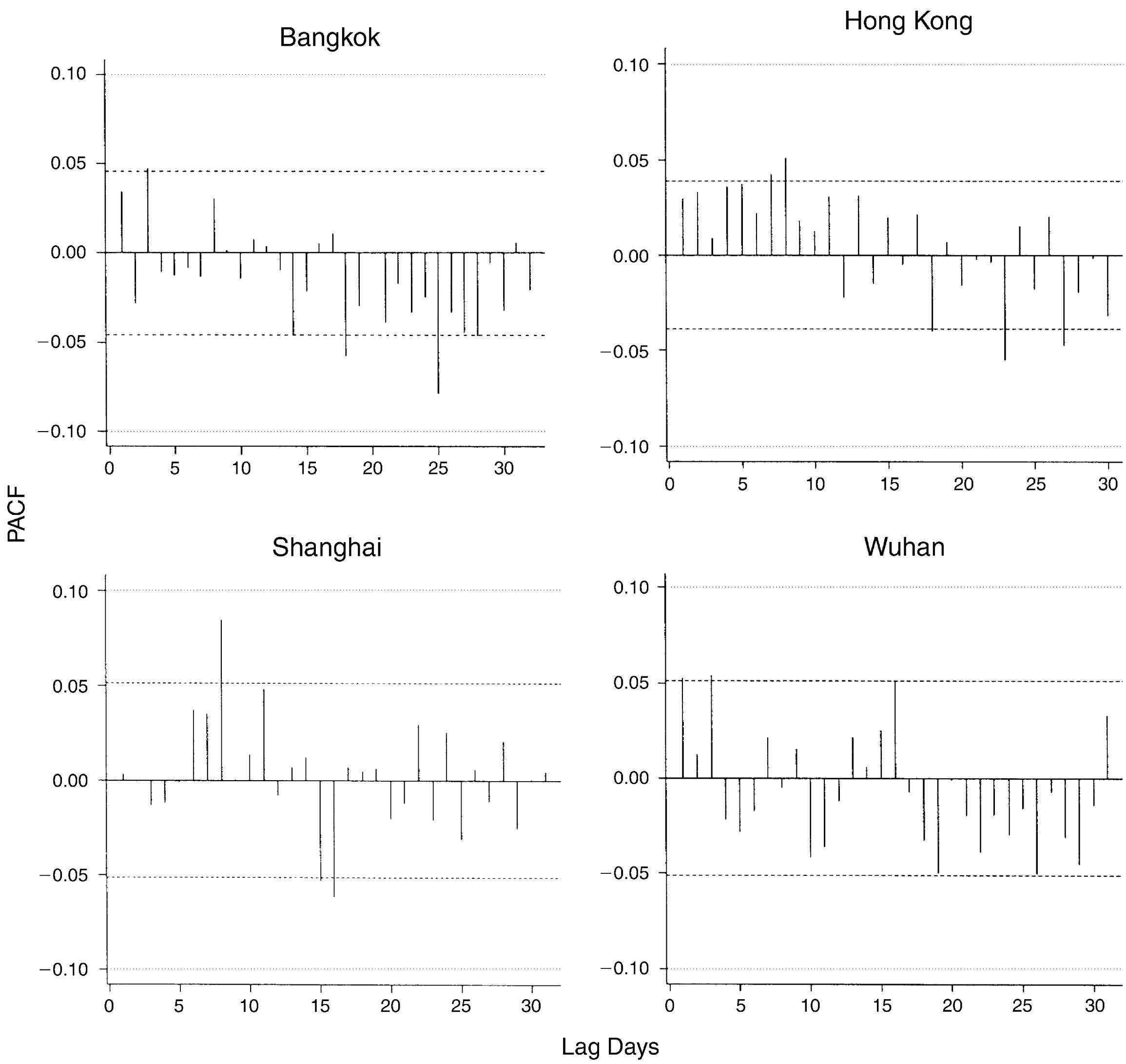


Figure D.5. PACF plot of the residuals from the core model for respiratory disease. Dotted lines at ± 0.10 indicate the acceptable range of PACF for acceptance of a core model according to the PAPA Common Protocol. Dashed lines at approximately ± 0.05 indicate the 95% CI for the observed PACF plots.

APPENDIX E. Comparison of Combined Effect Estimates of Various Multicity Studies for a 10-μg/m^3 Increase of Pollutants[a]

	PAPA		Asian Cities		NMMAPS		APHEA	
	Fixed Effects	Random Effects	Fixed Effects	Random Effects	Fixed Effects	Random Effects	Fixed Effects	Random Effects
NO_2[b]								
All natural causes, all ages	1.09 (0.90, 1.29)	1.23 (0.84, 1.62)	—	—	—	—	—	0.30 (0.22, 0.38)
Cardiovascular causes	1.26 (0.93, 1.58)	1.36 (0.89, 1.82)	—	—	—	—	—	0.40 (0.29, 0.52)
Respiratory causes	1.33 (0.84, 1.82)	1.48 (0.68, 2.28)	—	—	—	—	—	0.38 (0.17, 0.58)
SO_2[c]								
All natural causes, all ages	1.00 (0.75, 1.24)	1.00 (0.75, 1.24)	0.35 (0.26, 0.45)	0.52 (0.30, 0.74)	—	—	—	0.4 (0.3, 0.5)
Cardiovascular causes	1.09 (0.71, 1.47)	1.09 (0.71, 1.47)	—	—	—	—	—	—
Respiratory causes	1.47 (0.85, 2.08)	1.47 (0.85, 2.08)	—	—	—	—	—	—
PM_{10}[d]								
All natural causes, all ages	0.36 (0.27, 0.45)	0.55 (0.26, 0.85)	0.41 (0.25, 0.56)	0.49 (0.23, 0.76)	—	0.21 (0.04, 0.33)	—	0.6 (0.4, 0.8)
Cardiovascular causes	0.40 (0.26, 0.53)	0.58 (0.22, 0.93)	—	—	—	—	—	0.5 (0.1, 1.0)
Respiratory causes	0.48 (0.25, 0.71)	0.62 (0.22, 1.02)	—	—	—	—	—	1.0 (0.1, 1.8)
O_3[e]								
All natural causes, all ages	0.38 (0.23, 0.53)	0.38 (0.23, 0.53)	—	—	—	0.26 (0.14, 0.39)[f]	—	0.2 (0.0, 0.3)
Cardiovascular causes	0.34 (0.08, 0.59)	0.37 (0.01, 0.73)	—	—	—	0.32 (0.16, 0.49)[f]	—	0.4 (0.3, 0.5)
Respiratory causes	0.34 (−0.07, 0.75)	0.34 (−0.07, 0.75)	—	—	—	0.32 (0.16, 0.49)[f]	—	−0.1 (−0.5, 0.4)

[a] Data are presented as percentage of excess risk (95% CI) of mortality.

[b] PAPA study included 4 cities. APHEA study included 30 European cities (Samoli et al. 2006).

[c] PAPA study included 4 cities. Asian Cities study included 11 cities (HEI 2004). APHEA study included 12 European cities (Katsouyanni et al. 1997).

