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Multicity Study of Air Pollution and Mortality in Latin America (the ESCALA Study)

Isabelle Romieu, Nelson Gouveia, and Luis A. Cifuentes

Brazil Investigators: Antonio Ponce de Leon, Washington Junger

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Includes a Commentary by the Institute's Health Review Committee

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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 typically 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 research programs. The ESCALA study was supported with primary funding from 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 171, *Multicity Study of Air Pollution and Mortality in Latin America (the ESCALA Study),* presents a research project funded by the Health Effects Institute and conducted by Dr. Isabelle Romieu, formerly of the Instituto Nacional de Salud Pública, Cuernavaca, Morelos, México, and her colleagues. This report contains three main sections.

The HEI Statement, prepared by staff at HEI, is a brief, nontechnical summary of the study and its findings; it also briefly describes the Health Review Committee's comments on the study.

The Investigators' Report, prepared by Romieu and colleagues, describes the scientific background, aims, methods, results, and conclusions of the study.

The Commentary is prepared by members of the Health Review Committee with the assistance of HEI staff; it places the study in a broader scientific context, points out its strengths and limitations, and discusses remaining uncertainties and implications of the study's findings for public health and future research.

This report has 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 Commentary reflects the information provided in the final version of the report.

HEI STATEMENT

Synopsis of Research Report 171

Multicity Study of Air Pollution and Mortality in Latin America (the ESCALA Study)

BACKGROUND

For nearly two decades, scientists seeking to understand the role that air pollution might play in population health effects have relied heavily on epidemiologic studies known as time-series studies. Time-series studies use information on daily changes in air pollutant concentrations and daily counts of mortality and morbidity. Although initially conducted at the individual city level, coordinated analyses across many cities have recently emerged as the tool of choice for developing more reliable and comparable estimates of the short-term effects of air pollution on health in regions around the world. HEI has a long-standing interest in these coordinated analyses; it has funded studies such as the National Morbidity, Mortality, and Air Pollution Study; Air Pollution and Health: A European and North American Approach; and Public Health and Air Pollution in Asia.

The present study, referred to hereafter by its Spanish acronym ESCALA (Estudio de Salud y Contaminación del Aire en Latinoamérica), was initiated to address underlying data and methodologic limitations in the epidemiologic literature on the health effects of air pollution in Latin America that had been identified in a 2005 review by the Pan American Health Organization. The William and Flora Hewlett Foundation, which has a strong interest in understanding air pollution and health in Latin America, provided HEI with supplemental support to address gaps in the evidence necessary to inform regulatory decisions, and in the process to build a network of health experts capable of carrying out research on air pollution in the future. The multicenter study was led by Dr. Isabelle Romieu, then at the Instituto Nacional de Salud Pública in México, in collaboration with Dr. Nelson Gouveia in Brazil and Dr. Luis Cifuentes in Chile.

APPROACH

The primary objective of the ESCALA study was to estimate the effect of daily exposures to PM_{10} (particulate matter $\leq$ 10 µm in aerodynamic diameter) and to ozone on daily mortality from several causes (all natural causes, cardiopulmonary disease, respiratory disease, cardiovascular disease, cerebrovascular–stroke, and chronic obstructive pulmonary disease) and for several age groups (all-age, $\geq$ 65 years, < 1 year, 1–4 years, 1–14 years) in nine Latin American cities, and for the region as a whole, using a common analytic framework. The nine cities were Monterrey, Toluca, and Mexico City in México; Rio de Janeiro, São Paulo, and Porto Alegre in Brazil; and Santiago, Concepción, and Temuco in Chile. Of these, three cities (Porto Alegre, Concepción, and Temuco) were excluded from the ozone analyses because of the lack of adequate ozone monitoring data.

In the first stage of the analyses, the investigators estimated the percentage change in the risk of mortality per 10-µg/m^3 increase in PM_{10} or ozone for each combination of age group and cause of death for the individual cities in each country. They followed a common protocol for fitting the widely used Poisson regression models to the air pollution and mortality time-series data in each city while controlling for other factors that might also explain the temporal patterns of mortality (e.g., temperature, humidity, season, day-of-the-week, holidays). The investigators also carried out analyses to test the sensitivity of the results to various details of the models. Ultimately, the final models used in the individual cities were chosen to fit specific patterns of mortality in those cities.

