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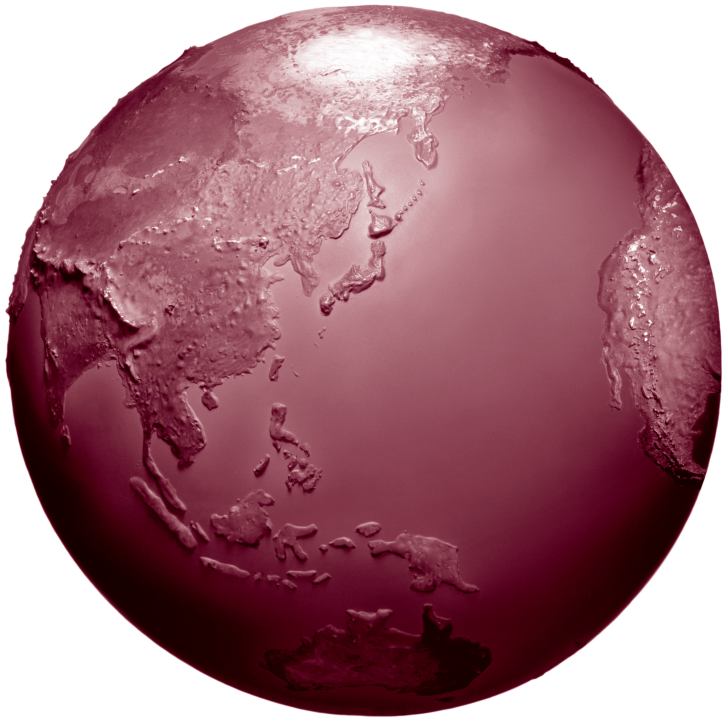

Public Health and Air Pollution in Asia (PAPA): Coordinated Studies of Short-Term Exposure to Air Pollution and Daily Mortality in Four Cities

HEI Public Health and Air Pollution in Asia Program

EXECUTIVE SUMMARY

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.

EXECUTIVE SUMMARY

Public Health and Air Pollution in Asia (PAPA): Coordinated Studies of Short-Term Exposure to Air Pollution and Daily Mortality in Four Cities

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

This Executive Summary is excerpted from 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,* comprising four individual studies by Kan et al., Qian et al., Vichit-Vadakan et al., and Wong et al., as well as a combined analysis conducted by Wong on behalf of the PAPA teams and commentaries by the HEI Review Committee. The entire report is available at *www.healtheffects.org* or from HEI.

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in 2003 to evaluate the impact of short-term changes in Shanghai in ambient air concentrations of particulate matter ≤ 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.

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.

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 μg/m^3 of pollutant at lag 0–1 day (average), calculated from the relative risk (RR) as follows: ER = (RR − 1) × 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.

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, al-though 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.

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 μg/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.

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.

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-μg/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 μg/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.

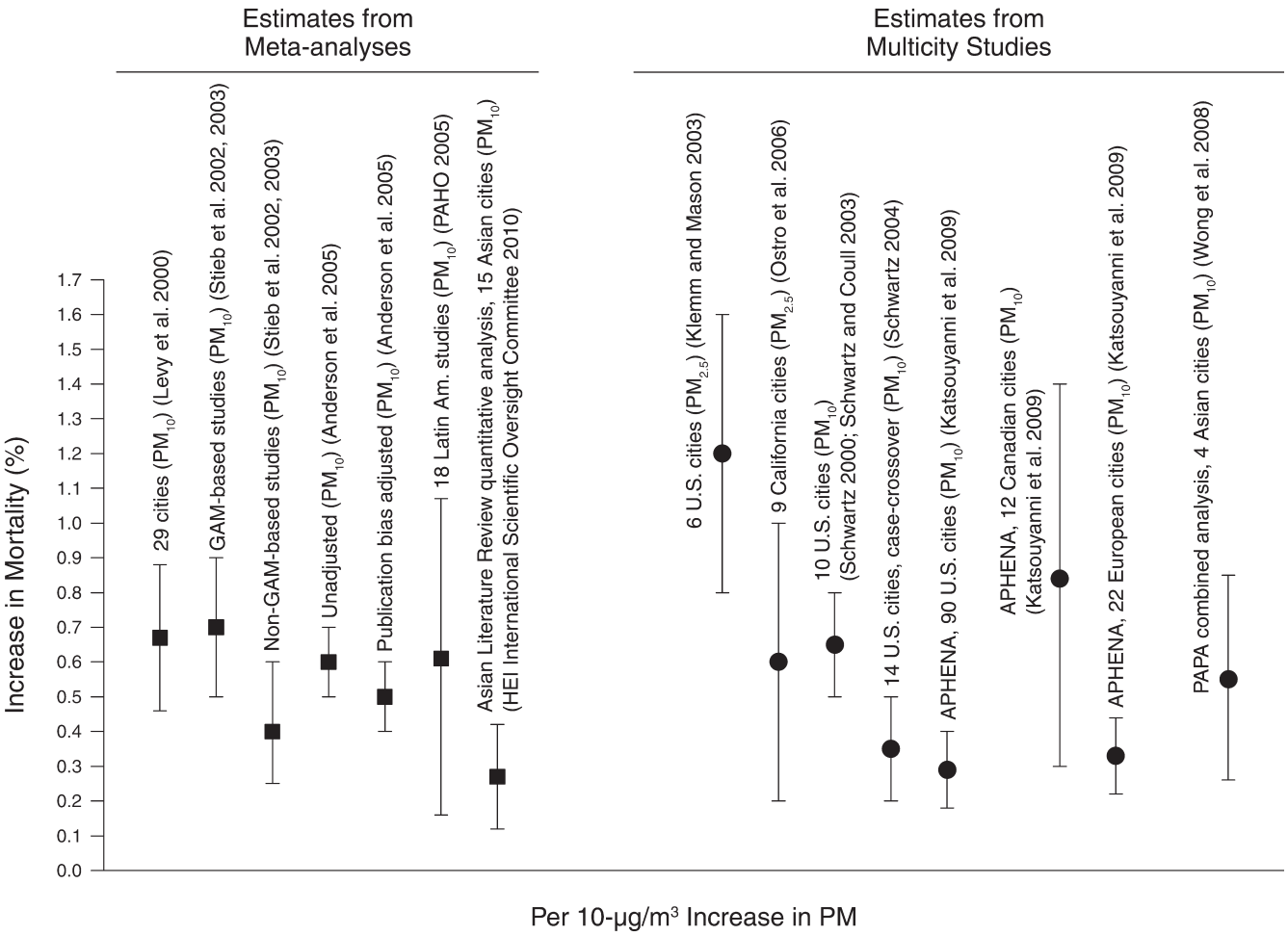
Bangkok

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.



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).

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 µg/m^3, but levels in the PAPA cities included daily levels severalfold 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 μg/m^3 in a Western city is the same as the effect of a change from 100 to 110 μg/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 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 as-sessed 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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