[d] PAPA study included 4 cities. Asian Cities study included 4 cities (HEI 2004). NMMAPS study included 90 U.S. cities (HEI 2003). APHEA study included meta-analysis of time-series and panel studies of PM and O_3 (Anderson et al. 2004). For APHEA study, data from 14 cities were included for mortality for all natural causes at all ages, 23 cities for mortality for cardiovascular causes, and 20 cities for mortality for respiratory causes.

[e] PAPA study included 4 cities. NMMAPS study included 95 U.S. cities (Bell et al. 2004). APHEA study included meta-analyses of time-series and panel studies of PM and O_3 (Anderson et al. 2004). For APHEA study, data from 14 cities were included for mortality for all natural causes at all ages, 23 cities for mortality for cardiovascular causes, and 20 cities for mortality for respiratory causes.

[f] A conversion factor of 2 was used to convert data from ppb to μg/m^3. Excess risks from cardiovascular and respiratory causes were combined into one group.

APPENDIX F. HEI Quality Assurance Statement

The conduct of each individual study under a common protocol was subjected to periodic, independent audits by a team from Hoover Consultants. This team consisted of auditors with experience in toxicology, epidemiology, and air quality data. The audits included in-process monitoring of study activities for conformance to the study protocols and examination of records and supporting data. The dates of each audit are listed in the table below with the phase of the study examined.

QUALITY ASSURANCE AUDITS

Date	Phase of Study
May 13–14 and 17, 2005	Hong Kong Study: Data for mortality, air quality parameters, and meteorology were audited. Documentation was examined for personnel qualifications and experience. Data were audited in the 5- and 10-Month Progress Reports supplied by HEI that were available at the time of the site visit.
May 19–20, 2005	Wuhan Study: Data for mortality, air quality parameters, and meteorology were audited. Documentation was examined for personnel qualifications and experience. Data were audited in the 5- and 10-Month Progress Reports supplied by HEI that were available at the time of the site visit.
May 23–24, 2005	Shanghai Study: Data for mortality, air quality parameters, and meteorology were audited. Documentation was examined for personnel qualifications and experience. Data were audited in the 5- and 10-Month Progress Reports supplied by HEI that were available at the time of the site visit.
May 26–27, 2005	Bangkok Study: Data for mortality, air quality parameters, and meteorology were audited. Documentation was examined for personnel qualifications and experience. Data were audited in the 5- and 10-Month Progress Reports supplied by HEI that were available at the time of the site visit.
July 30, 2010	A draft of the final study report was examined for internal consistency and conformance with the Common Protocol. This review resulted in no quality assurance comments.

A written report for each of the 2005 audits was provided to the Director of Science of the Health Effects Institute who transmitted these findings to the Principal Investigator. These quality assurance audits demonstrated that the study was conducted by experienced professionals in accordance with the common study protocol. The final report appears to be an accurate representation of the study.

B. Kristin Hoover
Hoover Consultants

OTHER PUBLICATIONS RESULTING FROM THIS RESEARCH

Kan H, London SJ, Chen G, Zhang Y, Song G, Zhao N, Jiang L, Chen B. 2008. Season, sex, age, and education as modifiers of the effects of outdoor air pollution on daily mortality in Shanghai, China: The Public Health and Air Pollution in Asia (PAPA) Study. Environ Health Perspect 116: 1183–1188.

Kan H, Wong CM, Vichit-Vadakan N, Qian Z, PAPA Project Teams. 2010. Short-term association between sulfur dioxide and daily mortality: The Public Health and Air Pollution in Asia (PAPA) study. Environ Res 110:258–264.

Qian Z, He Q, Lin HM, Kong L, Bentley CM, Liu W, Zhou D. 2008. High temperatures enhanced acute mortality effects of ambient particle pollution in the “oven” city of Wuhan, China. Environ Health Perspect 116:1172–1178.

Qian Z, He Q, Lin HM, Kong L, Liao D, Dan J, Bentley CM, Wang B. 2007. Association of daily cause-specific mortality with ambient particle air pollution in Wuhan, China. Environ Res 105:380–389.

Qian Z, He Q, Lin HM, Kong L, Liao D, Yang N, Bentley CM, Xu S. 2007. Short-term effects of gaseous pollutants on cause-specific mortality in Wuhan, China. J Air Waste Manag Assoc 57:785–793.

Thach TQ, Wong CM, Chan KP, Chau YK, Thomas GN, Ou CQ, Yang L, Peiris JSM, Lam TH, Hedley AJ. 2010. Air pollutants and health outcomes: Assessment of confounding by influenza. Atmos Environ 44:1437–1442.

Vichit-Vadakan N, Vajanapoom N, Ostro B. 2008. The Public Health and Air Pollution in Asia (PAPA) Project: Estimating the mortality effects of particulate matter in Bangkok, Thailand. Environ Health Perspect 116:1179–1182.

Wong CM, Ou CQ, Chang KP, Chau YK, Thach TQ, Yang L, Chung RY, Thomas GN, Peiris JS, Wong TW, Hedley AJ, Lam TH. 2008. The effects of air pollution on mortality in socially deprived urban areas in Hong Kong, China. Environ Health Perspect 116:1189–1194.

Wong CM, Vichit-Vadakan N, Kan H, Qian Z. 2008. The Public Health and Air Pollution in Asia (PAPA): A multicity study of short-term effects of air pollution on mortality. Environ Health Perspect 116:1195–1202.

Wong CM, Yang L, Thach TQ, Chau PY, Chan KP, Thomas GN, Lam TH, Wong TW, Hedley AJ, Peiris JS. 2009. Modification of influenza on health effects of air pollution in Hong Kong. Environ Health Perspect 117:248–253.

Zhang Y, Huang W, London SJ, Song G, Chen G, Jiang L, Zhao N, Chen B, Kan H. 2006. Ozone and daily mortality in Shanghai, China. Environ Health Perspect 114:1227–1232.

ABBREVIATIONS AND OTHER TERMS

APHEA	Air Pollution and Health: A European Approach
APHENA	Air Pollution and Health: A European and North American Approach
CI	confidence interval
CO	carbon monoxide
C–R	concentration–response
df	degree of freedom
GNP	gross national product
ICD-9	*International Classification of Diseases*, 9th revision
ICD-10	*International Classification of Diseases*, 10th revision
IQR	interquartile range
ISOC	International Scientific Oversight Committee
NMMAPS	National Morbidity, Mortality, and Air Pollution Study
NO_2	nitrogen dioxide
NO_x	nitrogen oxides
O_3	ozone
PACF	partial autocorrelation function
PAPA	Public Health and Air Pollution in Asia
$PM_{2.5}$	particulate matter ≤ 2.5 µm in aerodynamic diameter
PM_{10}	particulate matter ≤ 10 µm in aerodynamic diameter
SARS	severe acute respiratory syndrome
SO_2	sulfur dioxide
SMCDCP	Shanghai Municipal Center of Disease Control and Prevention
TEOM	tapered element oscillating microbalance
WHO	World Health Organization

Research Report 154, Part 5. *Public Health and Air Pollution in Asia (PAPA): A Combined Analysis of Four Studies of Air Pollution and Mortality*, C-M. Wong et al.