With the individual city data, the investigators also explored two-pollutant models, in which PM_{10} results were controlled for the presence of ozone

This Statement, prepared by the Health Effects Institute, summarizes a research project funded by HEI and conducted by Dr. Isabelle Romieu, at the Instituto Nacional de Salud Pública, Morelos, México, and colleagues. Research Report 171 contains both the detailed Investigators' Report and a Commentary on the study prepared by the Institute's Health Review Committee.

and vice versa; whether the association of ozone with mortality differed by warm and cold season; and whether lower socioeconomic status might increase the susceptibility of different age groups to the effects of air pollution.

In the second stage of the analyses, the investigators used two meta-analytic statistical techniques to analyze further the effect estimates from individual cities. First, meta-analysis was used to combine the individual city results, providing a weighted average effect of PM_{10} and ozone on the various categories of mortality for the region. These analyses were conducted for the all-age and the ≥ 65 age groups where sufficient data were available. Next, meta-regression was used to explore whether variables representing different aspects of city geography, density of the monitoring network, weather, age structure, smoking patterns, and health status could explain the varying effects of PM_{10} on individual categories of mortality that were observed across the nine cities. Meta-regression analyses were not conducted for ozone because data were available for only six of the nine cities.

RESULTS AND INTERPRETATION

In the individual city analyses, the ESCALA investigators found daily increases in PM_{10} to be associated with small percentage increases in daily mortality from all natural causes, cardiopulmonary disease, respiratory disease, cardiovascular disease, cerebrovascular–stroke, and chronic obstructive pulmonary disease in most of the cities studied; although the strength of the associations varied from city-to-city. In two-pollutant models, in which ozone was included as the second pollutant, the mean PM_{10} effects on mortality were not significantly different from those observed with PM_{10} alone. In some cities (for example, in Santiago) the effects appeared slightly strengthened, while in others they were slightly weaker (for example, in Mexico City).

The investigators observed a pattern of small, but positive, associations between daily increases in ozone and increases in cardiopulmonary and cardiovascular mortality in most cities except Toluca. Significant associations were least often observed for respiratory disease (only in São Paulo and Mexico City), cerebrovascular–stroke (only São Paolo), and chronic obstructive pulmonary disease (only in Mexico City). The associations were generally weaker and more variable across cities than were those for PM_{10} but were most consistently observed in the three largest cities — São Paulo, Rio de Janeiro, and Mexico City. When adjusted for PM_{10} in two-pollutant models, the estimated effects of ozone were weaker and no longer significant in most cities and for most causes of death (except in Santiago where they appeared stronger in several cases) than in models with ozone alone. The investigators reported seasonal effects of ozone on mortality; the effects were generally stronger in the warm season in São Paulo, Rio de Janeiro and Monterrey but were stronger in the cold season in Mexico City.

When the analyses were restricted to the population 65 years or older in each city, effects of both PM_{10} and ozone on mortality were, on average, slightly stronger than when all ages were included. These findings are consistent with those from other studies; however, the differences between age groups did not appear to be statistically significant in ESCALA.

The investigators also looked specifically at the effects of PM_{10} and ozone on respiratory mortality and on a subcategory of respiratory mortality, lower respiratory infection, among infants and children for the three largest cities — São Paulo, Santiago, and Mexico City. The results varied substantially among cities. With exposure to PM_{10}, significantly increased respiratory mortality was observed in infants (< 1 year) and children 1–4 years in Santiago, but not in São Paulo or Mexico City. The PM_{10}-associated risk of mortality from lower respiratory infection was significantly increased for infants only in Mexico City. For children 1–14 years, the risk of mortality from lower respiratory infection was increased in all three cities, but significantly so only in Santiago. Exposure to ozone was associated with significant increases in the risk of respiratory mortality in children 1–4 years and in the risk of mortality from lower respiratory infection in both infants and in children 1–14 years in Mexico City, but not in the other two cities. As in the analyses with adults, the seasonal effects of ozone on mortality were strongest in the cold season in Mexico City and in the warm seasons in the other two cities.

