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HEI Public Health and Air Pollution in Asia Program

Includes Commentaries by the Institute's Health Review Committee

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CONTENTS

ABOUT HEI

The Health Effects Institute is a nonprofit corporation chartered in 1980 as an independent research organization to provide high-quality, impartial, and relevant science on the effects of air pollution on health. To accomplish its mission, the institute

- Identifies the highest-priority areas for health effects research;
- Competitively funds and oversees research projects;
- Provides intensive independent review of HEI-supported studies and related research;
- Integrates HEI's research results with those of other institutions into broader evaluations; and
- Communicates the results of HEI's research and analyses to public and private decision makers.

HEI receives half of its core funds from the U.S. Environmental Protection Agency and half from the worldwide motor vehicle industry. Frequently, other public and private organizations in the United States and around the world also support major projects or certain research programs. The Public Health and Air Pollution in Asia (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.

HEI has funded more than 280 research projects in North America, Europe, Asia, and Latin America, the results of which have informed decisions regarding carbon monoxide, air toxics, nitrogen oxides, diesel exhaust, ozone, particulate matter, and other pollutants. These results have appeared in the peer-reviewed literature and in more than 200 comprehensive reports published by HEI.

HEI's independent Board of Directors consists of leaders in science and policy who are committed to fostering the public–private partnership that is central to the organization. The Health Research Committee solicits input from HEI sponsors and other stakeholders and works with scientific staff to develop a Five-Year Strategic Plan, select research projects for funding, and oversee their conduct. The Health Review Committee, which has no role in selecting or overseeing studies, works with staff to evaluate and interpret the results of funded studies and related research.

All project results and accompanying comments by the Health Review Committee are widely disseminated through HEI's Web site (*www.healtheffects.org*), printed reports, newsletters and other publications, annual conferences, and presentations to legislative bodies and public agencies.

ABOUT THIS REPORT

Research Report 154, *Public Health and Air Pollution in Asia (PAPA): Coordinated Studies of Short-Term Exposure to Air Pollution and Daily Mortality in Four Cities*, presents five studies funded by the Health Effects Institute. This report contains these main elements:

The Executive Summary, prepared by staff at HEI, is a brief, nontechnical summary of the four time-series studies and the fifth study, a combined analysis of the data; the Executive Summary also briefly describes the Health Review Committee's comments on the studies.

The Investigators' Reports on the five studies describe the scientific background, aims, methods, results, and conclusions of each of the studies.

The Overview, the four Commentaries on the time-series studies, and the Integrated Discussion included in the Combined Analysis were prepared by members of the Health Review Committee with the assistance of HEI staff; these sections place the studies in a broader scientific context, point out their strengths and limitations, and discuss remaining uncertainties and implications of the findings for public health and future research.

This report and the five component studies have gone through HEI's rigorous review process. When an HEI-funded study is completed, the investigators submit a draft final report presenting the background and results of the study. This draft report is first examined by outside technical reviewers and a biostatistician. The report and the reviewers' comments are then evaluated by members of the Health Review Committee, an independent panel of distinguished scientists who have no involvement in selecting or overseeing HEI studies. During the review process, the investigators have an opportunity to exchange comments with the Review Committee and, as necessary, to revise their report. The Commentaries and the Integrated Discussion reflect the information provided in the final version of the report.

PREFACE

Coordinated Time-Series Studies in Asian Cities

Exposure to outdoor air pollution is associated with short-term increases in daily mortality, higher rates of hospital admissions, increases in emergency room utilization, and exacerbation of chronic respiratory conditions in many parts of the world (WHO 2002). The World Health Organization (WHO) estimates that air pollution contributes globally to approximately 800,000 deaths and 4.6 million lost life-years (WHO 2002).

Developing nations are particularly affected by air pollution: as many as two-thirds of the deaths and lost life-years associated with air pollution on a global scale occur in Asia (WHO 2002). To date, estimates of the health effects resulting from exposure to air pollution in Asia have relied largely on the extrapolation of results from research conducted outside Asia — primarily in Europe and North America (Cohen 2004). However, the nature of the ambient air pollution mix in Asia, the high levels of pollutants in some parts of the continent, the environmental conditions, and the background health conditions of the population may all contribute to health outcomes that differ from those in Europe and North America.

To address some of the uncertainties in estimating the adverse health impact of air pollution in Asia, the Health Effects Institute, in partnership with the Clean Air Initiative for Asian Cities, initiated the Public Health and Air Pollution in Asia (PAPA) program in December 2002. The PAPA program had three major components:

1. Assessment and review of existing science on the effects of exposure to air pollution in Asia;
2. Initiation of significant new research in several large Asian cities, including major new epidemiologic studies on the health effects of air pollution; and
3. Development of the scientific and technical capacity of a network of Asian investigators, including targeted opportunities for training in epidemiology and related areas.

HEI set up the International Scientific Oversight Committee (ISOC), chaired by Dr. Frank Speizer of the Harvard School of Public Health and comprising members of HEI's Research and Review Committees and experts from the United States and Asia, in order to provide expert scientific advice and oversight of the PAPA program. A full list of ISOC members is included at the end of this report.

PAPA FIRST-WAVE STUDIES

In 2003 HEI issued a Request for Information and Qualification (RFIQ) for scientists interested in conducting epidemiologic studies of the health effects of air pollution in Asian cities. Through this RFIQ, HEI sought to ascertain potential investigators' qualifications and their access to appropriate study populations, pollutant monitoring data — such as levels of particulate matter (PM), carbon monoxide (CO), and ozone (O_3) — and health data (mortality and morbidity) in Asian cities. Thirty-two teams in eight Asian countries responded to the RFIQ.

ISOC evaluated all the proposals and decided to support a coordinated series of time-series studies in several Asian cities. In addition, ISOC decided to request applications from investigators who appeared to have both the best qualifications and quick access to the necessary information, allowing them to begin studies within a short period after receiving funding.

The PAPA program ultimately initiated four time-series studies of the health effects of air pollution in Bangkok, Hong Kong, Shanghai, and Wuhan. This was the first set of coordinated time-series studies ever undertaken in Asian cities and the first phase of an effort by ISOC to conduct a series of studies in Asian cities intended to deepen the understanding

of air pollution effects in local populations and inform extrapolation from the extensive body of existing science.

This "first wave" of PAPA studies comprised four time-series studies:

- **"Estimating the Effects of Air Pollution on Mortality in Bangkok, Thailand."** Principal Investigator Dr. Nuntavarn Vichit-Vadakan at Thammasat University in Thailand and her team proposed to examine the effects of PM ≤ 10 μm in diameter (PM_{10}) and several gaseous pollutants — O_3, nitrogen dioxide (NO_2), nitric oxide (NO), and sulfur dioxide (SO_2) — on daily mortality for the years 1997 through 2003 and for all 50 districts of Bangkok, which had a population of 10.4 million in 2000.
- **"Interaction Between Air Pollution and Respiratory Viruses: Time-Series Study of Daily Mortality and Hospital Admissions in Hong Kong."** Dr. Chit-Ming Wong of The University of Hong Kong and his team proposed to examine the short-term effects of PM_{10}, NO_2, SO_2, and O_3 on mortality and hospital admissions over the period 1996 to 2002. The confounding and modifying effects of influenza epidemics were also to be assessed. The study included the whole Hong Kong population of 6.8 million.
- **"A Time-Series Study of Ambient Air Pollution and Daily Mortality in Shanghai, China."** Dr. Haidong Kan from the Fudan University School of Public Health in China and his team proposed to evaluate the association between mortality outcomes and major air pollutants (PM_{10}, SO_2, NO_2, and O_3), using daily data from 2001 through 2004. The target population was all residents living in the urban area of Shanghai, which covers nine districts and encompasses a population of more than 6 million.
- **"Association of Daily Mortality with Ambient Air Pollution, and Effect Modification by Extremely High Temperature in Wuhan, China."** Dr. Zhengmin Qian at the Pennsylvania State College of Medicine in Hershey, Pennsylvania, and his team proposed to determine whether daily variations in ambient PM_{10}, SO_2, NO_2, or O_3 concentrations in Wuhan (with 4.5 million permanent residents in the nine urban core districts) from July 1, 2000, to June 30, 2004, were associated with variations in daily mortality due to all natural causes and daily cause-specific mortality.

A COORDINATED APPROACH TO ANALYSIS

Coordinated multicity studies currently provide the most definitive epidemiologic evidence of the effects of short-term exposure and, as a result, play a central role in health impact assessment and environmental policy. While robust and consistent results have been observed in Europe and North America (Samet 2000; Katsouyanni 2001), few coordinated, multicity time-series studies have been conducted elsewhere. These four studies compose the first coordinated multicity analysis of air pollution and daily mortality in Asia.

The principal investigators developed a common set of criteria for the inclusion and analysis of data in each city; this Common Protocol was codified in a "Protocol for Coordinated Time-Series Studies of Daily Mortality in Asian Cities," which is included at the end of this volume. In addition, at the end of the four studies, the investigators, led by Dr. C-M. Wong, undertook a Combined Analysis, incorporating data from all four cities. This Combined Analysis is also included in this publication as a separate report.

STUDIES IN INDIA

In recognition of the fact that India is a diverse, densely populated country where the burden of disease attributable to ambient air pollution is likely to be substantial, HEI put out a request for applications (RFA) for retrospective time-series studies of air pollution and mortality in Indian cities in the spring of 2004. This RFA was intended to facilitate a set of Indian time-series studies that would be an important addition to the group of studies currently in progress in other Asian cities.

Proposed studies would utilize existing sources of data to explore how daily death rates change in relation to contemporaneous daily concentrations of air pollutants while correcting for other risk factors. Investigators were requested to submit information related to the nature and availability of monitoring data for air pollution, including major air pollutants measured

(e.g., PM, O_3, and CO) and visibility data, as well as health data on measures of mortality (and morbidity, where available) in the corresponding cities. In order to maximize the capabilities of researchers from different disciplines, it was strongly recommended that interdisciplinary teams of scientists apply together.

HEI subsequently extended the PAPA research program to include three studies of air pollution and mortality due to all natural causes in Chennai, Delhi, and Ludhiana. The Indian studies focused on the association between increased air pollution and all natural (nonaccidental) mortality from 2002 though 2004:

- **"Short-Term Effects of Air Pollution on Mortality: Results from a Time-Series Analysis in Chennai, India."** Dr. Kalpana Balakrishnan from Sri Ramachandra Medical College and Research Institute and her team explored the association between air pollution and all natural mortality in Chennai, a city in Southern India.
- **"Time-Series Study on Air Pollution and Mortality in Delhi."** Dr. Uma Rajarathnam at The Energy and Resources Institute and her team explored the association between air pollution and all natural mortality in Delhi, the nation's capital.
- **"A Time-Series Study on the Relation of Air Pollution and Mortality in Ludhiana City, India."** Dr. Rajesh Kumar of the Postgraduate Institute of Medical Education and Research in Chandigarh and his team proposed to explore the association between air pollution and all natural mortality in Ludhiana, an industrial city in northern India.

Because of key differences in data availability and completeness between the first four PAPA studies and the Indian studies, however, the Common Protocol developed for the first four studies was not sufficient for use in the Indian context. Indeed, the Ludhiana study was terminated prematurely because of substantial limitations and uncertainties in the data that made it unclear that an interpretable result would be possible. Drs. Balakrishnan and Rajarathnam developed city-specific approaches for using available air quality data in order to develop daily estimates of exposure.

The PAPA studies were funded in order to bridge the gap between studies conducted in different localities with the intent of providing information to Asian decision makers making policy choices. The PAPA studies were designed and conducted by local investigators in concert with local air pollution and public health officials and international experts. These studies explore key aspects of the epidemiology of exposure to air pollution in each location — issues of local as well as global relevance — including the effects of exposure at high concentrations and at high temperatures, the potential influence of influenza epidemics on the relationship between air pollution and health, and the ways in which social class might modify risks associated with air pollution.

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Executive Summary

BACKGROUND

The effects on air quality of the rapid increases in industrialization, urbanization, and vehicularization are becoming increasingly apparent in many of Asia's cities and industrial areas. This rapid development, together with emission trends (e.g., those resulting from changes in energy, fuel, and vehicle use), population trends (the degree of urbanization), health trends (age structure and background disease rates), and other important factors (e.g., broad changes in regulatory approaches and improvements in control technology), will influence the extent to which exposure to air pollution affects the health of the Asian population over the next several decades. Accordingly, government decision makers, the private sector, and other local stakeholders are increasingly raising the issue of the health impacts of urban air pollution.

While two-thirds of the 800,000 deaths and 4.6 million lost life-years attributed to air pollution each year on a global scale occur in Asia (WHO 2002), risk estimates have relied largely on the extrapolation of results from research conducted outside Asia — primarily in Europe and North America (Cohen et al. 2004). In recognition of the possibility that the nature of the ambient air pollution mix in Asia, the high levels of pollutants in some parts of the continent, and the environmental and background health conditions of the population may all contribute to differences in health outcomes between Asia and Europe and North America, there has been a steady increase in research on the health effects of air pollution in Asian cities.

Coordinated multicity studies currently provide the most definitive epidemiologic evidence of the health effects of short-term exposure to air pollutants and, as a result, play a central role in health impact assessment and environmental policy. Multicity studies have a greater ability to explain the differences (*heterogeneity*) among cities in the relative rates of mortality associated with exposure to air pollution than single-city studies. Large multicity studies also have the statistical power to explore more definitively the shape of the air pollution concentration–response (C–R) function (Daniels et al. 2000; Schwartz 2000), the timing of effects related to air pollution, and the extent of life shortening (also known as *harvesting*) due to air pollution (Zeger et al. 1999; Zanobetti et al. 2000; Schwartz 2001).

While relatively robust and consistent results have been observed in Europe and North America (Samet 2000b; Katsouyanni et al. 2001), few coordinated multicity time-series studies have been conducted elsewhere. Acknowledging that a coordinated set of time-series studies in several Asian cities could further the understanding of air pollution effects in regionally relevant populations and inform extrapolation from the extensive global body of evidence, in 2003 HEI's Public Health and Air Pollution in Asia (PAPA) program funded the first set of coordinated time-series studies ever undertaken in Asian cities: four time-series studies of the health effects of air pollution in Bangkok, Hong Kong, Shanghai, and Wuhan. These studies were intended to help bridge the gaps between studies conducted in different localities with the intent of providing information to Asian decision makers considering policy choices.

Studies were designed and conducted by local investigators in concert with local air pollution and public health officials and international experts. These investigations explore key aspects of the epidemiology of exposure to air pollution in each location — issues of local as well as global relevance — including the effects of exposure at high concentrations and at high temperatures, the potential influence of influenza epidemics on the relations between air pollution and health, and the ways in which social class might modify risks associated with air pollution.

SHANGHAI

Dr. Haidong Kan from the Fudan University School of Public Health in Shanghai, China, and his team proposed in 2003 to evaluate the impact of short-term changes in Shanghai in ambient air concentrations of particulate matter $\leq$ 10 µm in aerodynamic diameter (PM_{10}), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), and ozone (O_3) on daily mortality using four years of data covering the period January 1, 2001, to December 31, 2004. The Shanghai study had a special focus on assessing the interaction of PM with gaseous copollutants, and assessed whether there are independent effects of PM and gaseous pollutants on mortality. The study also explored effect modification by season (warm vs. cool) and by level of education.

WUHAN

Dr. Zhengmin Qian from Pennsylvania State College of Medicine, Hershey, Pennsylvania, and his team proposed in 2003 to determine whether daily variations in ambient PM_{10} concentrations in Wuhan from July 1, 2000, to June 30, 2004, were associated with daily variations in mortality due to all natural (nonaccidental) causes and cause-specific mortality. Known as the "oven city" because of its extremely hot summers, this location provided an opportunity to assess how very high temperatures may modify the health effects of exposure to air pollution.