A Commentary on the Methods and Analyses of the PAPA Time-Series Studies

INTRODUCTION

Although most time-series studies have been carried out in Europe and North America, a substantial number have also been carried out in Asia and in other parts of the world (HEI International Scientific Oversight Committee 2004; WHO 2006). In light of the large number of time-series studies of air pollution worldwide that have been reported to date, it is reasonable to ask what another group of time series might be expected to contribute to the scientific literature (Samet 2002). One potential contribution would be an enhanced ability to compare pollutant effect estimates from Asian cities with those from Western populations. Such comparisons could provide insight into features of the pollutant mix or of populations that influence the size of the adverse health impacts of air pollution exposure. In an editorial that accompanied the initial journal publication of the four Public Health and Air Pollution in Asia (PAPA*) studies reported in this volume, the authors highlighted some features of developing countries in Asia that could influence air pollution health effect estimates from time-series studies (Speizer 2008). These included pollution sources and concentrations, population time–activity patterns, and characteristics of the built environment. To these could be added the age distribution and health status of the population, meteorology, and features of the data that might induce more or less measurement error. All of these features would be expected to differ to a varying degree from those that characterize Western countries and need to be considered in interpreting the results of the PAPA studies.

The PAPA project represents an effort to standardize collection and analysis for data from selected Asian cities in a fashion comparable to the multicity studies in North America and Europe (Samet et al. 2000; Katsouyanni et al. 2001, 2009). Coordinated multicity studies can reduce uncertainties in the interpretation of the many single-city studies that have been published over the past 20 years by reducing the likelihood that differences in estimates of effect among studies could be due to methodologic differences. Even with standardized approaches, relative rates of air pollution estimated in coordinated multicity time-series studies in Europe and North America differ from city to city, even within geographically small regions (Samet et al. 2000; Katsouyanni et al. 2001, 2009; Bell et al. 2006). Despite some efforts to identify predictors of this variability, we currently have little understanding of its sources, apart from random variation. It is critical therefore that we make explicit our prior expectations with regard to interpreting apparent differences and similarities in the results of time-series studies in Asia, as well as those in other world regions, and that we interpret them in light of the limitations of our methods.

THE PAPA METHODOLOGY AND THE COMMON PROTOCOL

An essential feature of any coordinated multicenter study is a protocol for the design of the data acquisition and analyses that is followed by all the centers. Adoption of such a protocol provides some assurance that the results for each city are unlikely to differ importantly due to differences in data quality or analysis and offers a more reliable foundation for meta-analysis. The PAPA investigators applied a common protocol in each city-specific analysis and in the Combined Analysis, which compares the results for all four cities and is discussed later in this Integrated Discussion. The Common Protocol is included at the back of this volume.

Dr. C-M. Wong's 3-month study, "Coordinated Time-Series Studies of Daily Mortality in Asian Cities," began in June 2006. Total expenditures were $100,000. The draft investigators' report from C-M. Wong and colleagues was received for review in November 2007. A revised report, received in September 2008, was accepted for publication in November 2008. During the review process, the HEI Health Review Committee and the investigators had the opportunity to exchange comments and to clarify issues in both the investigators' report and the Review Committee's Integrated Discussion.

* A list of abbreviations and other terms appears at the end of the investigators' report.

DESIGN AND QUALITY CONTROL OF DATA ON HEALTH OUTCOMES, POLLUTANT EXPOSURE, AND OTHER COVARIATES

Health Outcomes

Mortality data for the PAPA studies were provided by local health authorities in each of the four cities, coded using the World Health Organization's (WHO's) *International Classification of Diseases*, 9th revision or 10th revision (ICD-9 or ICD-10), depending on the year of death. The Combined Analysis focused on mortality from all natural (nonaccidental) causes for all ages. In addition, effects in the elderly ($\geq$ 65 years and $\geq$ 75 years) and on mortality from cardiovascular and respiratory disease were estimated. Analyses of mortality from accidental causes and non-cardiopulmonary causes, expected to be unrelated or less strongly related to air pollution exposure, were conducted as a form of control.

Air Pollution and Meteorology

Four pollutants were included in the PAPA studies: nitrogen dioxide (NO_2), sulfur dioxide (SO_2), particulate matter (PM) with an aerodynamic diameter $\leq$ 10 µm (PM_{10}), and ozone (O_3). All analyses used routine monitoring data provided by the local government agencies in each city. The measurement methods for NO_2, SO_2, and O_3 were similar in all four cities, but different methods were used to measure PM_{10}: tapered element microbalance was used in Wuhan, Shanghai, and Hong Kong, and the beta-gauge method was used in Bangkok. Exposure metrics used for NO_2, SO_2, and PM_{10} were 24-hour average concentrations; the O_3 analyses used 8-hour average concentrations (collected 10 am to 6 pm).

Monitoring data from each city had met local quality control and assurance standards. In addition, in compiling the exposure data, the investigators followed an independent, standardized procedure, specified in the Common Protocol, with regard to ensuring both the completeness and representativeness of the average daily exposure of the population. For example, data for a given day were included only if at least 75% of the 1-hour values were available; if more than 25% of a station's values for a particular pollutant were missing for the entire period of analysis, the data from that station were excluded. The number of missing data overall and in each city was minimal, and no attempt was made to impute missing data. Monitoring sites that appeared to be significantly affected by very local sources were removed.

DESIGN OF STATISTICAL ANALYSES

Each team followed the guidelines for statistical analysis specified in the Common Protocol. Although there was some room for city-specific approaches, the model options were constrained to limit the set of potential models; in particular, the spline used to control for seasonal and other slow changes over time was constrained to have between 4 and 6 degrees of freedom (df) per year.

A generalized additive modeling approach was used to obtain the excess risk of daily mortality or hospital admissions associated with daily increases in pollutant levels, assuming an overdispersed Poisson distribution. Quasi-likelihood methods were used to model the association between pollutants and daily mortality counts or hospitalization rates, with exposure lagged variously from 0 to 4 days and using distributed lag models. A dummy variable was included for public holidays. Because the daily variations in hospital admissions were greater than the variations in mortality, models for hospital admissions included more degrees of freedom in the spline smoothing functions of time trend, temperature, and relative humidity. Only natural splines were used for the hospitalization data because the investigators' preliminary data indicated similar findings for mortality using both natural and penalized splines. All results are presented as excess risk (ER) per 10 µg/m^3 of pollutant, calculated from relative risk (RR) as follows: ER = (RR − 1) × 100.