The meta-analyses pooled the results from the individual cities, providing estimates of the overall mean effects of increases in PM_{10} and ozone on mortality for the region. For PM_{10}, the investigators reported positive and statistically significant increases

in all-natural-cause (0.77%), cardiopulmonary (0.94%), respiratory (1.19%), cardiovascular (0.72%), cerebrovascular–stroke (1.10%), and chronic obstructive pulmonary disease (2.44%) mortality in the all-age group, with similar findings in individuals 65 years and older. For ozone, small positive and significant associations with increased mortality were observed for cardiopulmonary (0.23%), respiratory (0.21%), and cardiovascular (0.23%) disease mortality in the all-age group, with similar findings in the older age group. The HEI Health Review Committee concluded that the ESCALA study results were broadly consistent with findings from similar coordinated multicity time-series studies of air pollution and mortality in the United States, Canada, Europe, and Asia. The effect of PM_{10} on all-natural-cause, all-age mortality in ESCALA was also similar in magnitude to a result (0.61%) reported from a meta-analysis of 17 separate studies of Latin American cities by the Pan American Health Organization in 2005.

The HEI Health Review Committee thought that the meta-regression analyses, which were conducted to evaluate whether different city characteristics could explain differences in PM_{10} mortality in adults, were appropriate and well-done. However, it cautioned that conclusions identifying some city characteristics as "significant" predictors of the size of a city's PM–mortality coefficients should be considered suggestive rather than definitive. These few associations emerged from a large number of predictors considered and therefore might have arisen by chance. They also did not fit an obvious causative pattern. The Committee could not rule out the possibility that unidentified factors that could not be accounted for in the analyses might have affected the results in individual cities differently, thus causing spurious evidence of effect modification.

The investigators' evaluation of whether socioeconomic status could modify the adverse effects of PM_{10} and ozone on mortality was also well-conducted and an important facet of the study. The investigators reported patterns of higher risks of respiratory mortality among people with low socioeconomic status and higher risks of cardiovascular mortality among people with medium or high socioeconomic status, but these patterns were not consistently observed from city to city. Despite the ESCALA investigators' careful efforts, the Committee concluded that their analyses did not provide convincing evidence on this issue.

The HEI Health Review Committee concluded that the most robust estimates of the effect of air pollution on health were those for the larger cities, the larger age groups, and the causes of mortality with the larger number of deaths. For PM_{10}, this means greater confidence might be placed in the relative risks for all-natural-cause, all-age mortality (in particular for the Brazilian and Mexican cities) and for cardiovascular and cardiopulmonary mortality in the all-age and the $\geq$ 65 groups. For ozone, the more robust associations were also with all-natural-cause, all-age mortality and with cardiovascular and cardiopulmonary mortality in both the all-age and the $\geq$ 65 age groups. The high sensitivity of the main results to model choice for many of the other causes of death and age groups, particularly among children, suggests that caution should be exercised in their interpretation.

CONCLUSIONS

The ESCALA study is an important extension of coordinated multicity time-series methods to the study of the effects of ambient PM_{10} and ozone in a region of the world where these methods had not yet been applied — Latin America. The ESCALA investigators found small but significant effects of daily exposure to PM_{10} and ozone on daily mortality that were largely similar to those from other coordinated multi-city studies around the world. The relatively high degree of rigor used in carrying out ESCALA, with common protocols for data collection and analysis, and sensitivity analyses to test alternative model assumptions, should provide policymakers with reasonable assurance that the main findings of a relationship between air pollution and common types of mortality have a solid foundation and are the most reliable estimates for the region to date. Given the potential uncertainties associated with interpretation of specific results, caution should be exercised in the interpretation of the more complex patterns observed in these studies such as the patterns of results between cities, between socioeconomic status levels, and in the degree of effect modification by different covariates in the meta-regression analyses. The ESCALA investigators have established an important methodologic foundation for future work in Latin America. The ESCALA study could be readily expanded to include other cities in Latin America, used to explore alternative analytic methods, and improved upon by taking into account both the recommendations of the HEI Review Committee and the many insights gained by the investigators in the course of the study.

INVESTIGATORS' REPORT

Multicity Study of Air Pollution and Mortality in Latin America (the ESCALA Study)

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ABSTRACT

INTRODUCTION

The ESCALA* project (Estudio de Salud y Contaminación del Aire en Latinoamérica) is an HEI-funded study that aims to examine the association between exposure to outdoor air pollution and mortality in nine Latin American cities, using a common analytic framework to obtain comparable and updated information on the effects of air pollution on several causes of death in different age groups.

This report summarizes the work conducted between 2006 and 2009, describes the methodologic issues addressed during project development, and presents city-specific results of meta-analyses and meta-regression analyses.