BANGKOK

Dr. Nuntavarn Vichit-Vadakan of Thammasat University in Thailand and her team proposed to examine the effects of PM_{10} and several gaseous pollutants — O_3, NO_2, and SO_2 — on daily mortality for the time period June 1, 1997, through May 31, 2003, for all 50 districts of Bangkok. Dr. Vichit-Vadakan initially aimed to also examine whether reductions in local traffic levels during an economic recession could have affected mortality rates and the resulting C–R functions, but results were uninformative and ultimately removed from the analysis at the suggestion of HEI's Health Review Committee.

HONG KONG

Dr. Chit-Ming Wong of The University of Hong Kong and his team proposed to examine the short-term effects of air pollution on mortality and hospital admissions over the period 1996 to 2002. As influenza exerts tremendous health and economic costs in many areas of the world including Hong Kong, this study investigated the potential confounding and modifying effects of air pollution's adverse health effect by influenza epidemics. The study also explored whether social class modified any risks associated with air pollution in Hong Kong.

COMBINED ANALYSIS

In addition to conducting individual study analyses, investigators undertook a Combined Analysis, incorporating data from all four cities.

A COORDINATED AND COMBINED APPROACH TO ANALYSIS

All four studies were conducted using the same types of administrative data on mortality and air pollution levels used in time-series studies throughout the world. The studies also employed a methodologic rigor that matches or exceeds that of most published studies, including formal quality control in the form of detailed standard operating procedures for data collection and analysis, and external quality assurance audits of the data overseen by HEI.

The principal investigators developed a common set of criteria for the inclusion and analysis of data in each city, titled the "Protocol for Coordinated Time-Series Studies of Daily Mortality in Asian Cities." This Common Protocol specified design criteria for data on health outcomes, air quality measurements, and meteorologic factors, as well as a general approach to the analysis of time-series data. It benefited from recent efforts to strengthen and refine methods for the analysis of time-series data and was intended to be on par methodologically with the most recent U.S. and European analyses (HEI 2003). Adoption of such a protocol provides some assurance that the results for each city will not differ importantly because of differences in data quality or analysis and offers a more reliable foundation for a meta-analysis. The Common Protocol was implemented for each study in the following ways:

- Mortality data for the PAPA studies were provided by local health authorities in each of the four cities and were coded using the World Health Organization's (WHO's) *International Classification of Diseases,* either 9th revision or 10th revision (ICD-9 or ICD-10), depending on the year of death.
- Pollutant data for NO_2, SO_2, PM_{10}, and O_3 were provided by the local government agencies in each city and met local quality control and assurance standards. Exposure metrics used for NO_2, SO_2, and PM_{10} were 24-hour average concentrations; O_3 analyses used 8-hour average concentrations (measured from 10 am to 6 pm). Investigators followed an independent, standardized procedure with regard to ensuring both the completeness and representativeness of the average daily exposure of the population. As the number of missing data was minimal, no attempt was made to impute missing data.
- 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. Although the agreed-upon analytic approach left some room for city-specific variations, the model options were constrained to limit the set of potential models.

RESULTS

Executive Summary Tables 1 and 2 summarize, among other values, the city-specific average daily number of deaths and the maximum and mean pollutant levels and meteorologic variables during the study period. Executive Summary Table 3 summarizes the main epidemiologic findings of each report for excess risk (ER) for mortality. All analysis results are presented as ER per 10 $\mu g/m^3$ of pollutant at lag 0–1 day (average), calculated from the relative risk (RR) as follows: $ER = (RR - 1) \times 100$.

SHANGHAI

Short-term increases in the concentrations of PM_{10}, NO_2, SO_2, and O_3 were associated with increased daily all natural (nonaccidental) mortality in the Shanghai study.

Executive Summary Table 1. Summary Statistics of Daily Mortality Counts

	Minimum				Maximum				Mean				SD[a]			
Mortality Class	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	147	135	198	213	94.8	84.2	119.0	61.0	12.1	12.8	22.5	15.8
≥ 65 yr	13	34	46	18	63	113	175	159	34.3	65.4	99.6	43.8	6.7	11.6	20.6	13.4
≥ 75 yr	6	17	33	6	50	82	129	106	21.3	43.6	71.5	25.7	5.2	9.5	16.7	9.5
Cardiovascular causes	1	6	11	8	28	54	85	94	13.4	23.8	44.2	27.8	4.3	6.5	11.0	8.8
Respiratory causes	1	3	3	0	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.

Estimates for mortality due to cardiovascular causes were similar to the overall estimate for all natural mortality. For respiratory deaths, effect estimates for exposure to NO_2 and SO_2 were slightly larger than those for the other categories of death, but with overlapping confidence intervals. The risk estimates associated with specific age groups were generally consistent with the estimate for all ages, although the individual subgroup estimates were less stable.

The results of the two-pollutant models suggested that only the associations between health effects and exposure to NO_2 were relatively insensitive to the inclusion of other pollutant terms. In contrast, the health effects associated with PM_{10}, SO_2, and O_3 might be partly attributed to or modified by the effects of correlated pollutants.

With the exception of O_3, the mortality effects of the pollutants were greater in people with a lower level of education; effect estimates for all natural mortality were approximately two times higher for these people. Several pollutant effects were different in the warm and cool seasons, particularly for respiratory mortality. The respiratory mortality subgroup, however, had the smallest number of deaths, and several of the warm-season estimates for PM_{10}, SO_2, and NO_2 and respiratory mortality indicated possible protective effects, suggesting that these interactions should be interpreted with extreme caution.

The positive associations between individual pollutants and daily mortality in single-pollutant models were largely robust to differences in the degree of smoothing for time, choice of regression spline (natural or penalized), and centering of pollutant concentrations. The effects of PM_{10} were only slightly attenuated by the inclusion of longer lags for humidity and temperature; the effects of NO_2 and SO_2 were more substantially attenuated; and the effects of O_3 were unaffected.

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

	Minimum				Maximum				Mean				SD[b]			
	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	139.6	167.5	253.7	127.4	44.7	58.7	66.6	51.8	17.3	20.1	24.9	18.8
SO_2	1.5	1.4	8.4	5.3	61.2	109.3	183.3	187.8	13.2	17.8	44.7	39.2	4.8	12.1	24.2	25.3
PM_{10}	21.3	13.7	14.0	24.8	169.2	189.0	566.8	477.8	52.0	51.6	102.0	141.8	20.1	25.3	64.8	63.7
O_3	8.2	0.7	5.3	1.0	180.6	195.0	251.3	258.5	59.4	36.7	63.4	85.7	26.4	22.9	36.7	47.0
Temperature (°C)	18.7	6.9	−2.4	−2.5	33.6	33.8	34.0	35.8	28.9	23.7	17.7	17.9	1.7	4.92	8.5	9.2
Relative humidity (%)	41.0	27.0	33.0	35.0	95.0	97.0	97.0	99.0	72.8	77.9	72.9	74.0	8.3	10.0	11.4	12.5

[a] Values are $\mu g/m^3$ unless otherwise indicated.

[b] SD indicates standard deviation.

Executive Summary Table 3. Main Effect Estimates for Mortality 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.

WUHAN

In the study conducted in Wuhan, short-term increases in the concentrations of PM_{10}, NO_2, and SO_2 (but not O_3) were significantly associated with increased daily mortality due to all natural causes. Effect estimates were generally larger in people age 65 or older, particularly for those who died of cardiovascular causes. Generally, the effect estimate for respiratory deaths was higher than that of other causes. PM_{10}, NO_2, and SO_2 were also associated with increases in non-cardiopulmonary (nonaccidental) mortality. With the exception of SO_2, effect estimates for this death category were typically not larger in the older age category (age 65 or older).

In two-pollutant models, the associations of both PM_{10} and SO_2 with total all natural and cardiovascular mortality were greatly attenuated when NO_2 was included along with those pollutants. The estimated effects of NO_2 were somewhat attenuated with the inclusion of PM_{10} and also with the addition of SO_2 in the models.

Single-pollutant model results were largely robust to differences in the degree of smoothing for time in the model specifications or to the choice of regression spline (natural or penalized). The effects of PM_{10} were only slightly attenuated by the inclusion of longer lags for humidity and temperature, but the effects of NO_2 and SO_2 were greatly attenuated, often no longer showing any effect. The effects of PM_{10}, and to a lesser extent NO_2 on several causes of mortality, were larger on days in the upper 5th percentile of temperature.

BANGKOK

Short-term increases in the concentrations of PM_{10}, NO_2, SO_2, O_3, and NO were associated with increased daily all natural mortality in the Bangkok study. All pollutants were significantly associated with increases in natural, non-cardiopulmonary mortality. Effect estimates (excess risk) were largest in people age 65 or older and, except for SO_2, in those who died of cardiovascular causes and in those whose cause of death was coded as "senility." Associations between increases in the pollutant concentrations and respiratory mortality were positive (except for NO) but quite imprecise.

In two-pollutant models, the association of PM_{10} with daily total (nonaccidental) and cardiovascular mortality was relatively robust to adjustment for gaseous copollutants. The associations between the gaseous pollutants and daily mortality were generally sensitive to PM_{10} adjustment, however.

Results from sensitivity analyses demonstrated that results of single-pollutant models were largely robust to

differences in model specifications for the degree of smoothing for time, choice of regression spline (natural or penalized), and adjustment for confounders including "influenza." There was greater sensitivity to the inclusion of alternative lags for humidity and temperature on the effect on total (all natural) mortality, especially for NO_2 and NO. The effect of PM_{10} was also substantially reduced with longer-term weather lags but was still greater than zero, while those of SO_2 and O_3 were largely unaffected.

HONG KONG

Exposure to increased concentrations of individual air pollutants was associated with higher risks of mortality and hospitalization from cardiopulmonary disease.

Influenza was associated with cardiopulmonary mortality and hospital admissions at time scales ranging from 1 to multiple weeks. All three measures of influenza activity (influenza intensity, epidemic, and predominance) were associated with most respiratory and cardiovascular hospitalizations except for those due to stroke and asthma. Influenza did not confound the associations between any air pollutant and hospitalizations and mortality due to all natural causes or cardiovascular disease, but did affect the magnitude of some associations between individual pollutants and respiratory hospital admissions as well as respiratory mortality.

Residence in a neighborhood with low socioeconomic status, as defined by a social deprivation index, was associated with higher cardiovascular mortality, and the effects of increases in NO_2, SO_2, PM_{10}, and O_3 on mortality were generally consistent among the three socioeconomic groups. The investigators found little evidence to suggest that social deprivation influenced the effect of air pollution on rates of hospital admissions.

COMBINED ANALYSIS

In the Combined Analysis, which compared the results from all four cities, the investigators found that increases in all natural and cause-specific daily mortality rates were associated with air pollution, based on measurements of four different pollutants, in each of the four cities. A 10-$\mu g/m^3$ increase in PM_{10} concentration was associated with a 0.6% (95% confidence interval, 0.3–0.9) increase in mortality rate. Effects on cardiovascular and respiratory mortality were generally higher than for all natural mortality. Effect estimates varied across cities, however. For example, 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. In Hong Kong, Shanghai, and Wuhan, NO_2 effect estimates were more robust than those of other pollutants, including those of PM_{10}, in multipollutant models. In Bangkok, however, the effects of PM_{10} were less sensitive to the inclusion of other pollutants in the health models than were the effects of the other pollutants.

The investigators estimated the shape of the 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 relation over a range of ambient concentrations in excess of 100 $\mu g/m^3$, with no evidence of a threshold in all cases 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 METHODS AND ANALYSES OF THE PAPA TIME-SERIES STUDIES

CROSS-CUTTING ISSUES

Air Pollutant Monitoring and Exposure Assessment

Air Quality Data 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. No additional evaluations of the monitors using collocated instruments were conducted as part of the PAPA projects. The air quality data for the pollutants of interest were evaluated by the teams. For example, each study assessed how concentrations of individual pollutants vary between monitors and how different pollutant concentrations vary at individual monitors (as well as how the calculated averages correlate across pollutants). These correlations 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. The Common Protocol was used to exclude data and develop the daily metrics employed in the 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.

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. In the presence of sufficient spatio-temporal pollutant variation, however, results can be heavily influenced by the 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 inclusion or exclusion of individual stations will provide greater reassurance regarding the adequacy of the monitoring data (see, for example, Ivey et al. 2008).

Exposure Measurement Error The 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. The most critical component of exposure measurement 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 (Zeger et al. 2000). 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 carried out in other countries.

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 the atmospheric chemical and meteorologic determinants of air quality.

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, particularly when using multipollutant models.

Pollutants Addressed There were two potentially important pollutants whose concentrations were not regularly measured in the PAPA studies and whose 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 (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) was included in the analysis, inclusion of CO may not have had much additional impact.

Health Endpoints

Health endpoint data were obtained from the respective public health and census statistics agencies. Classification of 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), and results compare favorably with some recent U.S. estimates (Ives et al. 2009). Moreover, 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.

We recommend caution when interpreting findings in the PAPA studies for highly specific causes of death, noting that higher weight should generally 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, finer cause-of-death strata would be expected to be less so. We urge strong caution in the interpretation of any other cause-of-death categories, both because such associations are more likely to be due to chance (Ioannidis 2005) and because poor model specification can go unnoticed in these subgroups, particularly for outcomes with low event counts.

Time-Series Modeling

The general approach taken in these studies to time-series modeling (i.e., the use of overdispersed Poisson regression with smoothing functions of time and weather variables to control confounding) was broadly state of the art at the time of planning. The details of the selection of specific model terms are more controversial, however. We recommend that future studies carefully consider the following:

1. 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.
2. 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.
3. 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.
4. As was done in these studies, assessment of C–R should be included as part of the sensitivity analyses.

NO_2 Effects

A notable issue among 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. 2000b). Several possible explanations of these differences are that the NO_2 monitoring networks in both Europe and Canada use different siting criteria, that they may be more spatially dense, and that they 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 in more detail below, 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.

Single- Versus Multipollutant Models

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 in these studies, serve their intended purpose of providing pollutant effect estimates that are independent of the effects of other pollutants. While 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, there are obstacles to this interpretation, including residual confounding, and imprecise effect estimates and distortion of effects arising from highly correlated pollutant data. 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).

Sensitive Subgroups

The ER effect estimates were generally consistent across age, with a suggestion of larger effects in older ages in some cities, particularly Bangkok. While the separate city reports presented detailed subgroup analyses with multiple subgroups defined by age, season, influenza, and/or social class, given the large number of analyses and the small size of many subgroups, many of these subgroup analyses should be considered exploratory.

STUDY-SPECIFIC RESULTS

Shanghai

Outdoor air pollution in Shanghai was associated with mortality from all natural causes and cardiopulmonary-related mortality. These associations were present even at pollutant concentrations below those of the current Chinese air quality standards, and were generally unchanged by alternative model specifications. The magnitude and direction of study results were broadly consistent with estimates from meta-analyses of relevant published studies of other parts of China (Kan et al. 2005) and Asia (HEI International Scientific Oversight Committee 2004) and with meta-analyses of time-series studies conducted in North America and Europe (Stieb et al. 2002).

Although the study reported suggestive evidence that individuals with lower levels of education might experience greater health effects caused by pollutant exposure, this evidence should be interpreted cautiously, given the multiplicity of tests conducted and the conflicting evidence in the literature (O'Neill et al. 2003). There was only weak evidence of effect modification by season; given the analysis approach, residual confounding cannot be ruled out. As is common in many time-series studies, given the high correlation between PM and gaseous pollutants (NO_2 and SO_2), the ability to disentangle the individual effects of the pollutants on daily mortality was limited.