THE COMBINED ANALYSIS: RESULTS FROM A MULTICITY ANALYSIS USING THE PAPA METHODOLOGY

In the Combined Analysis, the investigators reported increases in all natural (nonaccidental) and cause-specific daily mortality rates associated with air pollution as measured by four different pollutants in each of the four cities. A 10-µg/m^3 increase in PM_{10} level was associated with a 0.6% increase (95% confidence interval, 0.3–0.9). Effects on cardiovascular and respiratory mortality were generally higher than for all natural mortality. Effect estimates varied across cities, however, generally more than can be easily explained by chance (see Table 4 in the Combined Analysis). For instance, the effects of PM_{10} and O_3 on all natural mortality were generally larger in Bangkok than in the three Chinese cities. The effects did not vary markedly with age except in Bangkok, where larger relative effects were observed for all pollutants in the elderly. In multipollutant models, the dominant pollutant also appeared to be different across cities (see Figures 7–10 in the Combined Analysis). In particular, in Bangkok the effects of PM_{10} were less sensitive to the inclusion of other pollutants in the health models than were the effects from the other pollutants. In the other three cities, however, NO_2 effect estimates were more robust than those of other pollutants, including those of PM_{10}, in multipollutant models.

The investigators estimated the shape of the concentration–response (C-R) function for mortality due to all natural causes. They reported that the shape of the C-R function for PM_{10} was consistent with a linear relationship over a range of ambient concentrations in excess of 100 μg/m^3, with no evidence of a threshold in all but Shanghai, where some nonlinearity was observed. They noted, however, that the estimated C–R curves were subject to substantial uncertainty, especially at the highest levels of air pollution (i.e., levels above the 75th percentile of the distribution of 24-hour average concentrations).

CRITICAL EVALUATION OF THE PAPA METHODOLOGY AND ITS APPLICATION

Air Pollutant Monitoring and Exposure Estimates

Each of the PAPA studies based its analyses on air pollutant concentrations and meteorologic data reported from routine monitoring networks, similar to those in large-scale studies in other countries. Such networks typically undergo quality assurance and control procedures on an ongoing basis, and in these four studies, those procedures were augmented by additional auditing. On the other hand, no additional evaluations of the monitors using collocated instruments were conducted as part of any of the PAPA projects. The air quality data for the pollutants of interest were evaluated by the teams, and a consistent protocol was used to exclude data and develop the metrics used in the health association analyses. The decision to remove certain types of monitors (e.g., those near roadways) and what data analyses led to removal decisions were study dependent. Daily metrics of the pollutant data were developed.

Each of the studies estimated how concentrations of individual pollutants varied between monitors and how different pollutant concentrations varied at individual monitors (as well as how the calculated averages correlated among pollutants). These analyses give insight into pollutant dynamics in the region, the representativeness of individual monitors, and the potential for confounding in the ensuing study analyses. Such correlation analyses can help identify if there are local sources that might be having large impacts at specific monitors, suggesting that the monitor should not be included in the analyses, as was done for some of the studies here,

One strength of the studies is that, in general, more than one monitoring station had measurements for each pollutant in the study areas, so the analyses were not dependent on values from a single monitor to estimate exposure, and all of the teams used some approach to developing an average estimate of pollutant concentration in the region of study. As part of the Common Protocol, a "centering" approach was developed and used by some of the teams in sensitivity analyses. Centering can reduce the impact of spatial variability when there are missing data at some monitors over time and there is not strong spatio-temporal variability in the region. The use of data averaging and centering was a positive addition to the analysis. A comparison of results between simple averaging and centering found small differences, however, so the use of simple averaging most likely had little impact on the results in these studies.

Of note is that even the centering approach has a weakness: in the presence of sufficient spatio-temporal pollutant variation, the results can be most heavily influenced by monitors with the greatest number of daily measurements available. Unless spatio-temporal variation can be ruled out, assessment of the sensitivity of the averaged values to the inclusion or exclusion of individual stations will provide greater reassurance regarding the adequacy of the monitoring data (e.g., see Ivy et al. 2008).

The four PAPA studies presented here included relatively little discussion of the likely impacts of specific sources on exposure. Although it was beyond the scope of the current projects, further assessment of the spatial variability in pollutant concentrations would be instructive to help inform the interpretation of the health effect estimates. A review of the other air quality data analyses done for the region would also be helpful, particularly if such work used the same data. For example, source apportionment work can describe the prevalence of local and regional sources and may also provide insight as to the likely size distribution of the aerosol (e.g., the amount of particulate from crustal material versus finer particulate generated by combustion). While such information may not directly affect the epidemiologic analyses, it can be used to better understand the air quality data being used, particularly if the data are consistent with the known sources and with the information on atmospheric chemical and meteorologic determinants of air quality.

Time-Series Modeling

The broad approach adopted by the PAPA team — the use of overdispersed Poisson regression with smoothing functions of time and weather variables to control confounding — is a standard approach in time-series studies. The details of the selection of specific model terms are more controversial. We comment here on the most important issues that apply to all four PAPA studies and, in particular, to the Combined Analysis.

Choice of Smoothing Function for Time The use of a smoothing function for time in air pollution time-series models is a standard approach to controlling for any possible confounding by unmodeled risk factors that change over time in a smooth fashion, and to reducing residual autocorrelation. The investigators' primary results use natural cubic splines for this purpose. This was a reasonable choice given the difficulties with some other smoothing methods (e.g., generalized additive models using backfitting), the absence of clear evidence favoring one particular method not employing generalized additive modeling, and some evidence that pollution effect estimates are not sensitive to this choice (Peng et al. 2006).

Degrees of Freedom for Smoothing Function for Time The analysts' choice about how "wiggly" the smooth function should be remains a controversial one. Some investigations (Peng et al. 2006) have illustrated the sensitivity of results to the number of degrees of freedom in the smoothing function for time. The Common Protocol specified minimization of the sum of the partial autocorrelation coefficients (PACFs) over the first 20 lags and/or restriction of the first- or second-order PACF to less than 0.1 as criteria (there was some variation between studies). To our knowledge, there is no theoretical rationale for this approach, either in these reports or elsewhere, and it is possible that when degrees of freedom are chosen in this way, important residual confounding could remain (Peng et al. 2006). The constraint given by the PAPA Common Protocol that the time smoother had to have 4 to 6 df per year, irrespective of PACF, reduces but does not eliminate concern about this point, and this level of control (6 df/year or less) may not completely control temporal confounding. However, the insensitivity of the main results to using up to 12 df per year was reassuring (see Figure 11 in the Combined Analysis).

Control for Weather The PAPA Common Protocol specified natural cubic spline functions of mean daily temperature and humidity with 3 df. Controlling the effects of weather with splines is sensible, since temperature effects, at least, are rarely found to be linear. The choice of 3 df is somewhat low (e.g., the NMMAPS project used 7 df [Samet et al. 2000]) and could leave room for residual confounding. The biggest potential problem, however, is the limitation in employing lag 0 in the analysis of the effects of temperature. There is considerable evidence that temperature effects persist considerably beyond lag 0 (Braga et al. 2001; Pattenden et al. 2003; McMichael et al. 2008; Anderson and Bell 2009). Omission of the temperature effects at longer lags is particularly of concern given the focus in these studies on the longer lag effects of pollution. Some sensitivity analyses to the specification of the temperature terms were carried out, and indeed results showed many pollution–mortality associations were sensitive to this specification — in particular, the inclusion of longer-lagged temperature terms. However, in many of these analyses the shorter lag terms were removed when longer lag terms were entered, leaving a potential for residual confounding beyond that explored. In the Combined Analysis, for example, mean temperatures over lags 1–2 and 3–7 were entered in two different sensitivity analyses, but not together (see Tables 5 and 6 in the Combined Analysis). Also, sensitivity analyses were carried out only for main effects, in single-pollutant models. For the second-order issues that were also investigated (multicause models, exposure–response shape, and effect modification), no investigation of sensitivity to temperature control was reported.