METHODS

The ESCALA project involved three teams of investigators responsible for collection and analysis of city-specific air pollution and mortality data from three different countries. The teams designed five different protocols to standardize the methods of data collection and analysis that would be used to evaluate the effects of air pollution on mortality (see Appendices B–F). By following the same protocols, the investigators could directly compare the results among cities.

The analysis was conducted in two stages. The first stage included analyses of all-natural-cause and cause-specific mortality related to particulate matter $\leq$ 10 µm in aerodynamic diameter (PM_{10}) and to ozone (O_3) in cities of Brazil, Chile, and México. Analyses for PM_{10} and O_3 were also stratified by age group and O_3 analyses were stratified by season.

Generalized linear models (GLM) in Poisson regression were used to fit the time-series data. Time trends and seasonality were modeled using natural splines with 3, 6, 9, or 12 degrees of freedom (*df*) per year. Temperature and humidity were also modeled using natural splines, initially with 3 or 6 *df*, and then with degrees of freedom chosen on the basis of residual diagnostics (i.e., partial autocorrelation function [PACF], periodograms, and a Q-Q plot) (Appendix H, available on the HEI Web site). Indicator variables for day-of-week and holidays were used to account for short-term cyclic fluctuations. To assess the association between exposure to air pollution and risk of death, the PM_{10} and O_3 data were fit using distributed lag models (DLMs). These models are based on findings indicating that the health effects associated with air pollutant concentrations on a given day may accumulate over several subsequent days. Each DLM measured the cumulative effect of a pollutant concentration on a given day (day 0) and that day's contribution to the effect of that pollutant on multiple subsequent (lagged) days. For this study, exposure lags of up to 3, 5, and 10 days were explored. However, only the results of the DLMs using a 3-day lag (DLM 0–3) are presented in this report because we found a decreasing association with mortality in various

This Investigators' Report is one part of Health Effects Institute Research Report 171, which also includes a Commentary by the Health Review Committee and an HEI Statement about the research project. Correspondence concerning the Investigators' Report may be addressed to Dr. Isabelle Romieu, Head, Section of Nutrition and Metabolism, International Agency for Research on Cancer, 150, cours Albert Thomas, F-69372 Lyon Cedex 08, France.

The ESCALA study was supported with primary funding from the William and Flora Hewlett Foundation. The contents of this document have not been reviewed by private party institutions, including those that support the Health Effects Institute; therefore, it may not reflect the views or policies of these parties, and no endorsement by them should be inferred.

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

age-cause groups for increasing lag effects from 3 to 5 days for both PM_{10} and O_3. The potential modifying effect of socioeconomic status (SES) on the association of PM_{10} or O_3 concentration and mortality was also explored in four cities: Mexico City, Rio de Janeiro, São Paulo, and Santiago. The methodology for developing a common SES index is presented in the report.

The second stage included meta-analyses and meta-regression. During this stage, the associations between mortality and air pollution were compared among cities to evaluate the presence of heterogeneity and to explore city-level variables that might explain this heterogeneity. Meta-analyses were conducted to combine mortality effect estimates across cities and to evaluate the presence of heterogeneity among city results, whereas meta-regression models were used to explore variables that might explain the heterogeneity among cities in mortality risks associated with exposures to PM_{10} (but not to O_3).

RESULTS

The results of the mortality analyses are presented as risk percent changes (RPC) with a 95% confidence interval (CI). RPC is the increase in mortality risk associated with an increase of 10 $\mu g/m^3$ in the 24-hour average concentration of PM_{10} or in the daily maximum 8-hour moving average concentration of O_3. Most of the results for PM_{10} were positive and statistically significant, showing an increased risk of mortality with increased ambient concentrations. Results for O_3 also showed a statistically significant increase in mortality in the cities with available data.

With the distributed lag model, DLM 0–3, PM_{10} ambient concentrations were associated with an increased risk of mortality in all cities except Concepción and Temuco. In Mexico City and Santiago the RPC and 95% CIs were 1.02% (0.87 to 1.17) and 0.48% (0.35 to 0.61), respectively. PM_{10} was also significantly associated with increased mortality from cardiopulmonary, respiratory, cardiovascular, cerebrovascular–stroke, and chronic obstructive lung diseases (COPD) in most cities. The few nonsignificant effects generally were observed in the smallest cities (Concepción, Temuco, and Toluca).