Wuhan

The Wuhan study provides estimates of the impacts of pollution on daily mortality in a city with unusually wide-ranging and occasionally extreme daily pollutant exposure levels and temperatures. Although the uncertainties are greater than is reflected in the confidence intervals, the existence of pollutant effects on mortality is a robust finding. For PM_{10}, at least, the effect estimates are consistent with those found in other cities in China, North America, and Europe.

While results on the relative toxicity of specific pollutants and the apparent modification of pollutant effects by temperature provide useful suggestive evidence, these subtle patterns are likely to be distorted by residual biases, and results should be interpreted with caution. More definitive answers to these questions will require additional research, in which Wuhan, with its unusual climate and pollutant patterns, may play an important role.

Bangkok

The excess relative risk of mortality from PM_{10} exposure in Bangkok was more than twice the size of those of the Chinese cities and, unlike in the Chinese cities, was more robust than the NO_2 association with mortality. The possible explanations for the higher estimated risks for PM_{10} remain speculative at present, however. While the authors suggested that because Bangkok has fewer monitors located close to roads, day-to-day fluctuations might reflect population exposure changes differently, this feature was not unique to Bangkok. For example, Wuhan also had few monitors close to roads. In addition, the higher excess relative risk of mortality from PM_{10} in Bangkok was estimated from a model that included a term for the "warm" season, implying a large between-season variation in the effects of air pollution. The investigators propose several explanations for this observation, including modification of effects by climatic factors and the prevalence of air conditioning, but residual confounding or other season-related bias could have influenced the results.

Moreover, the intercity variability in relative rates is not unique to Asia; even with standardized approaches, relative rates of air pollution estimated in coordinated multicity time-series studies in Europe and North America also differ from city to city, even within geographically small regions (Samet et al. 2000a; Katsouyanni et al. 2001, 2009; Bell et al. 2006). Here too, despite some efforts to identify predictors of this variability, there is similarly little understanding of its sources, apart from random variation. 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.

Hong Kong

Based on 7 years of data, the Wong study is the most extensive analysis to date of the effects of short-term exposure to air pollution and health in Hong Kong. It also presents the first comprehensive analyses in a major Asian city of the extent to which influenza activity and socioeconomic status may modify the effects of short-term exposure to air pollution on daily mortality and morbidity. Short-term increases in the levels of all the pollutants studied were associated with increases in daily mortality and hospitalization for cardiovascular and respiratory disease when weather, influenza activity, and other time-varying factors were taken into account. While the interpretation of the pollutant effects estimates from multipollutant models is challenging when pollutants are highly correlated, as discussed earlier, it would have been of interest to have at least assessed estimates from two-pollutant models for the robustness of the individual effects. The study provides little evidence that either influenza activity or socioeconomic status modified the ER of short-term air pollution on the measured health outcomes.

COMBINED ANALYSIS RESULTS

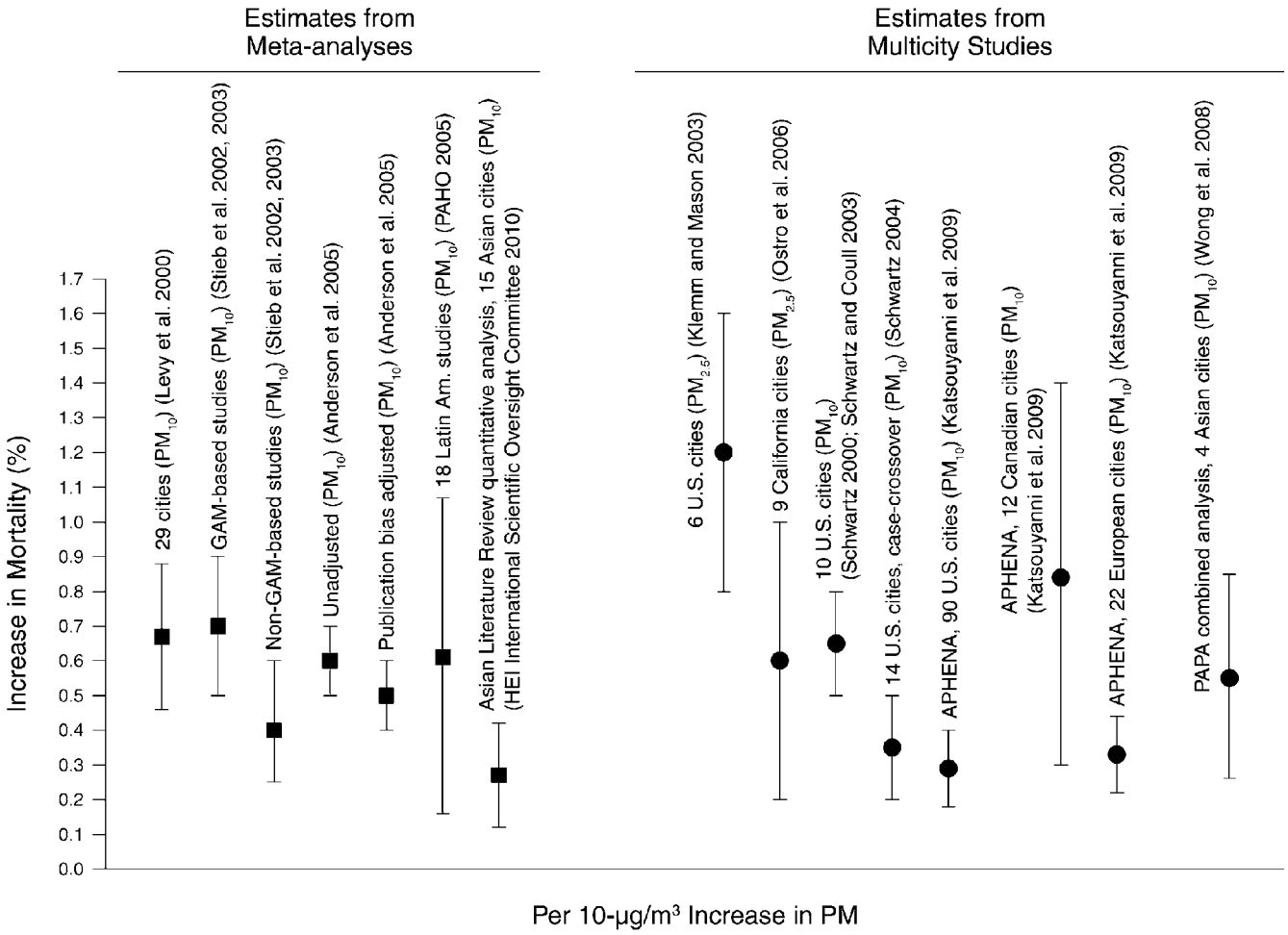
The consistency of finding that these markers of urban air pollution were associated with mortality and the qualitative robustness of these findings in sensitivity analyses suggest strongly that some aspect of air pollution has affected mortality in these cities. However, when it comes to subtler "second-order" 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), biases from 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. In addition, sensitivity analyses were reported only for the linear associations involving single pollutants, leaving greater uncertainty for the second-order results.

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 $\mu g/m^3$, but levels in the PAPA cities included daily levels several-fold higher. Despite these differences, the estimates of pollutant effect were not markedly different from those in North America and Europe (see Executive Summary Figure 1). It is, however, worth bearing in mind that the width of the confidence intervals (shown in Figure 1) indicates that these estimated effects are consistent with a wide range of true effects. In addition, 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 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 exposure and mortality 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



Executive Summary 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. (APHENA = Air Pollution and Health: A European and North American Approach; GAM = generalized additive model; $PM_{2.5}$ = particulate matter with aerodynamic diameter ≤ 2.5 µm; PM_{10} = particulate matter with aerodynamic diameter ≤ 10 µm; PAPA = Public Health and Air Pollution in Asia program).

effect estimates suggest that it remains useful to obtain locally generated estimates in some cases.

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 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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Overview

Assessing the Effects of Short-term Exposure to Air Pollution on Mortality in Four Asian Cities Using a Common Protocol

INTRODUCTION

It is estimated that approximately two-thirds of the 800,000 deaths worldwide attributed to exposure to ambient air pollution each year occur in urban Asia (WHO 2002). However, these estimates have relied largely on the extrapolation of results from research conducted outside Asia — primarily in Europe and North America (Cohen et al. 2005). In addition, given the uneven distribution of a limited set of air quality data across regions, analyses have relied on modeled rather than measured air pollution levels. Asia differs from Europe and North America in the nature of its air pollution, the conditions and magnitude of exposures to that pollution, and the health status of its populations. These differences create large uncertainties in estimating the burden of air pollution and any other effort to estimate the health impact of air pollution in Asia (Cohen et al. 2004).

The effects on air quality of recent, rapid development are clearly apparent in many of Asia's cities and industrial areas. As a result, government decision makers, the private sector, and other local stakeholders are increasingly raising concerns about the health impacts of urban air pollution. In recognition of the possibility that the nature of the ambient air pollution mix in Asia, the high levels of pollutants in some parts of the continent, and the environmental and background health conditions of the population may all contribute to differences in health outcomes between Asia and Europe and North America, there has been a steady increase in research on the health effects of air pollution in Asian cities.

TRENDS IN DEVELOPMENT

Asia is a dynamic region where increased population growth and economic development are occurring along with associated increases in industrialization and urbanization. Demographic and disease trends in rapidly developing countries of Asia suggest that *the size of the population susceptible to the adverse health impacts of air pollution is increasing*. Specifically, changes such as larger numbers of people living in cities and surviving to older ages, an increased prevalence of tobacco smoking, increasing rates of obesity, and evolving dietary patterns are leading to increases in the burden of disease from cardiovascular disease, chronic obstructive pulmonary disorder (COPD*), and cancer. Given that air pollution may contribute to the incidence of these diseases and may accelerate their progression, it is likely that the burden of disease related to air pollution in Asia will increase, even if air quality improves to some extent.

Asia is currently experiencing rapid increases in industrialization, urbanization, and vehicularization. As a result, emission trends (e.g., that resulting from changes in energy, fuel, and vehicle use), population trends (the degree of urbanization), health trends (age structure and background disease rates), and other important factors (e.g., broad changes in regulatory approaches and improvements in control technology) will influence the extent to which exposure to air pollution affects the health of the Asian population over the next several decades.

URBANIZATION

By the year 2030, Asia's urban population will make up over 50% of the world's urban population. While half of the 20 megacities (cities with a population of over 10 million) in the world are in Asia (UN-Habitat 2006), smaller towns and cities are the main drivers of urban growth. Moreover, decreases in family size and increased car ownership are also occurring along with urbanization, resulting in decreased population density and increased urban sprawl/suburbanization as populations expand beyond urban centers. Over time, this may result in increased local emissions of pollutants, as well as greater regional air pollution overall.

POPULATION HEALTH

The current burden of respiratory and cardiovascular disease is substantial in Asia, and there are indications the future burden will be as well (WHO 2002). In addition, while infectious diseases, infant and child mortality, and epidemics (Type I diseases) have been gradually declining with increased economic development, chronic diseases

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* A list of abbreviations and other terms appears at the end of this overview.

Overview Table 1. Deaths and DALYs (both in thousands) from Selected Health Outcomes by Selected WHO Region, 2004[a]

	Southeast Asia (SEAR B)[b] Population 304,830,000				East Asia (WPR B)[c] Population 1,581,888,000				World Population 6,436,826,000			
	Deaths		DALYs		Deaths		DALYs		Deaths		DALYs	
	n	%[d]	*n*	%[d]	*n*	%[d]	*n*	%[d]	*n*	%[d]	*n*	%[d]
Total	2,741		70,721		10,995		248,631		58,772		1,523,259	
Cause-specific												
Communicable diseases	659	24.0	19,644	27.8	1,432	13.0	47,417	19.1	17,971	31.0	603,993	39.7
Lower respiratory infection	168	6.1	2,405	3.4	346	3.1	5,282	2.1	4,177	7.1	94,511	6.2
Noncommunicable diseases	1,453	53.0	35,476	50.2	8,452	77.0	168,711	67.9	35,017	60.0	731,652	48.0
Malignant neoplasms	301	11.0	3,533	5.0	2,023	18.0	22,002	8.8	7,424	13.0	77,812	5.1
Trachea, bronchus, and lung cancer	51	1.9	492	0.7	425	3.9	3,980	1.6	1,323	2.3	11,766	0.8
Diabetes mellitus	81	3.0	1,556	2.2	192	1.7	4,087	1.6	1,141	1.9	19,705	1.3
Cardiovascular diseases	642	23.0	6,646	9.4	3,708	34.0	29,385	11.8	17,073	29.0	151,377	9.9
Ischemic heart disease	277	10.0	2,940	4.2	898	8.2	7,076	2.8	7,198	12.0	62,587	4.1
COPD and asthma	131	4.8	2,111	3.0	1,531	14.0	14,530	5.8	3,312	5.6	46,513	3.1
Injuries	629	23.0	15,601	22.1	1,112	10.0	32,503	13.1	5,784	9.8	187,614	12.3

[a] Abbreviations: COPD = chronic obstructive pulmonary disease; DALY = disability-adjusted life-year (years of life lost + years lived with disability); Region B = low child, low adult mortality; SEAR B = Southeast Asia Region B; WHO = World Health Organization; WPR B = Western Pacific Region B.

[b] Includes Thailand.

[c] Includes China.

[d] This percentage represents the regional proportion: (world cause-specific total/regional total) × 100%.

such as hypertension, diabetes, ischemic heart disease, and cancer (Type II, or "chronic," diseases)—especially those affecting older populations—have assumed proportionately greater importance because of changes in both age-specific death rates and the age structure of the population. Overview Table 1 summarizes the burden of disease from communicable and noncommunicable diseases in Asia, in comparison with the worldwide burden.

Cardiovascular Diseases

Previously considered "diseases of affluence," cardiovascular diseases are now seen as posing a serious health burden in developing countries (Yusuf et al. 2001; Reddy 2004; Goyal and Yusuf 2006; Abegunde et al. 2007). Several major risk factors for cardiovascular diseases are both prevalent and increasing across the region, including tobacco smoking, obesity, and dietary habits (Yusuf et al. 2001; WHO 2002; Ding and Malik 2008).

Chronic Respiratory Disease

The prevalence of chronic respiratory disease in most Asian countries is quite high, and its current contribution to mortality is substantial. COPD is predicted to increase in importance as a cause of death in Asia in the next two decades because of the past and current high prevalence of smoking (Murray and Lopez 1997; Lin et al. 2008). In 2003 COPD was estimated to affect 3% of Chinese; this percentage is expected to increase substantially, reflecting a tenfold increase in smoking prevalence between 1950 and 1990 (Zhang and Smith 2003).

Acute Lower Respiratory Infections in Children

Acute lower respiratory infections are the chief cause of death among children under 5 years worldwide, killing nearly 2 million children in 2001 (WHO 2002). A substantial fraction of the worldwide burden is experienced by populations in Asia; the annual incidence of lower respiratory infections is nearly half of the overall global annual total of 450 million cases for all ages.

ENVIRONMENTAL CONDITIONS

MAJOR SOURCES OF AIR POLLUTION

Mobile Sources: Vehicular

The three primary conditions leading to increases in the world's vehicle fleets are population growth, increased urbanization, and economic improvement. As described

earlier, trends show all three increasing in Asia and globally. Traffic-related emissions include tailpipe emissions, crankcase emissions, and road dust. Although standards for motor vehicles have been tightened, a substantial number of older, high-emitting vehicles are still operating in most of Asia, and the quality of the available fuel continues to be a barrier to either retrofitting controls on existing sources or applying controls on new ones.

Mobile Sources: Marine

Marine emissions, especially those arising from bunker fuel, include substantial amounts of particulate matter (PM) (black carbon and primary sulfate), hydrocarbons, and sulfur dioxide (SO_2). These emissions have been estimated to make substantial contributions to health impacts in coastal cities in Asia (Corbett et al. 2007).