Modeling Concentration–Response Functions The assumption of a linear concentration–response (C–R) model is common in air pollution time-series studies, and it was made in all the primary PAPA analyses. To the investigators' credit, they assessed the shape of C–R functions in all the single-city studies and in the Combined Analysis. Visual inspection of the C–R estimates (see Figure 12 in the Combined Analysis) suggests generally linear patterns with increasing concentrations across all cities and pollutants, with some exceptions. The exceptions to linearity were strongest in Shanghai and for PM_{10} and O_3. The C–R relation was linear at the higher concentrations with a slope that looks generally consistent with the slope at lower concentrations. In the Combined Analysis, the investigators also assessed the sensitivity of their results to removing days with pollutant measurements greater than the 75th or 95th percentile of the pollutant distribution. In all cities except Bangkok, this exclusion led to lower effect estimates; overall, the resulting effect estimates were broadly consistent with the primary results. Thus, these sensitivity analyses do not suggest the presence of thresholds or any other clear evidence against a linear concentration–response.

It is also pertinent to ask, however, how strongly these studies provide evidence against a "leveling off" of the C–R relation at very high PM exposures (say, above 100 μg/m^3), as has been assumed, for example, in some risk assessments (Cohen et al. 2004). This is a subtly but importantly different question from that of whether the studies provide evidence against linearity. The question is not addressed formally, but can be elucidated by consideration of the confidence intervals for the spline curves at such high exposures (e.g., see the C–R for PM_{10} in Figure 12 of the Combined Analysis). These suggest that though these data are not indicative of such leveling off, they are compatible with it.

Treatment of Multiple Comparisons The four PAPA reports include results on the associations between many pollutants and many causes of death. The causes of death are further stratified by age and subdivided into specific causes within broad categories. Two of the studies report investigations of the modification of pollutant effects by other factors — specifically, temperature and presence of an influenza epidemic — which further increase the number of associations studied. The large number of analyses mandates caution in interpreting the results. The investigators narrowed their focus to lags 0 and 1, which is a sensible set of lags on which to base the primary analyses. This reduced the possible effects of selective interpretations based on particularly large or otherwise striking estimates. In addition, some associations (e.g., the association between PM and cardiopulmonary mortality, and the modification of the effects of air pollution by age at death) are of clear primary a priori interest and should be given more weight in the assessment of results. Beyond these results, when interpreting all other associations that are found out of the many explored, we suggest caution, as it is likely that many of these may have arisen by chance or were "false discoveries."

Though the approach to time-series modeling taken in these studies was broadly state of the art at the time of planning, the Committee would recommend that future studies consider the following:

- Analysis strategy should avoid reliance on the identification of an "optimal" confounder model, since no such strategy can guarantee against residual confounding. Instead the protocol should specify an a priori primary analysis and supplement this with a comprehensive set of analyses of sensitivity to model construction, and ensure the inclusion in models of known determinants of fluctuations in mortality.
- Analysis of sensitivity to confounder control should be undertaken. This is often overlooked in "second-order" investigations, such as those examining putative effect modification, C–R modeling, or multipollutant models.
- Weather is usually a powerful determinant of mortality at lags extending well beyond 0 and is associated with pollution. As such, it is a strong potential confounder and needs more careful modeling in main and sensitivity analyses.
- As was done in these studies, assessment of concentration–response should be included as part of the sensitivity analyses.

Sensitive Subgroups

The Combined Analysis assessed the effects of pollution on mortality in two older age groups (≥ 65 and ≥ 75 years). The ER effect estimates were generally consistent across age, with a suggestion of larger effects in older ages in some cities, particularly Bangkok. The separate city reports presented detailed subgroup analyses with multiple subgroups defined by age, season, presence of influenza, and/or social class. For the most part, the Committee believes that, given the large number of analyses and the small size of many subgroups, many of these subgroup analyses should be considered exploratory.

Health Endpoints

As noted earlier (see the section Design and Quality Control of Data on Health Outcomes, Pollutant Exposure, and Other Covariates), health endpoint data in these PAPA cities were obtained from the respective public health and census statistics agencies. Classification of the cause of death was based on either ICD-9 or ICD-10 coding of the underlying cause of death, which is the typical approach to defining mortality endpoints in U.S. time-series studies. It is well known that there is some misclassification of the cause of death using these health statistics. At issue here is the extent to which this occurred in these studies, how the extent of misclassification varied by the cause of death category, whether misclassification varied across the four cities (three of which were in China and one in Thailand), and, most importantly, how misclassification may have affected estimates of the pollutant health effects.

The validity of cause-of-death statistics has been assessed recently in both China (Rao et al. 2007) and Thailand (Pattaraarchachai et al. 2010; Porapakkham et al. 2010). In six Chinese cities (including Wuhan and Shanghai), sensitivity (the percentage of those with the disease who are correctly classified) in classifying cerebrovascular disease, for example, was 82%, and the positive predictive value (PPV, the percentage of those classified as having the disease who actually have it) was 88% (Rao et al. 2007). In Thailand, these percentages for cerebrovascular disease were 53% and 77%, respectively (Pattaraarchachai et al. 2010). For ischemic heart disease, sensitivity and PPV were 69% and 84%, respectively, in Chinese cities, and 52% and 65%, respectively, in Thailand. However, misclassification was less frequent in Bangkok than in other cities in Thailand (Pattaraarchachai et al. 2010) and might be comparable to that in the Chinese cities. These results for Asian cities compare favorably with some recent U.S. estimates (Ives et al. 2009). Although no findings were presented for broader, aggregated, diagnostic categories, it is expected that misclassification would be less for broader cause-of-death categories such as "cardiovascular" and "respiratory" than for subcategories such as "cerebrovascular" and "ischemic heart disease." Only these broader categories of cause of death were utilized in the Combined Analysis, so misclassification should be less of a concern there than in the individual-city studies where effect estimates for several subcategories were also presented.

When misclassification of health outcomes is nondifferential (i.e., misclassification errors are not dependent on air pollutant concentrations), which seems likely in these studies, misclassification either produces no bias or a bias toward the null value of no effect (Rothman et al. 2008, pp. 142–143). If one can assume that the vast majority of those without the disease will, in most cases, not be classified as having it (Pattaraarchachai et al. 2010; Rao et al. 2007) — in other words, the specificity of the classification is nearly 100% — one would not expect much bias in the health effect estimates from misclassification of these mortality endpoints. Poor sensitivity of classification would reduce the number of death counts for specific causes of death (the true number of cases is estimated by the number of cases classified, divided by the fractional sensitivity) and, if counts are especially low, would result in statistically unstable estimates of the air pollution relative rate (Rothman et al. 2008, pp. 358–359).