The percentage increases in mortality associated with ambient O_3 concentrations were smaller than for those associated with PM_{10}. All-natural-cause mortality was significantly related to O_3 in Mexico City, Monterrey, São Paulo and Rio de Janeiro. Increased mortality risks for some specific causes were also observed in these cities and in Santiago. In the analyses stratified by season, different patterns in mortality and O_3 were observed for cold and warm seasons. Risk estimates for the warm season were larger and significant for several causes of death in São Paulo and Rio de Janeiro. Risk estimates for the cold season were larger and significant for some causes of death in Mexico City, Monterrey, and Toluca.

In an analysis stratified by SES, the all-natural-cause mortality risk in Mexico City was larger for people with a medium SES; however we observed that the risk of mortality related to respiratory causes was larger among people with a low SES, while the risk of mortality related to cardiovascular and cerebrovascular–stroke causes was larger among people with medium or high SES. In São Paulo, the all-natural-cause mortality risk was larger in people with a high SES, while in Rio de Janeiro the all-natural-cause mortality risk was larger in people with a low SES. In both Brazilian cities, the risks of mortality were larger for respiratory causes, especially for the low- and high-SES groups. In Santiago, all-natural-cause mortality risk did not vary with level of SES; however, people with a low SES had a higher respiratory mortality risk, particularly for COPD. People with a medium SES had larger risks of mortality from cardiovascular and cerebrovascular–stroke disease.

The effect of ambient PM_{10} concentrations on infant and child mortality from respiratory causes and lower respiratory infection (LRI) was studied only for Mexico City, Santiago, and São Paulo. Significant increased mortality risk from these causes was observed in both Santiago (in infants and older children) and Mexico City (only in infants). For O_3, an increased mortality risk was observed in Mexico City (in infants and older children) and in São Paulo (only in infants during the warm season).

The results of the meta-analyses confirmed the positive and statistically significant association between PM_{10} and all-natural-cause mortality (RPC = 0.77% [95% CI: 0.60 to 1.00]) using the random-effects model. For mortality from specific causes, the percentage increase in mortality ranged from 0.72% (0.54 to 0.89) for cardiovascular disease to 2.44% (1.36 to 3.59) for COPD, also using the random-effects model. For O_3, significant positive associations were observed using the random-effects model for some causes, but not for all natural causes or for respiratory diseases in people 65 years or older ($\geq$ 65 years), and not for COPD and cerebrovascular–stroke in the all-age and the $\geq$ 65 age groups. The percentage increase in all-natural-cause mortality was 0.16% (−0.02 to 0.33). In the meta-regression analyses, variables that best explained heterogeneity in mortality risks among cities were the mean average of temperature in the warm season, population percentage of infants (< 1 year), population percentage of children at least 1 year old but < 5 years (i.e., 1–4 years), population percentage of people $\geq$ 65 years, geographic density of PM_{10} monitors, annual average concentrations of PM_{10}, and mortality rates for lung cancer.

CONCLUSIONS

The ESCALA project was undertaken to obtain information for assessing the effects of air pollutants on mortality in Latin America, where large populations are exposed to relatively high levels of ambient air pollution. An important goal was to provide evidence that could inform policies for controlling air pollution in Latin America. This project included the development of standardized protocols for data collection and for statistical analyses as well as statistical analytic programs (routines developed in R by the ESCALA team) to insure comparability of results. The analytic approach and statistical programming developed within this project should be of value for researchers carrying out single-city analyses and should facilitate the inclusion of additional Latin American cities within the ESCALA multicity project.

Our analyses confirm what has been observed in other parts of the world regarding the effects of ambient PM_{10} and O_3 concentrations on daily mortality. They also suggest that SES plays a role in the susceptibility of a population to air pollution; people with a lower SES appeared to have an increased risk of death from respiratory causes, particularly COPD. Compared with the general population, infants and young children appeared to be more susceptible to both PM_{10} and O_3, although an increased risk of mortality was not observed in these age groups in all cities. Estimates of air pollution effects provided by the ESCALA study are currently being used for risk assessment analyses that support air pollution control programs in Latin America.

INTRODUCTION

Latin America is the most highly urbanized region in the developing world. In 1950, 42% of the region's population was living in urban areas (Cohen 2004). By 2000 this figure reached about 75% and is expected to grow to 89% by 2030 (Cohen 2004). Together, São Paulo, Mexico City, Rio de Janeiro, and Santiago host almost 34 million people (National Institute of Statistics, Chile [INE] 2002; Brazilian Institute of Geography and Statistics [IBGE] 2011; National Institute of Statistics, Geography and Informatics, México [INEGI] 2011).