Stationary Sources: Industrial

While some industrial sources in Asia, including coal-fired power plants, may be equipped with emission controls, many are not. Depending on its level of refinement, fuel oil contains potentially toxic materials. For example, plants may burn high-sulfur-content coals, leading to high emissions of SO_2 and PM.

Stationary Sources: Domestic

Domestic sources include boilers for commercial building heating as well as stoves for household heating and cooking. Household fuel use — including coal, agricultural residues, wood, and gas — varies by location, depending mainly on the affordability, availability, and reliability of the fuel supply. Open burning of solid waste may be a major source in cities where waste collection is not efficient.

Stationary Sources: Other

In addition to more common mobile and stationary sources, Asian cities face a wide array of diffuse, difficult-to-control sources (e.g., ambient emissions from combustion of low-quality indoor fuels and large numbers of uncontrolled small business and industries). There are also a number of noncombustion sources (e.g., construction dusts and desert sand blown from great distances), which also are associated with significant health impacts. A further challenge for Asia is the transport of air pollution from one region to the other and the challenges that poses for local jurisdictions that want to control emissions but do not have authority over the sources. This can be a problem within one country (e.g., the effects of the Pearl River Delta emissions on Hong Kong), between countries (e.g., the transport of pollutant-laden dusts from China to Japan), and globally (e.g., the transport of Asian pollutants to the west coast of the United States).

AVAILABLE EVIDENCE OF POLLUTION SOURCES

China: Beijing

Dust storms, vehicle emissions, and biomass burning are the main sources of fine particle air pollution at residential and downtown sites in Beijing (He et al. 2001). Major contributors on an annual basis include biomass burning (11%), secondary sulfates (17%), secondary nitrates (14%), coal combustion (19%), industry (6%), motor vehicle (6%), road dust (9%), and yellow dust (Song et al. 2006). Substantial seasonal variability exists; biomass combustion, traffic, and/or industrial emissions are the major contributors to organic carbon and elemental carbon in the atmosphere during summer, and coal combustion is the dominant contributor in winter (Duan et al. 2004).

China: Pearl River Delta

Air quality in the Pearl River Delta has been of particular interest as the region has rapidly (over the past two decades) developed from a primarily agricultural area to a major economic and industrial center. A recent study in Guangzhou found that vehicular emissions and coal combustion were responsible for 38% and 26% of summer ambient PM, respectively (Wang et al. 2006). Air quality in the Pearl River Delta is affected by both local sources and pollution within and beyond the region (HEI International Scientific Oversight Committee 2004). For example, concentrations of heavy metals in Hong Kong and Guangzhou have been associated with air mass originating in Northern China (Lee et al. 2007). This demonstrates the challenges of controlling local air pollution in the presence of both local and regional sources.

Thailand: Bangkok

Oanh and colleagues (Oanh et al. 2006) estimated source contributions in Bangkok for both the dry and wet seasons. They reported the contribution from mobile sources to be the greatest (35% in the dry season and 21% in the wet season), followed by biomass burning emissions (31% in the dry season and 29% in the wet season). A significant amount of secondary PM (29–36%) was also identified and quantified in this study.

AIR POLLUTANTS

Overall, estimates of emissions, as well as pollutant concentration measurements and estimates, indicate improving air quality throughout much of urban Asia. That trends in air quality have largely shown improvement during

Overview Table 2. Summary of Annual Pollutant Concentrations and Meteorologic Conditions During the Study Period

	PM_{10} (μg/m^3)				O_3 (μg/m^3)				NO_2 (μg/m^3)				SO_2 (μg/m^3)			
	Mean	SD	Min	Max	Mean	SD	Min	Max	Mean	SD	Min	Max	Mean	SD	Min	Max
Bangkok	52.0	20.1	21.3	169.2	59.4	26.4	8.2	180.6	44.7	17.3	15.8	139.6	13.2	4.8	1.5	61.2
Hong Kong	51.6	25.3	13.7	189.0	36.7	22.9	0.7	195.0	58.7	20.1	10.3	167.5	17.8	12.1	1.4	109.3
Shanghai	102.0	64.8	14.0	566.8	63.4	36.7	5.3	251.3	66.6	24.9	13.6	253.7	44.7	24.2	8.4	183.3
Wuhan	141.8	63.7	24.8	477.8	85.7	47.0	1.0	258.5	51.8	18.8	19.2	127.4	39.2	25.3	5.3	187.8

	Temperature (°C)				Relative Humidity (%)			
	Mean	SD	Min	Max	Mean	SD	Min	Max
Bangkok	28.9	1.7	18.7	33.6	72.8	8.3	41.0	95.0
Hong Kong	23.7	4.9	6.9	33.8	77.9	10.0	27.0	97.0
Shanghai	17.7	8.5	−2.4	34.0	72.9	11.4	33.0	97.0
Wuhan	17.9	9.2	−2.5	35.8	74.0	12.5	35.0	99.0

periods of dramatically increased energy use in Asia is a testament to the impact of effective air quality management, as well as improved energy efficiency. Air quality levels in Asian cities remain well above national and international standards, however, and pose a significant challenge to Asian megacities as their economies continue to grow at a record pace (HEI International Scientific Oversight Committee 2004). Overview Table 2 summarizes annual air pollutant concentrations and meteorologic conditions during the study periods in the four cities discussed in this report from the Public Health and Air Pollution in Asia (PAPA) project. Overview Table 3 shows a comparison of WHO guideline and national standard limits for PM_{10}, O_3, NO_2, and SO_2 concentrations. Overview Table 4 compares the WHO guidelines and national standard limits with the actual annual concentrations in the four PAPA cities.

PM

The aggregated annual average level of PM_{10} ($PM \leq 10$ μm in aerodynamic diameter) in Asian cities has decreased by approximately 25% from 1993 to 2005 (Clean Air Initiative for Asian Cities 2008). Although $PM_{2.5}$ ($PM \leq 2.5$ μm in aerodynamic diameter) is not yet part of most regulatory ambient air quality monitoring networks in Asia, systematic monitoring of $PM_{2.5}$ and PM_{10} has been conducted in some Asian cities (Oanh et al. 2006; Hopke et al. 2008). Reports by Oanh and colleagues and Hopke and colleagues suggest annual average $PM_{2.5}$ concentrations of generally more than 25 μg/m^3 and as high as 150 μg/m^3, with $PM_{2.5}/PM_{10}$ ratios ranging from roughly 0.4 to 0.7 in urban areas of rapidly developing countries in Asia. Based on these studies, longer-term concentrations well above

Overview Table 3. Comparison of Selected WHO Air Quality Guidelines and National Standards (μg/m^3) as of 2010[a]

	PM_{10}		O_3		NO_2			SO_2		
	24 Hour	Annual	1 Hour	8 Hour	1 Hour	24 Hour	Annual	1 Hour	24 Hour	Annual
WHO air quality guideline	50	20	—	100	200	—	40	—	20	—
US EPA	150	50	235	147	191	—	100	200	365	78
China[b]	150	100	200	—	240	120	80	500	150	60
Hong Kong	180	55	240	—	300	150	80	800	350	80
Thailand	120	50	200	140	200	—	—	785	300	100

Data from Schwela 2006; WHO 2006; U.S. EPA 2010.

[a] Dash indicates no standard.

[b] Grade II Standard, which applies to residential areas; mixed commercial/residential areas; and cultural, industrial, and rural areas.

Overview Table 4. Comparison of Selected WHO Air Quality Guidelines, National Standards, and Annual Average Concentrations During PAPA Study Period[a]

	PM_{10} (μg/m^3)		NO_2 (μg/m^3)		SO_2 (μg/m^3)	
	Annual Average Concentration	Guideline or National Standard	Annual Average Concentration	Guideline or National Standard	Annual Average Concentration	Guideline or National Standard
WHO air quality guideline		20		40		—
US (EPA NAAQS)		50		100		78
Bangkok	52	50	44.7	80	13.2	60
Hong Kong	51.6	55	58.7	80	17.8	80
Shanghai	102	100	66.6	100	44.7	78
Wuhan	141.8	100	51.8	100	39.2	78

Data from Schwela 2006; WHO 2006; U.S. EPA 2010.

[a] Abbreviations: EPA = U.S. Environmental Protection Agency; NAAQS = National Ambient Air Quality Standards; PAPA = Public Health and Air Pollution in Asia project; WHO = World Health Organization.

the WHO $PM_{2.5}$ guideline limit of 10 μg/m^3 would appear to be the norm in urban areas throughout much of Asia.

Average PM concentrations in China have declined gradually throughout the 90s, despite the steady rise in total energy consumption, partially as a result of changes in government policy. These policies have included relocating pollution sources away from population centers and the introduction of more stringent vehicle and stationary source emission standards, such as desulfurization in power plants (National Academy of Engineering and National Research Council 2008). Existing policies have not been sufficient to fully offset the emissions resulting from the significantly higher rates of growth in energy demand since 2000. As a result, population-weighted average PM concentrations in 2005 are about at the same levels as in 2000. Further, the strategy of relocating sources outside of populated areas as an approach to exposure reduction may not be sustainable if new urban areas develop adjacent to relocated facilities. PM levels have most likely been rising in many Chinese cities over the same period during which they have been falling in others. Similarly, PM levels in Southeast Asia have declined steadily during the early 1990s, stalled for a few years around the time of the Asian financial crisis starting in July 1997, and then continued their downward trajectory after 1998 (HEI International Scientific Oversight Committee 2010).

SO_2

Annual trends in air quality (1993–2005) across major Asian cities suggest roughly a 50% decline in SO_2 concentrations in average in Asian cities, with the exception of an increase in the annual average for 2005 (Clean Air Initiative for Asian Cities 2008). These reductions have occurred in spite of increasing fuel consumption. Regulations on the use of lower-sulfur-content fuels and mandating the relocation of major coal-fired power plants and industrial facilities outside of cities are likely responsible (HEI International Scientific Oversight Committee 2010). For example, in 1990, Hong Kong implemented a regulation restricting the sulfur content in fuels to a maximum of 0.5% by weight, resulting in an 80% and 41% decline in SO_2 and sulfate, respectively, in respirable particulates in the most polluted areas (Hedley et al. 2002).

NO_x

While annual average NO_x emissions in Asia are steadily increasing, nitrogen dioxide (NO_2) concentrations are experiencing a modest decline over the same period (HEI International Scientific Oversight Committee 2010). The apparent discrepancy between stable or decreasing concentration measurements in urban areas and sharply increasing emissions trends is most likely due to the fact that increased emissions are occurring throughout the Yangtze River Delta and rural areas of eastern China, where increases in concentrations are less likely to be captured by urban-oriented monitors (He et al. 2007). Indeed, remote sensing data suggest increases in NO_x concentrations, especially in both urban and rural areas of China (He et al. 2007).

Ozone

In Asia, major sources of NO_x, a precursor to ozone (O_3) production, include transportation, coal combustion in power plans, and industrial production. Although

transportation-related emissions remain a major source (32% of 2005 emissions), the contribution from power plants increased from 17% in 1980 to 35% in 2005, and they are now the leading source of NO_x emissions in Asia (Ohara et al. 2007). Emissions of non-methane volatile organic compounds (NMVOCs), another major O_3 precursor, have also steadily increased throughout Asia because of increased automobile use and the growth in production and use of chemicals, solvents, and petroleum products (Ohara et al. 2007). China and India clearly are the major emitters for NO_x, while Southeast Asia accounts for 30% of total NMVOC emissions (Ohara et al. 2007). In areas where two-stroke engines continue to be used, hydrocarbons from unburnt fuel can be a major contributor to O_3 formation.

META-ANALYSES OF LITERATURE ON HEALTH EFFECTS OF SHORTER-TERM EXPOSURE TO AIR POLLUTION IN ASIA

In 2003, during the initial phase of the PAPA program, the program's International Scientific Oversight Committee (ISOC) conducted a systematic review of the epidemiologic evidence on air pollution and health in the developing countries of Asia to help guide the development of the PAPA research program (HEI International Scientific Oversight Committee 2004). The aim of the review was to (1) provide a critical assessment of the currently available evidence to inform present decisions and (2) identify important gaps in the current evidence, so that new studies could be designed to fill these gaps and promote the development of health-based public policies. The review identified more than 130 epidemiologic studies in eight Asian countries focusing on the health effects of air pollution and found the Asian literature to be similar to the broader literature in terms of endpoints addressed and the relative frequency of study designs utilized.

This document included a critical, quantitative review — or *meta-analysis* — of a subset of time-series studies: studies that estimated the effect of shorter-term exposure to air pollution on daily mortality and hospital admissions for cardiovascular and respiratory disease. The meta-analysis estimated effects of exposure to PM that were qualitatively similar to those in the broader literature at the time (HEI International Scientific Oversight Committee 2004) — specifically, that every 10-μg/m^3 increase in PM_{10} was associated with a 0.49% increase in mortality due to all natural causes.

Since then, the number of published studies on the health effects of air pollution in Asia has continued to grow nearly exponentially; by 2007, more than 400 peer-reviewed publications on the health effects of air pollution in Asia had been identified in the literature; these are incorporated in an online database by HEI (PAPA-SAN 2008). An even more recent update (HEI International Scientific Oversight Committee 2010) also finds results that are broadly consistent with previous research.

PAPA COORDINATED TIME-SERIES STUDIES

In 2003, HEI's PAPA program released a Request for Information and Qualification for scientists interested in conducting health studies of air pollution in Asian cities. Responses suggested a range of possible studies, including time-series and panel studies of the effects of shorter-term exposure, and cross-sectional and cohort studies of the effects of longer-term exposure. After reviewing the responses, ISOC decided that a coordinated set of time-series studies in several Asian cities could further the understanding of air pollution effects in regionally relevant populations and inform extrapolation from the extensive body of existing science. The PAPA program initiated four time-series studies of the health effects of air pollution in Bangkok, Hong Kong, Shanghai, and Wuhan City.

- **Bangkok:** Panel studies in Bangkok had reported that episodes of high ambient-pollutant concentrations were associated with shorter-term increases in the frequency of respiratory symptoms (Vichit-Vadakan et al. 2001). Two time-series studies had been conducted in Bangkok (Ostro et al. 1998, 1999) to examine the associations between mortality and PM_{10} concentrations. One found that an increase of 30 μg/m^3 in ambient PM_{10} concentration was associated with a 3% to 5% increase in natural mortality (total mortality minus accidental mortality), a 7% to 20% increase in respiratory mortality, and a 2% to 5% increase in cardiovascular mortality (Ostro et al. 1998). The other found that each 10-μg/m^3 increase in PM_{10} concentration was associated with a 1% to 2% increase in natural mortality, a 1% to 2% increase in cardiovascular mortality, and a 3% to 6% increase in respiratory mortality (Ostro et al. 1999). However, neither study used systematically collected health and exposure data that had been subjected to rigorous quality control and quality assurance. Thus, concerns remained that the relationship between shorter-term exposure to pollutants and increases in mortality in Bangkok had not been adequately established.

  Principal Investigator Dr. Nuntavarn Vichit-Vadakan of Thammasat University in Thailand and her team proposed to examine the effects of PM ≤ 10 μm in aerodynamic diameter (PM_{10}) and several gaseous

pollutants — O_3, nitrogen dioxide (NO_2), and sulfur dioxide (SO_2) — on daily mortality for the years 1997 through 2003 and for all 50 districts of Bangkok.