As part of the Common Protocol, PAPA investigators also estimated pollutant effects for deaths coded as accidental and for non-cardiopulmonary deaths (i.e., the combination of all non-accidental categories not included among the cardiopulmonary causes of death). The rationale for doing this and the implications of the findings in these cause-of-death categories are discussed in the accompanying commentary on the Bangkok study (in Part 3 of this volume), so further discussion on this issue will not be included here. Suffice it to say that effect estimates for these strata of causes of death are not often included among the findings reported for time-series air pollution studies and were not included in the Combined Analysis. Inclusion of nonstandard categories of death, such as "senility" in the Bangkok study, may also introduce vagaries into the interpretation of effects in specific cause-of-death strata (see the Commentary on Vichit-Vadakan et al. in Part 3). Interestingly, it has been argued that dementia as an underlying cause of death in the United States is greatly underreported on death certificates (Ives et al. 2009), so it may be that senility as a cause of death is appropriate. However, neither dementia nor senility is a useful outcome for time-series studies.

The Committee recommends caution when interpreting findings in the PAPA studies for highly specific causes of death and suggests generally that higher weight be placed on aggregated causes of death (e.g., cardiopulmonary). Although the validity of classifying cause of death into cardiopulmonary and non-cardiopulmonary deaths should be relatively high, as noted earlier, finer cause-of-death strata would be expected to be less so. The Committee urges strong caution in the interpretation of any other cause-of-death categories, both because such associations are more likely to be due to chance (Ioannadis 2005) and because poor model specification can go unnoticed in these subgroups, particularly for outcomes with low event counts.

INTERPRETATION OF RESULTS

The consistency of the findings that these markers of urban air pollution were associated with mortality and the qualitative robustness of these findings in sensitivity analyses suggest strongly that some aspect of air pollution has affected mortality in these cities. However, when it comes to subtler "second-order" points (in particular, the relative strengths of the associations with each pollutant and the variations across cities), interpretation should be more cautious. Residual confounding (in particular, from temperature, as discussed earlier), biases from measurement error (discussed later in the section Exposure Measurement Error), and differences in the reporting and recording of causes of death could distort such subtle patterns, even if they do not threaten the main finding of an association of air pollution with mortality. As noted earlier, sensitivity analyses were reported only for the linear associations involving single pollutants, leaving greater uncertainty for the second-order results.

The aspects of the interpretation of results that the Committee considered of particular interest are discussed in more depth in the following sections.

Single- and Multipollutant Models

Focusing on individual pollutants, which has been the standard approach in air pollution epidemiology, actually may provide limited insight into their individual effects, particularly in the context of time-series studies of short-term exposure effects. In single-pollutant models, it is clear that the pollutant included could be acting as an indicator of any aspect of the pollution mix to which it is positively correlated. It is tempting to believe that including two or more pollutants in a multiple regression model would allow an interpretation of the coefficient of one pollutant as the effect of that pollutant controlled for the effects of the others in the model. However, there are obstacles to this interpretation. Mostly these are the same as the limits to interpreting single-pollutant models (residual confounding, in particular). Some are specific to the multipollutant context. Highly correlated pollutant data can lead to imprecise effect estimates easily distorted by biases. The effects of pollutants that have less exposure measurement error appear more robust in multiple regression models than the effects of correlated pollutants that have more exposure measurement error, whether or not the better-measured pollutants in fact are producing the estimated effects (Zeger et al. 2000). Correcting for measurement error in multivariable analyses is, in principle, possible, but requires information on the joint distributions of errors that is rarely available. Thus, reaching confident conclusions regarding individual-pollutant effects is unlikely.

So, although pollutant effect estimates in single-pollutant models can be difficult to interpret, there is little assurance that multipollutant models, or even two-pollutant models as used here, serve their intended purpose of providing pollutant effect estimates that are independent of the effects of other pollutants. A multipollutant framework, in which the focus is on the air pollution mixture instead of on individual pollutants, may allow a more meaningful assessment of air pollution impacts, especially for the purpose of air quality management (Stieb et al. 2008). However, there are many unresolved challenges to implementing a multipollutant approach (Dominici et al. 2010).

In addition to the general issues of interpreting specific pollutant associations with mortality, there were gaps in the types of pollutants measured in the PAPA studies: the concentrations of two potentially important pollutants were not regularly measured, and their effects were therefore not estimated — $PM_{2.5}$ (PM with an aerodynamic diameter $\leq$ 2.5 µm, which has not been routinely measured in Asian cities) and carbon monoxide (CO). It has often been argued that the effects of $PM_{2.5}$ are stronger and more consistently observed than those of PM_{10} or of the coarse fraction of PM_{10} ($PM_{10-2.5}$) (Pope and Dockery 2006), although there is evidence for the adverse effects of $PM_{10-2.5}$ exposure (Brunekreef and Forsberg 2005). Also, strong effects of CO relative to other pollutants have been estimated in some studies (e.g., HEI 2003), and new toxicologic and epidemiologic evidence has renewed interest in CO (Samoli et al. 2007; Reed et al. 2008). Since these pollutants may have had estimated effects different from those of the pollutants included in the analyses, the estimation of the health impacts of short-term exposure to ambient air pollution in these PAPA cities is incomplete. It may be, however, that the effects of PM_{10} largely account for those of $PM_{2.5}$. In addition, in the case of Bangkok, at least, where NO was included in the analysis (a pollutant that, like CO, is emitted from mobile sources and whose concentrations would theoretically be highly correlated with those of CO both temporally and spatially), inclusion of CO may not have had much additional impact.

Exposure Measurement Error

We noted earlier that estimated associations of pollutants and mortality in the PAPA studies are — as in all other studies — subject to bias if there is error in the exposure measurements. A general framework for the impacts of such measurement error in ecologic time-series studies such as these has been delineated by Zeger and colleagues (2000). A key insight of this work is that the most critical component of error in time-series studies is the discrepancy between the daily means of monitored concentrations and the true daily mean concentration of personal exposures in the city. As we discussed earlier, measurement error can also distort multipollutant model results as well as affect the apparent relative importance of individual pollutants in single-pollutant models.

For the PAPA studies (as indeed in most time-series studies), we have little information on the size of exposure measurement error. The procedures used in the individual studies and the Combined Analysis (specifically, pollutant averaging, with centering for sensitivity analyses and the evaluation of associations between individual monitor concentrations) are standard good practice. However, the observations also show that the areas where the monitors were sited within the cities have significant spatial variability in primary pollutant concentrations, suggesting that any estimation of a citywide mean will be subject to imprecision. While the Combined Analysis, as well as the individual studies, suggests associations between combustion-derived emissions and health effects, that is in part due to the types of pollutant data available (nitrogen oxides [NO_x], SO_2, and a potentially large fraction of PM_{10} are from combustion sources), and the lack of source apportionment analysis makes it difficult to quantify the fraction of PM_{10} from combustion. It is even more difficult to assess how much of the pollutant exposure is due to specific combustion sources (e.g., ships, diesel engines, cars, mopeds or motorcycles, and stationary sources involving combustion of coal, oil, and gas). The air quality impacts from such sources are most likely quite spatially variable, and their health impacts may also be quite different (e.g., due to metal content). Similar issues plague other large studies that have relied on routine monitoring in other countries.