A common problem in urbanized conglomerations is the high level of ambient air pollution associated with rapid and unplanned urbanization. In parallel with the growth of large urban areas, the number of vehicles, and consequently vehicular exhaust, rapidly increases. Between 1994 and 2002, the vehicular fleet increased by 52.5% in México (Secretaria del Medio Ambiente y Recursos Naturales — SEMARNAT 2002 [Secretary of Environment and Natural Resources]), by 37.1% in Brazil, and by 13.6% in Chile (United Nations 1995). The profile of the fleet is different in each country. For example, in Mexico City 95% of the vehicles use gasoline, 4% diesel, and 1% liquefied petroleum gas (Gobierno del Distrito Federal–Secretaría del Medio Ambiente 2008). In Brazil about 4% of the registered light duty vehicles run on diesel, while in Chile this figure is around 15%. Moreover, 70% of the light duty vehicles sold in Brazil in 2005 had flex-fuel engines that use any mix of ethanol and gasoline (United Nations Environment Programme 2010). Despite the implementation of control measures in major cities, high emission levels have occurred together with frequent episodes of air pollution.

Outdoor particulate matter (PM) air pollution is estimated to be responsible for about 1% of the acute respiratory infection mortality in children from urban areas worldwide (Cohen 2005). In Latin America, children under 5 represent close to 9% of the population. 75% of them reside in urban settings where acute respiratory infection is one of the principal causes of childhood morbidity and mortality.

Topography and climate also play an important role in the high air pollution levels observed in the major cities of Latin America. Mexico City and Santiago are each located in a valley surrounded by mountains. Mexico City, Toluca, Monterrey, Santiago, and São Paulo are all located at more than 500 m above sea level and frequently have thermal inversions that keep air pollution from dispersing.

Considering the high levels of air pollution in and around these cities, the large population of children, the wide socioeconomic disparities, the scarcity of well-designed local studies, and the lack of comparable health effect estimates of air pollutants among cities, there was a great need for a large time-series study of the major cities in Latin America.

ESCALA is a project funded by HEI and carried out by an international team of investigators from several institutions in Latin America. The ESCALA project brought together three groups of investigators from three countries, each group headed by an investigator who had previously conducted time-series analyses to evaluate the effects of air pollution on health: Brazil (Nelson Gouveia), Chile (Luis Cifuentes), and México (Isabelle Romieu).

Although a large number of epidemiologic studies have shown associations between air pollution levels and adverse health effects, ESCALA contributes to the current understanding of the effects of PM_{10} and O_3 on mortality in nine Latin American cities by using a standardized approach and a large data set that includes nine years of daily data for an area with a total population of 34,666,067 million (INEGI 2011, INE 2002, IBGE 2011).

The project was developed in two stages. In the first stage, data from each city were analyzed separately using a

standard protocol. In the second stage, pooled results were obtained to explore the variations in the estimates across cities.

One of the study objectives was to determine whether some socioeconomic groups within the population of a city are more susceptible to the effects of air pollution than others. Therefore, in the first stage the feasibility of constructing an index to evaluate the potential role of SES as a modifier of the effect of air pollution on mortality was also evaluated. We present results of the effect of air pollution on mortality by SES for the largest cities in the project — Mexico City, São Paulo, Rio de Janeiro, and Santiago.

SPECIFIC AIMS

The primary goal of this project was to obtain comparable and updated information on the effects of air pollution on several causes of mortality for different age groups. The investigators developed and used a common analytic framework to examine the association between exposure to outdoor air pollution and mortality in several Latin American cities. An important focus of this project was to examine in detail the effect of such exposures on the mortality rates of specific subgroups of the population that are considered to be most vulnerable. The primary objectives included:

- Develop a common protocol for the design and analysis of time-series data from multiple Latin American cities that would be followed by all investigators involved in the project.
- Conduct a coordinated analysis to examine the effects of exposure to outdoor air pollution on mortality from various causes and in subgroups defined by age in different Latin American cities.
- Assess the effects of air pollution in sensitive populations such as infants, young children, and people 65 years or older.
- Conduct meta-analyses and meta-regression analyses of mortality results from all of the cities in the study.
- Contribute to the international scientific discussion about the conduct and interpretation of time-series studies that report the effects of short-term exposure to air pollution.
- Report the results of these coordinated analyses in the broader peer-reviewed literature.
- Provide relevant information to decision makers in Latin America to support prevention and control strategies for air pollution.