- **Hong Kong:** Before the current investigation, a few time-series studies associating ambient air pollution with daily mortality (U.S. Congress 1977; U.S. EPA 1996) and with an increased rate of hospital admissions for respiratory and cardiovascular morbidity (Wong CM et al. 1999; Wong TW et al. 1999; Wong CM et al. 2001; Wong TW et al. 2002a, 2002b) had been conducted in Hong Kong. These studies found that NO_2, PM_{10}, SO_2, and O_3 were associated with hospital admissions for respiratory and cardiovascular diseases (Wong CM et al. 1999) and with mortality from respiratory diseases and ischemic heart disease (Wong TW et al. 2002a). In season-specific analyses, positive exposure–response relationships between NO_2, SO_2, and O_3 were found during Hong Kong's cool season but not during its warm season (Wong CM et al. 2001).

  Dr. Chit-Ming Wong of The University of Hong Kong and his team proposed to examine the shorter-term effects of air pollution on mortality and hospital admissions over the period 1996 to 2002. The confounding and modifying effects of influenza epidemics were also to be assessed. The study included the whole Hong Kong population of 6.8 million (Hong Kong SAR Government 2000).

- **Shanghai:** Before 2003, only one study of air pollution effects on daily mortality had been done in Shanghai (Kan and Chen 2003). That study included 1½ years of data and examined associations between daily mortality and PM_{10}, NO_2, and SO_2.

  Dr. Haidong Kan from the Fudan University School of Public Health in China and his team proposed in 2003 to evaluate the impact of shorter-term changes in Shanghai in ambient air concentrations of PM_{10}, NO_2, SO_2, and O_3 on daily mortality using four years of data covering the period January 1, 2001, to December 31, 2004. The target population was all residents living in the urban area of Shanghai, covering nine districts and having a population of more than 6 million.

- **Wuhan:** An association between air pollution and children's respiratory morbidity had been observed in Wuhan as part of the "Four Chinese Cities" study (Zhang et al. 2002) assessing the association between longer-term exposure to ambient and indoor air pollution and respiratory health outcomes in urban and suburban districts of Lanzhou, Chongqing, Wuhan, and Guangzhou. Before 2003, there were no shorter-term studies of air pollution conducted in Wuhan.

  Dr. Zhengmin Qian from Pennsylvania State University and his team proposed in 2003 to determine whether daily variations in ambient PM_{10} concentrations in Wuhan (with 4.5 million permanent residents in the nine urban core districts) from July 1, 2000, to June 30, 2004, were associated with daily variations in mortality due to all natural (nonaccidental) causes and cause-specific mortality.

OVERALL OBJECTIVES AND APPROACH

These studies were designed to explore key aspects of the epidemiology of exposure to air pollution in each location — issues of local as well as global relevance — including the effects of exposure at high concentrations and at high temperatures, the potential influence of influenza epidemics on the relationship between air pollution and health, and the ways in which social class might modify risks associated with air pollution.

The principal investigators, with input from the ISOC and HEI staff, developed a Common Protocol for the design and analysis of data from the four PAPA cities. The "Protocol for Coordinated Time-Series Studies of Daily Mortality in Asian Cities" (reprinted at the end of this volume) specified design criteria for data on health outcomes, air quality measurements, and meteorologic factors, as well as a general approach to the analysis of time-series data. It benefited from recent efforts to strengthen and refine methods for the analysis of time-series data and was intended to be on par methodologically with the most recent U.S. and European analyses (Health Effects Institute 2003). The Common Protocol and its application are discussed in greater detail in the HEI Review Committee's Integrated Discussion, found in Part 5 of this volume.

All four studies were conducted using the same types of administrative data on mortality and air pollution levels that were used in time-series studies throughout the world, and with methodologic rigor that matches or exceeds that of most published studies, including formal quality control in the form of detailed standard operating procedures for data collection and analysis, and external quality assurance audits of the data overseen by HEI.

SPECIFIC SCIENTIFIC CONTRIBUTIONS

Higher Concentrations

The studies provide additional information on the shape of the exposure–response function at higher concentrations.

High Temperatures

Known as the "oven city" because of its extremely hot summers, Wuhan provides an opportunity to assess how very high temperatures may modify the health effects of exposure to air pollution.

Air Pollution and Influenza

Influenza exerts tremendous health and economic costs in many areas of the world including Hong Kong. At the highest risk of morbidity due to influenza are the elderly, the very young, and those with pre-existing cardiorespiratory disease (U.S. EPA 1996). Air pollution has been linked to acute respiratory inflammation, asthma attack, COPD exacerbation, and cardiorespiratory mortality in a number of studies (Bates et al. 1990; Schwartz and Dockery 1992; Schwartz et al. 1993; Dockery and Pope 1994; Atkinson et al. 2001). Recently, an ecologic study from China suggested the presence of a positive interaction between air pollution and the severe acute respiratory syndrome virus in their associations with mortality (Cui et al. 2003). Influenza has been shown to cause some confounding in estimates of mortality due to air pollution (Braga et al. 2000), but the inclusion of a variable for influenza epidemics had only a modest effect (Braga et al. 2000) and did not remove the significance of the effect of air pollution on mortality (Samet et al. 2000a). Though previous studies of air pollution and health have been conducted in Hong Kong, none specifically investigated the potential modification of air pollution's adverse health effect by influenza epidemics.

Air Pollution, Poverty, and Health

There is emerging evidence, largely from studies in Europe and North America, that economic deprivation increases the magnitude of air-pollution–related morbidity and mortality (Krewski et al. 2000). There are two major reasons why this may be true (O'Neill et al. 2003): (1) the poor experience higher levels of air pollution; and/or (2) the poor, because of poorer nutrition, reduced access to medical care, and other factors, experience more health impact per unit of pollution exposure. In addition, air pollution could exacerbate the conditions of poverty.

The public health and social policy implications of the relations among health, air pollution, and poverty are thus likely to be important in Asia, where air pollution levels are high and many live in poverty. There have, however, been few studies of the interaction between poverty and the health effects of air pollution conducted in developing countries in general and in Asia in particular. Therefore, results from Western studies can be extrapolated only with considerable uncertainty (Cohen et al. 2004). In Asia, the composition and relative contribution of indoor and outdoor sources of exposure are likely to be very different from those in the West, and the impacts of exposure — and the influence of economic deprivation on those impacts — may be greater. The Hong Kong and Shanghai studies explore effect modification by indicators of social deprivation, focusing on social class and education, respectively.

Copollutants

The Shanghai study has a special focus on assessing the interaction of PM with gaseous copollutants. The study also assesses whether there are independent effects of PM and gaseous pollutants on mortality.

A COORDINATED APPROACH TO ANALYSIS

In the last decade, large studies have been conducted using uniform methods for assembling and analyzing data from multiple cities. Examples are the Air Pollution and Health: A European Approach (APHEA2) study (Katsouyanni et al. 2001) and the U.S. National Morbidity, Mortality, and Air Pollution Study (NMMAPS) (Samet et al. 2000a, 2000b). These multicity studies have confirmed the findings of earlier studies in single cities: daily mortality and daily hospital admissions rates are positively associated with high concentrations of PM and other pollutants, such as O_3. Multicity studies have also attempted to explain the differences (heterogeneity) among cities in relative rates of mortality associated with exposure to air pollution. For example, the APHEA2 investigators found that the mortality relative risk of PM was greater in cities with higher annual mean concentrations of NO_2 (Katsouyanni et al. 2001). In the NMMAPS study, a similar association between exposure to air pollution and mortality was observed for cities with greater annual mean concentrations of PM_{10}. In another analysis, Levy and colleagues reported that the effects of PM_{10} were greater in cities in which $PM_{2.5}$ comprised a higher proportion of PM_{10} (Levy et al. 2000). Large multicity studies also have the statistical power to explore more definitively the shape of the air pollution concentration–response function (Daniels et al. 2000; Schwartz 2000), the timing of effects related to air pollution, and the extent of life shortening (also known as "harvesting") due to air pollution (Zeger et al. 1999; Zanobetti et al. 2000; Schwartz 2001).

Coordinated multicity studies currently provide the most definitive epidemiologic evidence of the effects of shorter-term exposure and, as a result, play a central role in health impact assessment and environmental policy. While robust and consistent results have been observed in Europe and North America (Katsouyanni et al. 2001; Samet et al. 2000a, 2000b), few coordinated multicity time-series studies have been conducted elsewhere. The four PAPA studies represented here compose the first coordinated multicity analyses of air pollution and daily mortality in Asia.

PAPA COMBINED ANALYSIS

At the end of the four studies, the investigators, led by Dr. Chit-Ming Wong, undertook a Combined Analysis incorporating the data from all four cities. The results of

this Combined Analysis are included in this publication as a separate investigators' report.

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ABBREVIATIONS

APHEA	Air Pollution and Health: A European Approach
COPD	chronic obstructive pulmonary disorder
ISOC	International Scientific Oversight Committee
NMMAPS	National Morbidity, Mortality and Air Pollution Study
NMVOC	non-methane volatile organic compound
NO_2	nitrogen dioxide
NO_x	nitrogen oxides
O_3	ozone
PAPA	Public Health and Air Pollution in Asia project
PM	particulate matter
$PM_{2.5}$	particulate matter ≤ 2.5 μm in aerodynamic diameter
PM_{10}	particulate matter ≤ 10 μm in aerodynamic diameter
SO_2	sulfur dioxide

Public Health and Air Pollution in Asia (PAPA) Common Protocol

Protocol for Coordinated Time-Series Studies of Daily Mortality in Asian Cities

The PAPA Teams

PROTOCOL FOR COORDINATED TIME-SERIES STUDIES OF DAILY MORTALITY IN ASIAN CITIES

I. RATIONALE

The time-series studies of daily mortality in Asian countries are anticipated to produce a large international literature on air pollution and daily rates of mortality and hospital admissions, strengthening both that literature and the conclusions one could draw from the individual PAPA studies. Within Asia a wider breadth of such studies, especially if designed from the start to be comparable, would enhance region-specific combined analyses, providing more definitive estimates of local effects for decision makers.

Recent meta-analyses (Cohen AJ, Anderson HR, Ostro B, et al. 2004[1]; PAPA Review) suggest that proportional increases in daily mortality per 10μg/m^3 increase in PM_{10} are similar among North America, Western Europe, and developing countries. However, there are relatively few meta-analysis studies in Asia. Most studies are not geographically representative, and have taken inconsistent approaches to the definition of health outcomes and data analyses that complicate comparisons with each other and with 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, and the reasons for these differences (e.g., differences in air pollution, population characteristics).

Efforts to bring the world's data together for such analyses are underway with funding from HEI and the EC in the APHENA project. These efforts would also be strengthened by the additional variability in air pollution, climate and population characteristics that Asian studies could contribute. The results of a coordinated set of time-series studies in Asia would also inform extrapolation to Asia of the results of US and European studies of the effects of long-term exposure on mortality from chronic cardiovascular and respiratory diseases.

[1] Cohen AJ, Anderson HR, Ostro B, Pandey KD, Krzyzanowski M, Kuenzli N, Gutschmidt K, Pope CA, Romieu I, Samet JM, Smith KR. 2004. Mortality impacts of urban air pollution. In: Comparative Quantification of Health Risks: Global and Regional Burden of Disease Due to Selected Major Risk Factors (Ezzati M, Lopez AD, Rodgers A, Murray CJL, eds), vol 2. World Health Organization, Geneva, Switzerland.

II. SPECIFIC OBJECTIVES

The specific objectives of a coordinated analysis of multi-city Asian data are to:

- Develop a protocol for the design and analysis of data from multiple Asian cities;
- Develop a management framework to conduct the coordinated analysis;
- Conduct coordinated analyses of common exposures and health endpoints according to the protocol, including meta-analyses to the extent possible;
- Contribute to the international scientific discussion on the conduct and interpretation of time-series studies of the effects of short-term exposure;
- Report the results of the coordinated analyses in an HEI final report and papers in the broader peer-reviewed literature.
- Stimulate the development of routine systems for recording daily deaths and admissions for the purpose of time-series analysis.

III. ELEMENTS OF A COORDINATED STUDY

The conduct of a coordinated set of time-series studies in Asia requires the development of a detailed protocol that describes the methodology. The methodology is described under the **Materials and Methods** section below, and includes a description of the participating centers, the design of the coordinated multi-city database, the design of the coordinated analyses, and the approach that will be taken by the participating investigators to the management of the coordinated analysis.

IV. MATERIALS AND METHODS

A. PARTICIPANTS

i. Participating Research Centers

- City selection includes rationale for selection, and description of city location (geographic, degree of urbanization, etc).
- Selection of cities has been governed by interests expressed by existing investigators through responses to RFIQs issued by HEI. The responses comprised cities with the current information and research capacity to conduct analyses in the cities to which they have access, and those who expressed interest but could not proceed without development of new databases or statistical capacity.

- Description of individual studies including population, available data, and personnel are as follows:

  - **Bangkok**

  Bangkok is proposing to examine the effects of PM_{10} and several gaseous pollutants, i.e., ozone, nitrogen dioxide, and sulfur dioxide, on daily mortality for the years 1997 through 2003 and for all 50 districts of Bangkok. With the population of six to ten million people, Bangkok has an average of about 100 deaths per day. Both mortality and air quality data are computerized and readily available from the Registrar Office and the Pollution Control Department, respectively.

  The team will test for gender- and age-stratified associations with mortality. It will also investigate disease-specific associations with mortality focusing on cardiovascular and pulmonary causes. In addition, during part of the period of the proposed study, Thailand experienced a serious recession. As a result, it will be able to assess whether an air pollution-mortality association existed during this period and also whether the likely reductions in traffic during the recession were associated with lower mortality rates. The proposed research team of Thai and U.S. researchers has had considerable experience conducting time-series studies and in working in Thailand. The team is composed of Dr. Nuntavarn Vichit-Vadakan (PI), Dr. Bart Ostro, Dr. Nitaya Vajanapoom, and Dr. Wichai Akeplakorn.

  - **Hong Kong**

  In Hong Kong, time-series studies will be performed for short-term effects of air pollution on mortality and hospital admissions. The confounding and modifying effects of influenza epidemics will also be assessed. The studies will include the whole Hong Kong population of 6.8 million with an age distribution: 23% < 20; 62% 20-59 and 15% 60+ years. The period of the study spans from the year 1996 to 2002. During this period, the health outcome data, air pollution data, and other covariates are available in electronic form. In addition, there are By-Census (5 yearly) and Census data (10 yearly) within the period, thus providing socioeconomic and demographic information about the population for better interpretation of the results of the study. The investigators from the Hong Kong team include: Dr. CM Wong (PI), Prof. JSM Peiris, Prof. AJ Hedley, Dr. TQ Thach, Dr. GN Thomas and Prof. TH Lam of the University of Hong Kong as well as Prof. TW Wong of the Chinese University of Hong Kong.

- **Shanghai**

In Shanghai, a time-series study will be conducted to evaluate the association between mortality outcomes and major air pollutants, using four years of daily data (2001-2004). The target population will include all residents living in the urban area of Shanghai covering nine districts and having a population of more than six million. Daily mortality data will be extracted from the database of Shanghai Municipal Center of Disease Control and Prevention, and will be classified into deaths due to cardiovascular diseases, respiratory diseases according to the International Classification of Diseases, Revision 10. Daily air pollution data during the study period, including PM_{10}, SO_2, NO_2 and O_3, will be monitored at six fixed-site stations by the Shanghai Environmental Monitoring Center. The investigators from Shanghai team include: 1. Drs Haidong Kan (PI), Bingheng Chen, and Naiqing Zhao from Fudan University School of Public Health; 2. Drs Guixiang Song and Changyi Guo from the Shanghai Municipal Center of Disease Control and Prevention; 3. Drs Guohai Chen and Zuci Shan from the Shanghai Environmental Monitoring Center.