In summary, while we have no reason to believe that measurement error is a greater source of concern in the PAPA studies than in other studies of large cities, any interpretation should take into account possible distortions from measurement error, in particular when using multipollutant models.

Atypical Associations in Bangkok

In several respects noted earlier, the pollution–mortality associations from Bangkok stood out from those from the Chinese cities. In particular, the excess relative risk of mortality from PM_{10} exposure was more than twice the size of those of the Chinese cites and, unlike in the Chinese cities, was more robust than the NO_2 association with mortality (see Figures 7 and 9 in the Combined Analysis). At this time, any hypotheses to explain this pattern must be speculative. The authors note some unusual features of the data in Bangkok — notably that measurements were taken by monitors further from roads than those in the Chinese studies — suggesting that day-to-day fluctuations might reflect population exposure changes differently. However neither this feature nor others noted were unique to Bangkok (Wuhan also had few monitors close to roads). The much higher excess relative risk of mortality from PM_{10} exposure in Bangkok estimated from a model that included a term for the "warm" season (see Table 5 in the Combined Analysis) implies large between-season variation in the effects of air pollution. The investigators propose several explanations for this observation, including modification of the effects by climatic factors and the prevalence of air conditioning, but an additional potential explanation is residual confounding or other bias related to season in the Bangkok results. The finding of elevated risk per unit of PM_{10} is consistent with observations in most cities worldwide. The larger relative excess risk compared with the other PAPA cities is currently unexplained, and it would be premature to assume that this result reflects real differences in risk for the population of Bangkok rather than effects of data quality or analytic approach.

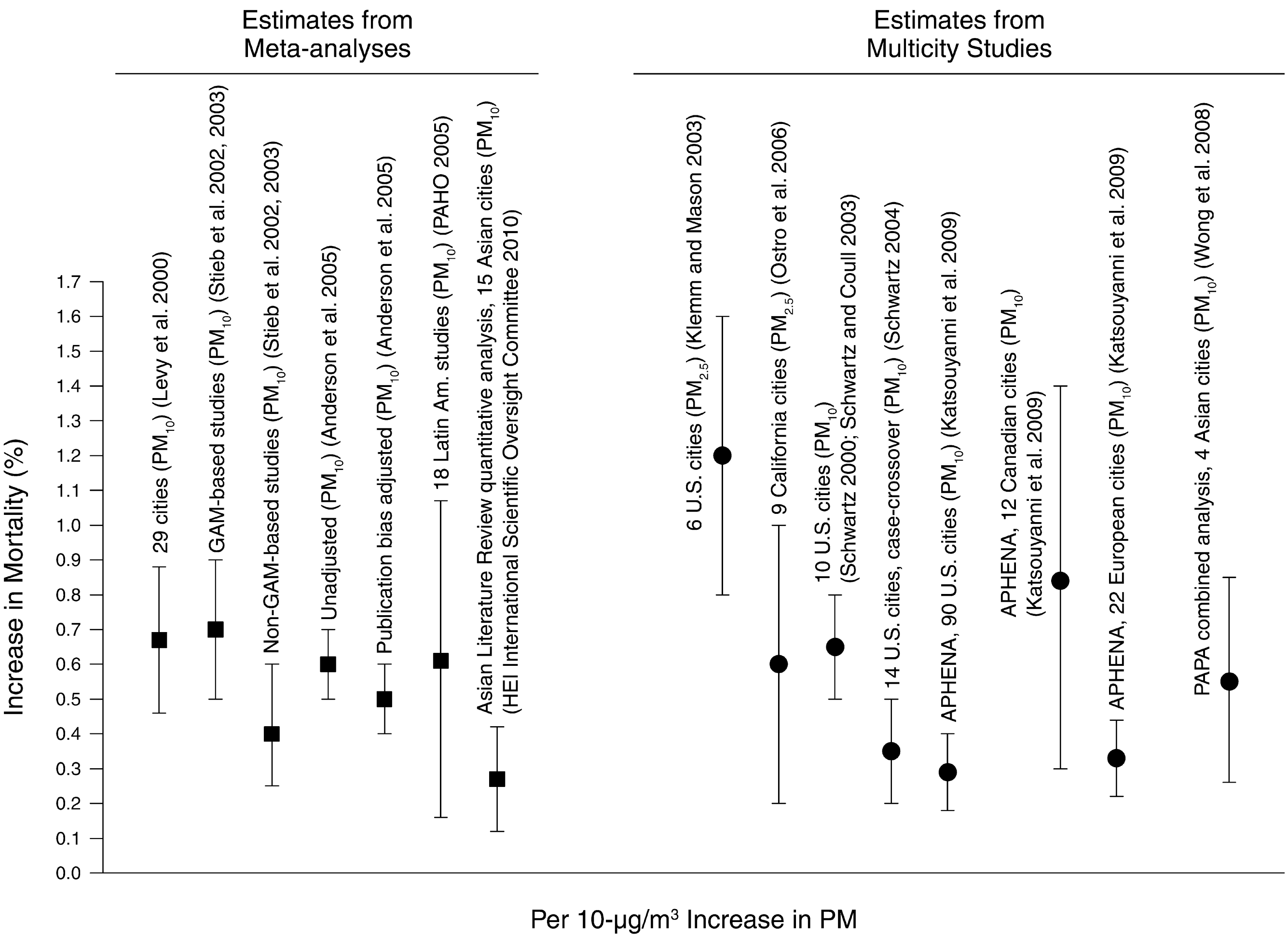
The PAPA Studies in the Global Context

Pollutant concentrations in the four cities in the PAPA studies were dramatically different from concentrations in most Western cities. For example, median daily levels of PM_{10} in Europe and North America did not exceed 65 $\mu g/m^3$ (Katsouyanni 2009), but levels in the PAPA cities included daily levels severalfold higher (see the Combined Analysis). Despite these differences, the estimates of pollutant effect were not markedly different from those in North America and Europe (Integrated Discussion Figure 1). It is, however, worth bearing in mind that the width of the confidence intervals shown in Figure 1 of this Integrated Discussion indicates that these estimated effects are consistent with a wide range of true effects. Also, as has also been observed in Western cities (Katsouyanni et al. 2009), there is some heterogeneity of effect among the PAPA cities, with Bangkok estimates, in particular, being often substantially larger than those in the other three cities.

At face value, the broad consistency between the effect estimates from the PAPA studies and those from the United States and Europe implies that the differences in concentrations, pollutant sources and mixtures, population susceptibility, and population time–activity patterns do not substantially modify the relationship between change in mortality risk and change in absolute pollutant concentration. Regarding concentration differences, as a hypothetical but realistic example, this consistency implies that the mortality effect of a change in PM_{10} from 10 to 20 $\mu g/m^3$ in a Western city is the same as the effect of a change from 100 to 110 $\mu g/m^3$ in a PAPA city; even more extreme but not entirely unrealistic examples could be proposed. While possible, this scenario conflicts with other evidence. In an analysis of London mortality from 1958 to 1972, a period of relatively high pollutant concentrations, a steeper C–R relationship for PM was seen at lower concentrations than at the higher concentrations (Schwartz and Marcus 1990). This is not what is found in the PAPA studies. While the reason for this difference in the shapes of the C–R functions is not known — and may be due to chance or residual biases — if the difference is in fact real, some possible explanations include differences in the pollutant mix or in population susceptibility.