A secondary objective was:

- Explore the feasibility of evaluating the role of SES as a potential modifier of the effect of air pollution on mortality, using the same SES indicators in México, Brazil, and Chile.

METHODS

STUDY DESIGN AND AREA

A multicity time-series study of air pollution and mortality was conducted to assess the effects of short-term exposure to PM_{10} and O_3 on daily mortality in nine cities from three countries including:

- Brazil: São Paulo, Rio de Janeiro, and Porto Alegre;
- Chile: Santiago, Temuco, and Concepción;
- México: Mexico City, Monterrey, and Toluca.

These cities, described in Table 1 and Figure 1, were included because of their large populations (and consequently, large numbers of deaths per year) and the quality of their air pollution data. The HEI Research Committee and the investigators agreed that the analyses of cause-specific mortality in young age groups with a small number of events would include data only from the largest cities (Mexico City, Santiago, São Paulo, and Rio de Janeiro).

DATABASES

Daily air pollution and mortality data were collected from 1997 to 2005, according to data availability in this period for the different cities. After the data sets were completed, an extensive data review was undertaken to check data quality in each country. The team established two protocols that would be used by all three groups of investigators: Quality Assurance and Quality Control (QA/QC) Mortality Data Protocol (Appendix B) and QA/QC Air Pollution Protocol (Appendix C).

Because the data were collected from various sources, a relational database was assembled and stored on a server at the Instituto Nacional de Salud Pública (INSP) in México. Both the original and the processed data were available to the researchers through an internet interface. The ESCALA data were derived from sources described in the next sections.

Mortality Data

Daily mortality for several causes and for several age groups were considered in this study (Table 2). A relatively wide range of cause-of-death categories were chosen to reduce misclassification of the underlying causes of death. The data from earlier years were codified using the *International Classification of Diseases, Revision 9* (ICD-9).

Table 1. Characteristics of the Nine Cities

	Population	Elevation (m)[a]	Seasonal Mean Average Temperatures (°C)		Annual Mean Average Levels	
			Warm	Cold	Temperature (°C)	Humidity (%)
Brazil						
São Paulo	10,886,518	750	21.5	18.3	19.9	78
Rio de Janeiro	6,093,472	40	26.1	23.1	24.6	78
Porto Alegre	1,420,667	10	23.0	16.9	19.9	77
Chile						
Santiago	4,985,893	500 to 750	19	13	16.0	63.0
Temuco	363,964	120	14	9	11.8	78.8
Concepción	593,111	12	15	11	13.3	74.8
México						
Mexico City	8,720,916	2240	20.6	12	17	33
Monterrey	1,133,814	537	28.0	18.5	24	56
Toluca[b]	467,712	2668	15.0	9.0	13.5	35

[a] Meters above sea level.

[b] Toluca is located at 2668 meters above sea level, which makes it cold all year round with temperatures showing a large variability (data not shown).

At different times during the study period, government agencies switched to Revision 10 (ICD-10). To create a database with standardized mortality data coding, a program was developed for the Mexican and Chilean cities that converted their ICD-9 data into ICD-10 data. The Brazilian data were already coded using ICD-10.

The age groups chosen allowed the investigators to focus on two subgroups of young children (< 1 year and from 1 to 4 years) and one subgroup of older people (≥ 65 years) (Table 3). These age groups are considered to be more susceptible to the effects of air pollution. Some of the cities included in this study have a large population of children.

In Brazil, mortality data for Rio de Janeiro and Porto Alegre were obtained directly from the Ministry of Health, which collects and processes all of the death certificates of the country. At the city level the death certificates are collected and the information is entered into a data file. The data encoded from the death certificates are assembled by the health department of each state. The health departments perform quality control checks before sending a final data set to the Ministry of Health. The city of São Paulo has its own mortality information system and directly provided the data for this project.

The mortality data for Chile were obtained from the Ministry of Health, which is the government agency in charge of death certificates. The certificate is digitized at the Ministry of Health Statistics Division, where a team of specialists codifies the causes of death. Consistency checks are performed regularly, and summary statistics are published annually. Data collected at the beginning of this study (1997) were codified in ICD-9. Beginning in 1998 the data were codified in ICD-10.