- **Wuhan**

This study will be conducted to determine whether daily variations in ambient PM_{10} concentrations in Wuhan during the four years from July 1, 2000 to June 30, 2004 are associated with daily variations in non-accidental mortality and with daily cause-specific mortality. Five fixed-site air-monitoring stations of the Wuhan Air Quality Automatic Monitoring System, operated by the Wuhan Center of Environmental Monitoring and certified by the U.S. Environmental Protection Agency, will provide daily mean concentrations of PM_{10}, SO_2, and NO_2. (O_3 will be provided by only two stations.) Daily mortality data from approximately 4.3 million permanent residents in the nine urban core districts of Wuhan will be available during the study period. The investigators include Dr. Zhengmin Qian (PI), Pennsylvania State University (PSU); Prof. Qingci He (Co-PI), Wuhan Academy of Environmental Science (WAES); Dr. Hung-Mo Lin, PSU; Dr. Duanping Liao, PSU; Dr. Lingli Kong, WAES; Dr. Dunjing Zhou, Wuhan Centres for Disease Prevention and Control; and Dr. Beiwei Wang, Wuhan Center of Environmental Monitoring.

ii. HEI:

- The International Scientific Oversight Committee (ISOC) acting on behalf of HEI, will oversee the conduct of the coordinated analyses via a combination of regular progress reports, periodic site visits, conference calls, and participation in HEI Annual Conferences. The ISOC and HEI staff will be available to provide support and technical advice to the investigators as needed upon request. Once the analyses have been completed a final report will be published by HEI after review by the HEI Review Committee. The Review Committee will also prepare a Commentary on the report that will be published with it.

B. DESIGN OF DATA

i. Health outcomes

The focus of the coordinated analysis will be on: 1) estimating daily mortality relative rates for all natural causes, and cardiovascular and respiratory diseases; and 2) estimating daily mortality relative rates for the causes of death categories by age and sex, as specified below. The quality of the health data will be assessed and taken into account in both analysis and interpretation of results, to the extent possible.

Causes of death	Age group	Sex	ICD-9	ICD-10	Notes
All natural causes	all ages, 0-4, 5-44, 45-64, 65+, 45+ (optional)	both sexes; stratified by male and female	001-799	A00-R99	All natural causes include all non-traumatic, non-suicidal and non-poisoning causes.
Cardio-pulmonary	all ages	both sexes	390-459, 460-519	I00-I99, J00-J98	This includes both cardiovascular and respiratory diseases rubrics.
Cardiovascular	all ages	both sexes	390-459	I00-I99	This is the whole circulatory disease rubric. However, cardiovascular is a better term and one that is commonly used. This would include *cor pulmonale* including acute and chronic pulmonary heart diseases with ICD-9 = 415-416; ICD-10 = I26-I27.
Stroke	all ages	both sexes	430-438	I60-I69	(Optional) This includes the whole cerebrovascular diseases rubric. However, calling it stroke may reduce confusion with cardiovascular. It will include a few uncommon cerebrovascular conditions not manifested as stroke.
Cardiac or heart diseases	all ages	both sexes	390-398, 410-429	I00-I09, I20-I52	(Optional)
Respiratory	all ages	both sexes	460-519	J00-J98	This is the whole respiratory disease rubric.
Lower respiratory infections	all ages	both sexes	466, 480-487	J10-J22	(Optional) This includes influenza, which at this level is usually pneumonic.
Chronic obstructive pulmonary diseases (COPD)	all ages	both sexes	490-496	J40-J47	(Optional) This is not really COPD in younger persons as it would also contain asthma (ICD-9 = 493; ICD-10 = J45-J46). This is acceptable because asthma is not a common cause of death, and because in the elderly there is little point in distinguishing between asthma and COPD.
Tuberculosis	all ages	both sexes	010-018	A15-A19	(Optional)
Control diseases: digestive and genitourinary	all ages	both sexes	520-629	K00-K93, N00-N99	(Optional) All these categories had been used as controls in an intervention study for Hong Kong with results published in Hedley et al. (Lancet 2002; 360: 1646-52).
all neoplasm excluding lung cancer	all ages	both sexes	140-161, 163-239	C00-C32, C37-D48	

We chose the above relatively wide range of categories of cause of death for this coordinated time-series study for we expect that this approach may reduce misclassification of underlying cause of death among the four study cities.

It is recognized that ICD-9 and ICD-10 coded mortality datasets will be used to compile mortality time-series, with different degree of combination by study cities. The proposed study periods and dates of change from ICD-9 to ICD-10 in the four cities are as follows:

	Bangkok	**Hong Kong**	**Shanghai**	**PSU-Wuhan**
Study period	June 1st, 1997- May 31st, 2003	January 1st, 1996-December 31st, 2002	January 1st, 2001-December 31st, 2004	July 1st, 2000-June 30th, 2004
Date of change to ICD-10	1994	January 1st, 2001	January 1st, 2002	January 1st, 2003

To facilitate conversion and checking between ICD-9 and ICD-10 codes, a supplementary information sheet for the two coding systems is provided in Annex A. Special attention from each city will be paid to recognize and identify a potential shift in mortality data around the change of ICD coding period. Utilization of ICD-9 or ICD-10 is often the decision of the respective national center for disease control (CDC) or equivalent health surveillance agency. The investigators in these four studies have no influence on the decision. In other words, they were bounded by whatever is available from their respective CDCs. Since the time series data will be compiled according to the four very wide ranges of cause-specific mortality, potential misclassification of such widely-defined causes of death is less serious a problem than analyzing smaller categories of causes of death.

ii. Assessment of quality of health outcome data

Using mortality datasets that contain individual-level information, each city will conduct descriptive analyses to obtain the frequency distributions and/or univariate distributions for all categorical variables (e.g., sex) as well as continuous variables (e.g., age). Investigators in each city will carefully check these distributions for the miscoded, missing, and out of range data. Errors, questions, and/or concerns regarding specific data points will be discussed, validated, answered, and corrected in each city.

We notice that documentation of cross validation for causes of death (causes of death from death certificates vs. true causes of death from hospital chart review) may be available locally among the four study cities. Each city should make efforts to assemble the relevant literature and government publications documenting the validity and accuracy of classified causes of death.

In addition to examining univariate distributions for all categorical and continuous variables in each city, it will be important to examine the distributions of the causes of death as well.

iii. City-specific considerations (additional efforts each city needs to take and the difficulties each city would encounter in order to implement this protocol)

- **Bangkok**
  The Bangkok team wishes to capitalize on the natural economic occurrence that occurred in 1997 by examining whether the reductions in local traffic levels during the recession impacted mortality rates and resultant concentration-response functions.

- **Hong Kong**
  The Hong Kong team will not study the optional outcome, tuberculosis, as the numbers are small; but it will study mortality due to control diseases.

- **Shanghai**
  (No specific considerations)

- **Wuhan**
  The PSU-Wuhan team will test interactions between PM_{10} exposure and low or high temperatures on daily mortality. It may also perform district stratification analyses, depending on the results of correlations among the pollutants' measurements from the five monitoring stations, as well as the results of relevant sensitivity analyses.

iv. Air Pollution
The major analytic objective is to estimate the population daily average air pollution exposure in each city. Mortality relative rate ratios will be estimated for selected particulate and gaseous components of the air pollution mixture measured daily. The same averaging times will be applied to each pollutant. The quality of the air pollution data will be evaluated for each city and taken into account in both analysis and interpretation of results via review and analysis of the data, as well as documentation of past and current QC procedures, to the extent possible.

v. Monitoring period

- **Bangkok:** June 1st, 1997 – May 31st, 2003
- **Hong Kong:** January 1st, 1996 – December 31st, 2002
- **Shanghai:** January 1st, 2001 – December 31st, 2004
- **Wuhan:** July 1st, 2000 – June 30th, 2004

vi. Air quality indicators

After discussion at the PAPA Investigators' Workshop in Bangkok, the following air quality indicators are proposed:

Pollutant	Averaging time
Sulphur dioxide (SO_2)	24-hr average
Nitrogen dioxide (NO_2)	24-hr average
Particulate matter (aerodynamic diameter of 10 micrometres or smaller) (PM_{10})	24-hr average ($PM_{2.5}$ as optional indicator where available)
Ozone (O_3)	8-hr average (from 10:00 – 18:00)
Carbon monoxide (CO)	as optional indicator where available

vii. Site selection criteria

With respect to the site selection criteria of PAPA, it is recommended to use the criteria established below:

- Basically, the sites to be selected should be representative of the exposure of population and take into account the time scale of their effects on health. The sites shall reflect the urban background level of air pollution, thereby excluding those in the direct vicinity of traffic or of industrial sources. The location shall also avoid buildings housing large emitters such as coal-, waste-, or oil-burning boilers, furnaces, and incinerators.
- The sites should not be influenced by local sources (highways, industries, open burning).
- The sites should be large enough to ensure the availability of space for monitoring, and should be located in flat space and elevated between one and 14 m above ground level. The elevated height shall be determined according to the relevant rules & regulations of each country. (Note: In the US, the monitoring site shall be elevated between 3 and 15 m above ground level according to "*40 CFR - CHAPTER I - PART 58 Probe and Monitoring Path Siting Criteria for Ambient Air Quality Monitoring".* However, European urban background sites are approximately 3m closer to the ground in general.)
- Curbside (or roadside) stations should not be included.
- The sites should be located 5 m upwind from building exhausts and at least 2 m from walls.
- A single monitor may be insufficient to assess the population exposure level in the study region. Therefore, it is recommended that a number of monitoring stations be used to reflect the exposure of the population at risk. These stations should comply with the site selection criteria described above. The correlations among the measurements from various stations will be examined.

viii. Measurement methods

The measurement methods used for air quality assessment in the four cities should comply with the relevant rules & regulations of each country. Methods of measurement for gaseous pollutants, for

example, have been fairly standardized, in that UV fluorescence for SO_2 and chemiluminescence for NO_2 are usually used. For PM_{10}, the measurement will be performed with TEOM or Beta absorption instruments in the four cities.

ix. QA/QC

Two primary documents, QAPP (Quality Assurance Program Plan) and SOP (Standard Operating Procedure), are needed for each city. Each city will obtain these documents and review them to answer data quality questions to be provided.

All four cities have a quality control programme in order to conform to each country's requirements. In Wuhan and Shanghai, air quality data should generally be collected at the monitoring stations under National Quality Control.

x. Completeness criteria

For the calculation of 24-hour average concentration of NO_2, SO_2 and PM_{10}, it is required to have at least 75% of the one-hour values on that particular day. For the 8-hour average of O_3, at least six hourly values from 10:00 to 18:00 have to be available.

If a station has more than 25% of the values missing for the whole period of analysis, the entire station should be excluded from the study.

xi. Missing data

According to the completeness criteria, there may be missing values in the air pollutant series for a small **(NB the proportion may not be "small")** proportion of the study period. In the primary analysis in stage 1, only the actual collected data (based on each day having at least 75% of the hours collected and at least 75% of daily data being available for the whole study period for each station) will be used, and missing data will not be filled in. In the sensitivity analysis, the individual study centers will use a method of centering to adjust for the effect of difference in weighting between stations, as described below.

Box No.1: Method of Centering:

Non-missing daily means are first centered for each station *i* [i.e., individual daily concentrations (X_{ij}) are subtracted by an annual station mean (X_i) for each day *j*]. The centered data from all centers are then combined and added into the annual mean of all stations (X) to form $X'_{ij} = (X_{ij} - X_i + X)$. The daily (mean) concentrations of individual pollutant are computed for analysis by taking the mean of X'_{ij} over all stations (Wong *et al.* 2001).

Wong, C.M., Ma, S., Hedley, A.J., Lam, T.H. 2001. Effect of air pollution on daily mortality in Hong Kong. *Environmental Health Perspectives 109*: 335-340.

xii. PAPA/ISOC request for basic monitoring information
In order to facilitate harmonization and comparison of the information relevant to the exposure assessments in the 4 cities of PAPA, a questionnaire was prepared and attached below as Annex B in this protocol.

xiii. Other co-variates
The analytic objective is to identify and specify for purposes of analysis a common set of time-varying potential confounders to be controlled. These comprise meteorological, social, and medical factors.

- **Meteorological covariates**
  Temperature: daily average
  Humidity: daily average RH/Dew point
- **Calendar variables**
  Special events e.g., strikes
  Dummy variables for:
  (1) Official public holidays
  (2) Days of the week
- **Use of data on Influenza/other epidemics (optional)**
  The Hong Kong team will assess the effect of influenza in its city specific study. For all cities, influenza epidemics could be defined as weekly number of respiratory mortality above the 90^{th} percentile in each year of the city, and be taken into account as one of the model improvement methods (Box No.2) in sensitivity analysis.

C. DESIGN OF ANALYSIS

A two-stage analysis of multi-city time-series data collected as part of the PAPA project is envisaged. The design of the second stage analysis will be constrained by the small number of studies that will be conducted (anywhere from 4 to 8). Nevertheless, summary estimates should be estimable at a minimum.

i. Single-city (1^{st} stage) analysis
For the core model, all of the four study centers will use the same regression model. Specifically, the procedure will involve the following:

1. Generalized Additive Model (GAM) with penalized and natural spline smoothers in R.
2. Poisson function with mortality due to cardiovascular, respiratory and all natural causes as dependent variables.
3. Smoother for time using 4-6 dfs per year of data.
4. Smoothers for the mean daily temperature and mean daily humidity using 3 dfs (whole period of study) each at a zero day lag. (Individual study centers can employ sensitivity analysis to examine other specifications for weather terms.)

5. Day of week terms (i.e, dichotomous variables for each day of the week from Monday through Saturday).
6. Dichotomous variables relevant to individual city, if available: public holidays (Hong Kong) and extreme weather conditions (Wuhan).
7. Exposure at single-day lags of 0 to 4 days, a two-day average of lags 0 and 1 and a five-day average of lags 0 to 4 (inclusive).

The results will be reported to the Technical Support Group or to a website along with statistics indicating the degree of overdispersion and a graph of the autocorrelation function. The AIC will not be used as a model selection criterion for this core model. If there is overdispersion in the variance, this will then be adjusted in a second model. If first- or second-order autocorrelation of the residuals with $|\boldsymbol{rho}|>0.1$ is present (independent of the associated p-values) based on the partial autocorrelation function (PACF), the study center will then alter (probably increase) the degrees of freedom in the smoother of time until $|\boldsymbol{rho}|\leq 0.1$.

After this base case core model is developed, other specifications, using selected lags, will be used to examine the common mortality outcomes.

Ultimately, each study center will conduct sensitivity analyses on their own data sets (as detailed). For example, some centers will want to control for flu epidemics, examine different disease aggregations, weather variables, etc. However, more harmonization of approaches to sensitivity analyses among centers will be suggested. Some analyses can and should be done by all.

For implementation of the core model development and data analysis, the following guidelines were established as shown in Box No.2 on the next page.

Box No. 2: Data Analysis Guidelines (Notes of meeting on April 18, 2005, 6:00-7:30 pm in Baltimore)

1. Criteria for adequacy in core models: When the absolute magnitude of PACF plot is less than 0.1 for the first two lag days as specified in items no.1-7 of Section C (i) above, the core model is regarded as adequate. If these criteria are not met, it is advisable to take some steps to meet these criteria, as described in item No. 2 below.
2. Improvement of model adequacy by trying the following three methods in order and selecting 1-3 methods as appropriate.
    a. Localized smoothing:
        - Identify and define dummy variables (q) for periods with extra and/or systematic variation in the residual plot
        - Define interaction variables I = q x time
        - Add smoothing function of I with certain degrees of freedom
    b. Inclusion of epidemic variables as defined in item No.6 (b) below
    c. Introduction of auto-regression terms:
        Other than localized smoothing and inclusion of influenza epidemic indicator variables, the model can be improved by introduction of auto-regression terms for lag up to 7 days. This method is particularly useful when the PACFs are consistently positive or negative for the first several lag days. This method was added after discussion with members subsequent to the Baltimore meeting.
3. Missing data handling and centering: Clarify that missing data will not be filled in. But to eliminate discrepancies between stations daily data in each center will be centered (Box No.1) on each individual overall station mean before computation of city specific daily data. However, since Shanghai does not have pollutant data for individual stations and cannot perform centering for the data, we may use simple averaging for the main analysis and use centering for the sensitivity analysis.
4. Multiple pollutant modeling: Decide to use same lag for pair of co-pollutants (PM_{10} with SO_2 and PM_{10} with NO_2) in the best model developed for all natural causes.
5. Dose-response curve: Smoothing function of each pollutant with 3-4 dfs using natural spline will be fitted for model of all natural causes of death. Y-axis should be residual after fitting of non-pollutant variables.
6. Sensitivity analysis: This should include changes in effect estimates (a) using definition of daily pollutant data with centering; (b) adjustment for epidemics defined by weekly respiratory mortality >90^{th} percentile each year; (c) varying the dfs of time smoother from 3 to 15.
7. Cross validation of results: Each team will validate the estimates derived from model of one other team.

ii. Multi-city (2^{nd}-stage) analysis

In the 1^{st} stage of the project, some common data analysis methods and guidelines have been established, in which a standardized analytical framework is applied to time-series data across 4 cities. In this way, this should have avoided some sources of biases which might have otherwise occurred and enable us to carry out a meta-analysis.