One interpretation of the relative consistency in the pollutant effect estimates, as put forward in the editorial that accompanied the recent publication of these PAPA studies in *Environmental Health Perspectives* (Speizer et al. 2008), is that effect estimates from studies carried out on Western populations are applicable to settings with substantially different pollutant concentrations and factors related to population health. This implies that it is not unreasonable for policymakers, in the absence of locally generated pollutant effect estimates, to use effect estimates generated elsewhere in order to estimate pollutant health impacts locally. However, the consistency observed is not total. Even within the PAPA cities, the differences among the effect estimates suggest that it remains useful to obtain locally generated estimates in some cases.

Another notable issue regarding the findings reported in this group of PAPA studies is that the estimated effect of NO_2 is most often more robust and larger than those of the other pollutants. This finding is more in line with those from Europe (Samoli et al. 2006) and Canada (Burnett et al. 2004; Brook et al. 2007) than those from the United States, where the effects of NO_2 are less robust than those of PM (Samet et al. 2000). Several possible explanations of these differences are that the NO_2 monitoring networks in both Europe and Canada use different siting criteria, may be more spatially dense, and may possibly better reflect population exposure to NO_2 than the monitoring networks in the United States. Another possibility is that NO_2 reflects different toxic pollutant mixtures in these different regions. As discussed earlier, residual biases may also play a part. At this point, however, there is no good explanation as to why the effects of NO_2 seem to be so different.



Integrated Discussion Figure 1. Estimates of the effect on all natural mortality per 10-μg/m^3 increase in PM reported in several recent meta-analyses and multicity studies.

CONCLUSIONS / IMPLICATIONS

1. *The PAPA studies provide the most comprehensive and rigorous investigation of air pollution and mortality in Asia to date.* Because of the relative rigor used in carrying out these PAPA studies, with the common and considered approaches to data collection and analysis, pollutant effect estimates reported from these studies are arguably the most reliable estimates currently available from China and Southeast Asia to date. While (as with all research) these can be improved on and residual uncertainties persist as outlined earlier, policymakers now have more assurance that the estimation of pollutant health impacts in their respective countries is on a more sound footing. Some questions that remain have been identified and provide a focus for future research efforts.

2. *The finding of a consistently positive association of pollution concentrations with mortality is likely to represent a true adverse effect of some aspect of urban pollution. However, pollution-specific effect estimates, whether from single- or multipollutant models, should also be interpreted with the expectation that, if they reflect a causal effect, they may well represent the effects of an aspect of the pollution mixture correlated with the pollutant rather than of the pollutant itself.* All four pollutants (PM_{10}, O_3, NO_2, and SO_2) evaluated in these four PAPA cities showed positive short-term associations with mortality in all the cities using the base models. This nonspecificity with respect to pollutant effects, which is characteristic of many air pollution time-series studies, has several possible, and not mutually exclusive, explanations: (a) many different individual pollutants have similar

effects on mortality; (b) individual pollutants serve as surrogates of possibly different aspects of the ambient pollutant mixture, with the mixture possibly having a greater effect than any single component; and (c) with any pollutant, residual confounding continues to be a concern. The degree to which each of these, or even other, possible explanations contributes to nonspecificity in the findings is not known.

3. *The results of these PAPA studies are consistent with the effects on mortality per unit concentration found elsewhere in the world, especially for the risk per unit of PM_{10}.* To the extent that the pollutant health effect estimates show reasonable consistency with those estimated in Western cities, an argument can be made that the effects estimated from the much larger number of time-series studies carried out in Western cities can be generalized to other parts of the world, despite differences in the characteristics of air pollution and the populations at risk. As is the case in other air pollution time-series studies, estimated pollutant effects in these PAPA cities were usually larger for the elderly and in those for whom the cause of death was coded as cardiopulmonary.

4. *Residual confounding and biases from errors in measuring exposure and in coding for the cause of death imply uncertainty in the effect estimates that can be considerably larger than is expressed in the confidence intervals.* Of all of the factors assessed in sensitivity analyses, sensitivity to a more aggressive control for the effects of meteorology through the inclusion of longer temperature lags had the greatest impact on reducing pollutant effect estimates. A good case can be made for this aggressive control of the effects of meteorology in principle, leading to the conclusion that pollutant effect estimates in models with better control of meteorologic effects are less biased. However, there remains some concern that such aggressive control for meteorology underestimates some true pollutant effects given the measurement error associated with pollutant concentrations; as of now, this issue is not completely resolved (HEI 2003).

   As in most time-series studies, population exposure in the PAPA studies was estimated based on existing monitoring networks. Because spatio-temporal variability in time-series studies involving pollutant concentrations is expected to be different for each of the pollutants, and because the monitoring networks capture this variability to different degrees, the exposure measurement error is expected to vary by pollutant and by city. Improved pollutant exposure estimation, which would be helped by improvements to the air monitoring networks, would allow for more confidence in the estimated health effects of pollutants in the cities of developing Asia.

5. *The potential for residual confounding and other biases also suggests caution in the interpretation of the more complex patterns found in these studies, including the apparent linearity of relationship between estimated effects and concentrations, up to high concentrations, and apparent dominance of NO_2 over PM_{10} effects in most cities. The evidence on these questions should be considered as suggestive rather than strong.* The shape of C–R curves across the wide range of concentrations covered in these studies is important for risk assessment where concentrations are high. There appears to be little evidence in these four cities for nonlinearity or, more specifically, for a flattening off at higher concentrations. However, the data are sparser at higher concentrations, even in these cities, and the shapes of the curves are subject to residual confounding and other biases as noted earlier, so absence of evidence for nonlinearity cannot be taken as evidence for linearity. It is possible that these data are compatible with substantially nonlinear models also.

6. *The methodology applied in the PAPA time-series studies and embodied in the Common Protocol can provide an initial foundation for further research in developing Asia.* The PAPA studies add to the growing number of time-series studies across Asia — 82 having been published as of 2007 (HEI International Scientific Oversight Committee 2010). These studies, though consistent in showing increases in daily mortality associated with short-term exposure, have been conducted largely in China; Taipei, China; and South Korea. The lack of data on air quality and mortality, especially cause-specific mortality, remains a major impediment to conducting such studies in many parts of developing Asia. As a result, major population centers in South and Southeast Asia (India, Pakistan, Vietnam, the Philippines, Indonesia, and Malaysia) remain understudied, though HEI-funded studies are soon to be completed in India and Vietnam. Expanded, coordinated multicity studies conducted across the region, with rigorous quality control of air quality and health data, and designed and analyzed consistently, with additional methodologic improvements noted earlier, could provide more definitive answers.

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HEALTH EFFECTS INSTITUTE

101 Federal Street, Suite 500
Boston, MA 02110, USA
+1-617-488-2300
www.healtheffects.org

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