The main aim of meta-analysis is to enable the results of the studies to be visually inspected using Forest plots so that a judgment could be made about the overall direction of the evidence. We test for heterogeneity (variation between cities in individual studies) and calculate combined estimate for effect on mortality.

1. **Quality assurance:**
   Before performing meta-analysis for combined estimates of effects across cities, quality of the data collection methods and data quality have to be recorded and assessed first. The size of the data and other factors, which would affect the variation in the estimates, should also be recorded and assessed first. The factors can then be taken into account when calculating a combined estimate for an effect.

   First a standardized data format is designed (Annex C) so that the coordinator of the project could arrange validation of the study results. Data sets documented in the standardized format are sent to other groups for re-running the models or re-analysis of the data.

   Each team should also record the main effect estimates in another standardized forms (Annex D and E) and send them to the coordinator for cross-checking with results derived from re-analysis.

2. **Further analysis:**
   Single lag effects: In order to make results comparable to estimates from Poisson regression, log-relative risks (regression estimates) will be converted into a standard metric: log-relative risk associated with a 10 $\mu g/m^3$ increase in the pollutant.

3. **Co-pollutant effects:**
   In the first stage, we performed two pollutant models in which PM_{10} or NO_2 were analyzed with other pollutants in the model as part of sensitivity analysis. The aim was to see how robust each of these pollutants was to the inclusion of other pollutants. The concept is that those pollutants that are most robust in two pollutant or multi-pollutant models have a more convincing case for being closer to the causal pathway. Caution must be exercised in the interpretation of such analyses, however, because the estimates obtained tend to be less precise. This means that confidence intervals may be widened even when the point estimate is relatively unchanged.

   It is proposed to obtain combined estimates for the following

- PM_{10} single estimates
- PM_{10} controlling for NO_2
- PM_{10} controlling for O_3
- PM_{10} controlling for SO_2

4. **Meta-analysis and summary estimates:**
   Regression estimates and standard errors for studies will be used to obtain combined effect estimates based on fixed- and random-effects models (DerSimonian and Laird, 1986).

5. **Cross-validation of results and sensitivity analysis:**
   The guidelines for performing the sensitivity analysis were developed during the regional meeting held in Hong Kong on November 30th and December 1st of 2005. The notes of the meeting are outlined in Box 3 below.

Box No. 3: Notes from regional meeting held in Hong Kong on November 30, 2005 and December 1, 2005.

Cross-validation, sensitivity analysis and information for meta-analysis:

1. Cross-validate results by each other within Hong Kong-Wuhan, and Bangkok-Shanghai for
   a. All causes, 65+ with NO_2 and all lags
   b. All natural causes, all ages with PM_{10} and all lags
2. Present dose-response curve of all pollutants for all causes with 4 df over time
3. Sensitivity analysis: repeat the analysis for all-cause and cardiovascular mortality (all lags) (with city-specific "best" core model) with
   a. PM_{10} & O_3: Top 5% percentile removed;
   b. PM_{10}: Measurements restricted to ≤ 180 $\mu g/m^3$ (2 separate analyses);
   c. PM_{10}: Monitors with the two highest NO/NO_X ($NO = NO_X - NO_2$) dropped, where NO/NO_X is a good marker for auto traffic (if data are not available, drop the two stations which are highly influenced by traffic or largely from industrial sources); and
   d. PM_{10}: Only the non-rainy period adopted (the non-rainy period varies according to cities)
4. Information required for meta-analysis:
   a. In order to perform the meta-analysis, the HK team needs the attached information (spreadsheets of Annex C, D, E and F) from all the cities.
   b. Ideally, the information should be based on city-level. If a city does not have the required information by city-level, district- or provincial-level would be acceptable.
   c. It is not necessary to have up-to-date information. If not all the above-mentioned information could be obtained, the cities should provide the information available.
   d. Unavailable information should be marked "NA" in the spreadsheets.

6. **Task and Budget Justification for coordinated studies:**
   a. Basic analysis - to be performed by each individual team (Budget $20,000x4)
      - Model for health outcomes specified in common protocol
      - Display and tabulate diagnostic results
      - Tabulate effect estimates
      - Submit the data sets and the effect estimates to the coordinator
      - Validate (repeat) the models for one other team
      - Participate in data analysis and interpretation of results
      - Contribute to report writing

   b. Meta analysis - to be undertaken by Hong Kong team ($10,000)
      - Receive the original and validated results from all other teams
      - Assess the validity of the models
      - Perform pooled or metal analysis for effect estimates of 4 cities
      - Plot and tabulate results
      - Write the methods and results sections for the meta-analysis

   c. Report writing - to be undertaken by Hong Kong team ($5,000)
      - Write the introduction section with a literature review
      - Write the methods and results sections with input from b above
      - Address the issues of the coordinated studies
      - Finalize the report for the coordinated studies

   d. Communication - to be undertaken by Bangkok ($5,000)
      - Set time line
      - Facilitate tasks among teams and communication with HEI and APHENA
      - Organize and prepare materials for meetings and workshops
      - Communicate the main tasks of the coordinated studies
      - Consult (Dr Bart Ostro) for statistical methods in Tasks b and c
      - Assist in producing the final report

D. PROJECT COORDINATION AND INTERACTION AMONG INVESTIGATORS

There are two main parallel courses in the implementation of the mortality time-series study for the 4 cities, that is, the individual city study and the coordinated study among the 4 cities.

A system of coordination and communication is needed to implement the study effectively and efficiently. In terms of interaction among the investigators, web-based communication (i.e. project message board with link to e-mail notification, and webpage for updating study activities) is developed. Summary of activities and problems encountered with remedial plan of each of the project components listed below may be posted on the message board. HEI is responsible for development and maintenance of the message board. For each of the components, one member from each team acts as the site facilitator who passes on relevant messages to other team members, and regularly posts updates from the team on the message board. One member from each team will be designated the first point of contact. The critical issues for the coordinated study focus on (1) the data management, (2) data analysis, report writing and (3) dissemination of results. A steering committee is to be coordinated by the Hong Kong team to manage the coordinated study. The main functions include the following:

1. Guide the investigators during the study period when needed
2. Monitor the adherence of protocol, specifically, the aforementioned critical issues
3. Develop guideline for dissemination of results
4. Resolve any disagreement

The steering committee is composed of two to three representatives including the P.I. from each of the four teams. The main communication mechanism is web-based, i.e., e-mail mainly and chat room. The steering committee, once formed, schedules a monthly forum (to be determined) to discuss specific issues. The regional meeting as proposed by HEI may also be used to resolve any challenges and update activities.

In addition, the coordination tasks may be divided into 2 main categories, i.e., coordination on technical issues and coordination on administrative issues. It is proposed that CM Wong, Bart Ostro, Hung-Mo Lin and Dr. Naiqing Zhao take the role of coordinators in the Technical Support Group for technical matters, and Aaron Cohen and Wei Huang assume the role of administrative coordinators.

----------End of Protocol----------

Annex A: Supplementary information updated in May 2004 (not part of the protocol) – Conversion of ICD-9 to ICD-10

ICD-9		ICD-10	
Underlying cause of death	Codes	Underlying cause of death	Codes
Natural/nonaccidential	1-799	Natural/nonaccidential	A00-R99
Respiratory (RD)	460-519	Respiratory (RD)	J00-J98
Acute nasopharyngitis	460	Acute upper respiratory infections	J00-J06
Acute sinusitis	461	Acute nasopharyngitis (common cold)	J00
Acute pharyngitis	462	Acute sinusitis	J01
Acute tonsillitis	463	Acute pharyngitis	J02
Acute laryngitis and tracheitis	464	Acute tonsillitis	J03
Acute upper respiratory infections of multiple or unspecified sites	465	Acute laryngitis and tracheitis	J04
Acute bronchitis and bronchiolitis	466	Acute obstructive laryngitis and epiglottitis	J05
Deviated nasal septum	470	Acute upper respiratory infections of multiple and unspecified sites	J06
Nasal polyps	471	Influenza and pneumonia	J10-J18
Chronic pharyngitis and nasopharyngitis	472	Influenza due to identified influenza virus	J10
Chronic sinusitis	473	Influenza, virus not identified	J11
Chronic disease of tonsils and adenoids	474	Viral pneumonia, not elsewhere classified	J12
Peritonsillar abscess	475	Pneumonia due to Streptococcus pneumoniae	J13
Chronic laryngitis and laryngotracheitis	476	Pneumonia due to Haemophilus influenzae	J14
Allergic rhinitis	477	Bacterial pneumonia, not elsewhere classified	J15
Other diseases of upper respiratory tract	478	Pneumonia due to other infectious organisms, not elsewhere classified	J16
Viral pneumonia	480	Pneumonia in diseases classified elsewhere	J17
Pneumococcal pneumonia	481	Pneumonia, organism unspecified	J18
Other bacterial pneumonia	482	Other acute lower respiratory infections	J20-J22
Pneumonia due to other specified organism	483	Acute bronchitis	J20
Pneumonia in infectious diseases classified elsewhere	484	Acute bronchiolitis	J21
Bronchopneumonia, organism unspecified	485	Unspecified acute lower respiratory infection	J22
Pneumonia, organism unspecified	486	Other diseases of upper respiratory tract	J30-J39
Influenza	487	Vasomotor and allergic rhinitis	J30
Bronchitis, not specified as acute or chronic	490	Chronic rhinitis, nasopharyngitis and pharyngitis	J31
Chronic bronchitis	491	Chronic sinusitis	J32
Emphysema	492	Nasal polyp	J33
Asthma	493	Other disorders of nose and nasal sinuses	J34
Bronchiectasis	494	Chronic diseases of tonsils and adenoids	J35
Extrinsic allergic alveolitis	495	Peritonsillar abscess	J36
Chronic airway obstruction, not elsewhere classified	496	Chronic laryngitis and laryngotracheitis	J37
Coal workers' pneumoconiosis	500	Diseases of vocal cords and larynx, not elsewhere classified	J38
Asbestosis	501	Other diseases of upper respiratory tract	J39
Pneumoconiosis due to other silica or silicates	502	Chronic lower respiratory diseases	J40-J47
Pneumoconiosis due to other inorganic dust	503	Bronchitis, not specified as acute or chronic	J40
Pneumonopathy due to inhalation of other dust	504	Simple and mucopurulent chronic bronchitis	J41
Pneumoconiosis, unspecified	505	Unspecified chronic bronchitis	J42
Respiratory conditions due to chemical fumes and vapors	506	Emphysema	J43
Pneumonitis due to solids and liquids	507		
Respiratory conditions due to other and unspecified external agents	508		
Empyema	510		
Pleurisy	511		
Pneumothorax	512		
Abscess of lung and mediastinum	513		

Pulmonary congestion and hypostasis	514	Other chronic obstructive pulmonary disease	J44
Postinflammatory pulmonary fibrosis	515	Asthma	J45
Other alveolar and parietoalveolar pneumonopathy	516	Status asthmaticus	J46
Lung involvement in conditions classified elsewhere	517	Bronchiectasis	J47
Other diseases of lung	518	Lung diseases due to external agents	J60-J70
Other diseases of respiratory system	519	Coalworker's pneumoconiosis	J60
		Pneumoconiosis due to asbestos and other mineral fibres	J61
		Pneumoconiosis due to dust containing silica	J62
		Pneumoconiosis due to other inorganic dusts	J63
		Unspecified pneumoconiosis	J64
		Pneumoconiosis associated with tuberculosis	J65
		Airway disease due to specific organic dust	J66
		Hypersensitivity pneumonitis due to organic dust	J67
		Respiratory conditions due to inhalation of chemicals, gases, fumes and vapours	J68
		Pneumonitis due to solids and liquids	J69
		Respiratory conditions due to other external agents	J70
		Other respiratory diseases principally affecting the interstitium	J80-J84
		Adult respiratory distress syndrome	J80
		Pulmonary oedema	J81
		Pulmonary eosinophilia, not elsewhere classified	J82
		Other interstitial pulmonary diseases	J84
		Suppurative and necrotic conditions of lower respiratory tract	J85-J86
		Abscess of lung and mediastinum	J85
		Pyothorax	J86
		Other diseases of pleura	J90-J94
		Pleural effusion, not elsewhere classified	J90
		Pleural effusion in conditions classified elsewhere	J91
		Pleural plaque	J92
		Pneumothorax	J93
		Other pleural conditions	J94
		Other diseases of the respiratory system	J95-J99
		Postprocedural respiratory disorders, not elsewhere classified	J95
		Respiratory failure, not elsewhere classified	J96
		Other respiratory disorders	J98
		Respiratory disorders in diseases classified elsewhere	J99
Cardiovascular (CVD)	390-459	Cardiovascular (CVD)	I00-I99
Rheumatic fever without mention of heart involvement	390		
Rheumatic fever with heart involvement	391	Acute rheumatic fever	I00-I02
Rheumatic chorea	392	Rheumatic fever without mention of heart involvement	I00
Chronic rheumatic pericarditis	393	Rheumatic fever with of heart involvement	I01
Disease of mitral valve	394	Rheumatic chorea	I02

Disease of aortic valve	395
Disease of mitral and aortic valves	396
Disease of other endocardial structures	397
Other rheumatic heart disease	398
Essential hypertension	401
Hypertension heart disease	402
Hypertension renal disease	403
Hypertension heart and renal disease	404
Second hypertension	405
Acute myocardial infarction	410
Other acute and subacute forms of ischemic	411
Old myocardial infarction	412
Angina pectoris	413
Other forms of chronic ischemic heart disease	414
Acute pulmonary heart disease	415
Chronic pulmonary heart disease	416
Other diseases of pulmonary circulation	417
Acute pericarditis	420
Acute and subacute endocarditis	421
Acute myocarditis	422
Other diseases of pericardium	423
Other diseases of endocardium	424
Cardiomyopathy	425
Conduction disorders	426
Cardiac dysrhythmias	427
Heart failure	428
Ill-defined descriptions and complications of heart diseases	429
Atherosclerosis	440
Aortic aneurysm and dissection	441
Other aneurysm	442
Other peripheral vascular disease	443
Arterial embolism and thrombosis	444
Polyarteritis nodosa and allied conditions	446
Other disorders of arteries and arterioles	447
Disease of capillaries	448
Phlebitis and thrombophlebitis	451
Portal vein thrombosis	452
Other venous embolism and thrombosis	453
Varicose veins of lower extremities	454
Hemorrhoids	455
Varicose veins of other sites	456
Noninfectious disorders of lymphatic channels	457
Hypotension	458
Other disorders of circulatory system	459

Chronic rheumatic heart diseases	I05-I09
Rheumatic mitral valve diseases	I05
Rheumatic aortic valve diseases	I06
Rheumatic tricuspid valve diseases	I07
Multiple valve diseases	I08
Other rheumatic heart diseases	I09
Hypertensive diseases	I10-I15
Essential (primary) hypertension	I10
Hypertensive heart disease	I11
Hypertensive renal disease	I12
Hyptertensive heart and renal disease	I13
Secondary hypertension	I15
Ischaemic heart diseases	I20-I25
Angina pectoris	I20
Acute myocardial infarction	I21
Subsequent myocardial infarction	I22
Certain current complications following acute myocardial infarction	I23
Other acute ischaemic heart diseases	I24
Chronic ischaemic heart disease	I25
Pulmonary heart disease and diseases of pulmonary circulation	I26-I28
Pulmonary embolism	I26
Other pulmonary heart diseases	I27
Other ischaemic heart vessels	I28
Other forms of heart disease	I30-I52
Acute pericarditis	I30
Other diseases of pericardium	I31
Pericarditis in diseases classified elsewhere	I32
Acute and subacute endocarditis	I33
Nonrheumatic mitral valve disorders	I34
Nonrheumatic aortic valve disorders	I35
Nonrheumatic tricuspid valve disorders	I36
Pulmonary valve disorders	I37
Endocarditis, valve unspecified	I38
Endocarditis and heart valve disorders in diseases classified elsewhere	I39
Acute myocarditis	I40
Myocarditis in diseases classified elsewhere	I41
Cardiomyopathy	I42
Cardiomyopathy in diseases classified elsewhere	I43
Atrioventricular and left bundle-branch block	I44
Other conduction disorders	I45
Cardiac arrest	I46
Paroxysmal tachycardia	I47
Atrial fibrillation and flutter	I48
Other cardiac arrhythmias	I49
Heart failure	I50
Complications and ill-defined descriptions of heart disease	I51
Other heart disorders in diseases classified elsewhere	I52
Diseases of arteries, arterioles and capillaries	I70-I79
Atherosclerosis	I70
Aortic aneurysm and dissection	I71

		Other aneurysm	I72
		Other peripheral vascular diseases	I73
		Arterial embolism and thrombosis	I74
		Other disorders of arteries and arterioles	I77
		Diseases of capillaries	I78
		Disorders of arteries, arterioles and capillaries in diseases classified elsewhere	I79
		Diseases of veins, lymphatic vessels and lymph nodes, not elsewhere classified	I80-I89
		Phlebitis and thrombophlebitis	I80
		Portal vein thrombosis	I81
		Other venous embolism and thrombosis	I82
		Varicose veins of lower extremities	I83
		Haemorrhoids	I84
		Oesophageal varices	I85
		Varicose veins of other sites	I86
		Other disorders of veins	I87
		Nonspecific lymphadenitis	I88
		Other noninfective disorders of lymphatic vessels and lymph nodes	I89
		Other and unspecified disorders of the circulatory system	I95-I99
		Hypotension	I95
		Postprocedural disorders of circulatory system, not elsewhere classified	I97
		Other disorders of circulatory system in diseases classified elsewhere	I98
		Other and unspecified disorders of circulatory system	I99
Stroke	430-438	Stroke	I60-I69
Subarachnoid hemorrhage	430	Subarachnoid haemorrhage	I60
Intracerebral hemorrhage	431	Intracerebral haemorrhage	I61
Other and unspecified intracranial hemorrhage	432	Other nontraumatic intracranial haemorrhage	I62
Occlusion and stenosis of precerebral arteries	433	Cerebral infarction	I63
Occlusion of cerebral arteries	434	Stroke, not specified as haemorrhage or infarction	I64
Transient cerebral ischemia	435	Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction	I65
Acute, but ill-defined, cerebrovascular disease	436	Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction	I66
Other and ill-defined cerebrovascular disease	437	Other cerebrovascular diseases	I67
Late effects of cerebrovascular disease	438	Cerebrovascular disorders in diseases classified elsewhere	I68
		Sequelae of cerebrovascular disease	I69
Others	1-389, 520-799	Others	A00-H95, K00-R99

Annex B: PAPA/ISOC request for basic monitoring information

The following questionnaire was prepared as a general guideline by Dr. Kenneth Demerjian, following our discussion in Bangkok. It is designed to compile information regarding the monitors and their measurements being used by PAPA investigators.

Monitor site characterization

1) Measurement characterization
2) Monitoring network characterization

This information, which should be routinely available in the documentation of monitoring networks (and described in the current draft protocol), will be helpful in characterizing and harmonizing data quality across the study regions and in ensuring the quality of the data that you rely upon in your city. In order to not place too heavy a burden on you in starting your study, we have indicated with "*" the items in information category 1) and 2) that are of highest priority and with which you should begin. The other items are optional to be answered at the current stage, but you should try to obtain such information as much as possible during the study period. Information on monitoring network characterization is also very important for data analysis; you should try to provide this information as soon as you have obtained full access to air monitoring data in your region.

Monitor site characterization (important to determine how well sites represent population exposure)

*Site ID:
*Site Name:
*Site Address:
*Latitude: *Longitude:
*Site elevation:
*Inlet description, placement and height above ground:
*Classification (i.e., by land use: urban (commercial/residential), suburban, regional/rural, local source oriented):
*Emissions information in vicinity of site (~2 km):

Estimate of population density within site region:
Available GIS data for the site/region:
Photographs providing panoramic views:

Measurement characterization (required[#] for each measurement parameter reported – important to understand the quality of individual pollutant measurements)

*Measurement parameter: (e.g., NO_2)
*Instrumentation manufacturer:
*Principal of operation:
*Instrument time resolution and operational averaging time:
*User averaging time and averaging period:
*Date and time stamp (e.g., start and stop times, LST, GMT, required for hourly data):
*Data validation flags[a] (meaning "indicators", see example below):
*Concentration units (e.g., $\mu g/m^3$, ppm, ppb):
*Missing values reported as (e.g., -999, NA, other):
*Calibration method (e.g., NO_2 traceable certified gas standard):
*Frequency of calibration (e.g., zero and span checks once a day, multi-point calibrations once a week):

Measurement accuracy: Method of Determination:
Measurement precision: Method of Determination:
Measurement detection limit (DL, sometimes referred to as MDL, LDL, LOD):
Reporting of DLs (may be coupled to flagging scheme):
External audit frequency (e.g., once or twice a year): Date of last audit:
Completeness criteria (e.g., summarized by flagging criteria):

*SOP available: (i.e., in your possession)
*QA documentation/protocols available (i.e., in your possession):

[#]Each team will try its best to obtain the information required as much as possible, and report it if it is available.

[a]For example

	Valid value
V1	*Valid value but comprised wholly or partially of below detection limit data*
V2	*Valid estimated value*
V3	*Valid interpolated value*
V4	*Valid value despite failing to meet some QC or statistical criteria*
V5	*Valid value but qualified because of possible contamination (e.g., pollution source, laboratory contamination source)*
V6	*Valid value but qualified due to non-standard sampling conditions (e.g., instrument malfunction, sample handling)*
V7	*Valid value but set equal to the detection limit (DL) because the measured value was below the DL*
M1	*Missing value because no value is available*
M2	*Missing value because invalidated by data originator*
H1	*Historical data that have not been assessed or validated*

Monitoring network characterization (important to understanding how well a set of monitoring sites reflect regional population exposures)

There are a variety of routine data analyses that can be performed to better understand the representativeness of the monitoring site with respect to local source orientation, spatial, and temporal characteristics as well as the spatial homogeneity of measurement parameters across the monitoring network. These analyses will provide information to help access the quality of pollutant exposure estimates in the study region based on the network data. Some examples are presented below, but are certainly not all-inclusive.

In addition to basic summaries of air quality and meteorological data providing statistics on data completeness; daily, monthly or yearly mean, max, min, and std; monthly/seasonal distributions; and the identification of acute air pollution episodes and variety of standard data analyses should be considered to demonstrate spatial and temporal representativeness of the measurement sites: For example: 1) perform site-to-site correlation analyses to establish spatial homogeneity of primary and secondary pollutants and potential impacts of local source emissions; 2) analyze diurnal pattern of pollutants (those with hourly data) to assess the influence of local source emission patterns, boundary layer dynamics and the production of secondary pollutants on the individual measurement sites; and 3) analyze for week-day versus week-end differences in pollutant.

Annex C: Standardized sample of data for multi-city PAPA project

city	date	NO_2	PM_{10}	time	temp	hum	day_wk	hol	influ	all.all	all.card
HK	01/01/96	94.42910	77.94594	1	16.5	54	1	1	1	122	103
HK	02/01/96	122.78653	91.92738	2	17.5	63	2	0	1	107	86
HK	03/01/96	120.53335	125.59167	3	18.2	56	3	0	1	96	79
HK	04/01/96	59.64616	96.22601	4	17.4	59	4	0	1	107	80

Variable name:

city	BK: Bangkok, HK: Hong Kong, SH: Shanghai, WH: Wuhan
date of death	dd/mm/yy
NO_2	daily average NO_2
PM_{10}	daily average PM_{10}
temp	temperature in Celsius, 1 decimal place
hum	relative humidity in percentage
day_wk	dummy variables for days the week 1- Monday 2-Tuesday…6-Saturday; Sunday = reference
hol	public holiday 0-No 1-Yes
influ	influenza epidemics 0- No 1- Yes
all.all	all-natural cause all ages
all.card	cardiovascular diseases all ages

Notes

1. **Please specify the terms included in the CORE model for each outcome, the degrees of freedom and the order of AR used, for example in HK:**

   log(all.all) = S(time, 5 df/year) + S(temp, 3) + S(hum,3) + factor(day_wk) + hol + influ

2. **Other cities may not use the same variables as that of HK so please add/delete the appropriate variables in the database accordingly.**
3. **Code NA for missing values.**

Annex D: Log relative risk (RR) of mortality per 1 µg/m^3 for city: _____ Period: _____

Cause of mortality	Pollutant	Lag													
		0		1		2		3		4		0-1		0-4	
		log RR	std error	log RR	std error	log RR	std error	log RR	std error	log RR	std error	log RR	std error	log RR	std error
All causes All ages	NO_2 SO_2 PM_{10} O_3														
Respiratory All ages	NO_2 SO_2 PM_{10} O_3														
Cardiovascular All ages	NO_2 SO_2 PM_{10} O_3														
All causes 65+	NO_2 SO_2 PM_{10} O_3														

Note: Figures should be given in 9 decimal places

Annex E: Log relative risk (RR) of mortality per 1 μg/m^3 for PM_{10} with co-pollutant for city: _____ Period:_____

Cause of mortality	Co-Pollutant	Lag													
		0		1		2		3		4		0-1		0-4	
		log RR	std error	log RR	std error	log RR	std error	log RR	std error	log RR	std error	log RR	std error	log RR	std error
All causes All ages	$PM_{10}+NO_2$ $PM_{10}+SO_2$ $PM_{10}+O_3$														
Respiratory All ages	$PM_{10}+NO_2$ $PM_{10}+SO_2$ $PM_{10}+O_3$														
Cardiovascular All ages	$PM_{10}+NO_2$ $PM_{10}+SO_2$ $PM_{10}+O_3$														
All causes 65+	$PM_{10}+NO_2$ $PM_{10}+SO_2$ $PM_{10}+O_3$														

Note: Figures should be given in 9 decimal places

Annex F

Table 1: Selected environmental factors (Hong Kong data given as example)

Environmental factors	Hong Kong (1996)
Population (millions)	6.2
Area (Km^2)	1092
Climate:	Subtropical, with rain and tropical cyclones in the summer months
Mean January/July temperatures (deg C)	16/29
Rainfall per year	224 cm, most falling in the summer months
Topography	Peninsula with offshore islands
Life style	
Smoking rates (15 or older)	Male 26.7%; female 3.1%[1]
Regular alcohol consumers (at least once per week) (25-74 yrs)	Male 20.0%; female 2.0%[2]
Dietary intake	Energy from fat 29%; protein 18%; carbohydrate 53%[2]
	Daily cholesterol intake <300 mg[2]; male 33%, female 64%
Health Care System	Primary care services provided mainly by private sectors (85%)
	Hospital services provided mainly by public sectors (86%)
Median size of private dwellings	40.0-69.9 m^2
GNP per capita (US$)	US$24,061 per capita (1996 data)
Leading causes of death	(1996 data)
	1. Malignant neoplasms 31.3%
	2. Heart diseases 15.8%
	3. Cerebrovascular disease 10.7%
	4. Pneumonia, all forms 10.6%
	5. Injury and poisoning 5.1%

[1] Census and Statistics Department. Social data collected via the general household survey.

[2] Janus ED, Cockram CS, Fielding R, Hedley AJ, Ho P, Lam KSL, Lam TH, Lau CP, Lo M, Lo SC, Ma PL, Masarei JRL, Tai YT, Tomlinson B, Wong SP, Woo JLF. Hong Kong Cardiovascular Risk Factor Prevalence Study 1995 – 1996. Hong Kong: HK Cardiovascular Risk Factor Prevalence Study Steering Committee, 1996, 145pp. ISBN 962-8310-0

Table 2: Selected health and air pollution statistics (Hong Kong data given as example)

Health variable	Hong Kong (1996)
Population < 15 yrs and > 64 yrs	18.9%; 10.0%
Infant Mortality Rate (per 1000 live births)	4.0‰
Age standardized mortality[1]	
From all causes	3.7‰
From respiratory diseases	0.7‰
From cardiovascular diseases	0.9‰
Emergency admissions for respiratory diseases	
Age standardized rate (per 1,000 population)[1]	12.9‰
Age distribution (%)	
0-14 years	33%
15-64 years	22%
64+ years	45%
Emergency admissions for cardiovascular diseases	
Age standardized rate (per 1,000 population)	5.8‰
Age distribution (%)	
0-14 years	2%
15-64 years	37%
64+ years	61%
Sources of pollutant emissions	(1997 data including TSP)
PM_{10}	
Traffic	61.3% #
Industry	5.9% †
Power generation	32.50%
NO_x	
Traffic	41.1% #
Industry	7.5% †
Power generation	45.40%
SO_2	
Traffic	13.8% #
Industry	20.8% †
Power generation	65.40%
Composition of PM_{10}	(1996 data)
NO_3-	5.40%
NH_4^+	4.30%
C	54.00%
SO_4-	17.00%
$PM_{2.5}$ in PM_{10}	68.20%

vehicle, marine vessel, aircraft

† fuel combustion, cement plant

[1] Census and Statistics Department. Social data collected via the general household survey. Special Topics Report No. 20.

Table 3: Summary statistics of daily concentrations of pollutants (μg/m^3) and meteorological measurements

Pollutant	City	Season	Concentration (in μg/m^3)						
		(Warm/Cool)	Min.	1st Qu.	Median	Mean	3rd Qu.	Max.	SD
NO_2	HK	(50.8/ 66.3)	10.3	45.0	56.3	58.5	69.2	167.5	20.1
SO_2	HK	(19.5/16.2)	1.4	9.6	14.7	17.8	22.2	109.3	12.2
PM_{10}	HK	(40.9/62.4)	14.2	31.8	45.5	51.6	66.8	189.0	25.3
O_3	HK	(32.9/39.1)	2.0	41.0	69.0	73.7	98.0	314.0	40.5

Meteorological measure	City	Season	Meteorological						
		(Warm/Cool)	Min.	1st Qu.	Median	Mean	3rd Qu.	Max.	SD
Temperature (^{o}C)	HK	(27.2/20.1)	6.9	19.8	24.7	23.7	27.8	33.8	4.9
Humidity (%)	HK	(81.0/74.9)	27.0	74.0	79.0	77.9	84.0	97.0	10.0

HK team: warm season April – September; cool season October – March

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