The mortality data for México were obtained from INEGI and have been further checked for consistency at the INSP. Death certificates are registered by three agencies: the Civil Office, the Ministry of Health, and the INEGI. Data are cross checked and the official death certificate is released by INEGI. Data collected at the beginning of this study (1997) were codified in ICD-9. Beginning in 1998 the data were codified in ICD-10.

Air Pollution and Meteorologic Data

Different environmental agencies are responsible for the collection, validation, and reporting of air pollution measurements in each country. In Brazil these tasks are the responsibility of Companhia Ambiental do Estado de São Paulo for São Paulo, Fundação Estadual de Engenharia do Meio Ambiente for Rio de Janeiro, and Fundação Estadual de Proteção Ambiental for Porto Alegre. The investigators reviewed the documentation from these agencies to compare the procedures employed for air pollution collection, validation, and reporting.

Population Major Urban Areas	
São Paulo	10,886,518
Rio de Janeiro	6,093,472
Porto Alegre	1,420,667
Santiago	4,985,893
Concepción	363,964
Temuco	593,111
Mexico City	8,720,916
Monterrey	1,133,814
Toluca	467,712

Figure 1. Cities in the ESCALA study.

Table 2. Causes of Death, ICD Codes, and Age Groups

Cause of Death	ICD-9[a]	ICD-10[b]	Age Groups
All-natural-cause	001–799	A00–T98, Z00–Z99	All-age
Cardiovascular	390–459	I00–I99	All-age, ≥ 65
Cardiopulmonary	390–459	I00–I99	All-age, ≥ 65
	460–519	J00–J98	
Cerebrovascular–stroke	430–438	I60–I69	All-age, ≥ 65
Respiratory	460–519	J00–J98	All-age, < 1, 1–4, ≥ 65
COPD	490–492	J40–J44	All-age, ≥ 65
	494–496	J46–J47	
Lower respiratory infection	466,	J10–J22	< 1, 1–14
	480–487		

[a] ICD-9: International Classification of Diseases 9th revision.

[b] ICD-10: International Classification of Diseases 10th revision.

Table 3. Total Number of Deaths for the Study Period of Each City by Age Group

Country / City, Period of Study	Age Group						Missing
	< 1 *n* (%)	1–4 *n* (%)	5–44 *n* (%)	45–64 *n* (%)	65–74 *n* (%)	≥ 75 *n* (%)	*n* (%)
Brazil							
São Paulo, 1997–2005	26,950 (4.51)	4023 (0.67)	114,105 (19.12)	141,179 (23.65)	107,579 (18.02)	179,559 (30.08)	23,542 (3.94)
Rio de Janeiro, 2001–2005	6,651 (2.66)	1124 (0.45)	38,166 (15.26)	60,016 (23.99)	51,726 (20.68)	91,683 (36.65)	803 (0.32)
Porto Alegre, 2002–2005	1,019 (2.47)	157 (0.38)	6,407 (15.52)	9,973 (24.16)	8,505 (20.60)	15,208 (36.84)	15 (0.04)
Chile							
Concepción, 1997–2005	623 (3.17)	68 (0.35)	1,317 (6.71)	4,361 (22.21)	4,447 (22.65)	8,819 (44.91)	0 (0.00)
Santiago, 1997–2005	5,659 (2.73)	784 (0.38)	12,625 (6.08)	40,277 (19.40)	44,775 (21.57)	103,502 (49.85)	0 (0.00)
Temuco, 1997–2005	403 (3.22)	61 (0.49)	828 (6.61)	2,577 (20.57)	2,749 (21.95)	5,907 (47.16)	0 (0.00)
México							
Mexico City, 1997–2005	45,916 (7.51)	5812 (0.95)	95,684 (15.64)	142,354 (23.27)	114,443 (18.71)	207,154 (33.86)	391 (0.06)
Toluca, 1997–2005	8,257 (14.53)	1061 (1.87)	10,346 (18.20)	12,744 (22.42)	8,629 (15.18)	15,729 (27.68)	65 (0.11)
Monterrey, 1997–2005	8,079 (6.40)	1151 (0.91)	17,263 (13.68)	30,227 (23.96)	25,078 (19.88)	43,510 (34.48)	868 (0.69)

SEMARNAT is responsible for monitoring the ambient pollutant concentrations in México. The National Institute of Ecology, SEMARNAT's decentralized agency, gathers and disseminates the data generated by the major air quality monitoring networks in México, including the ones from Mexico City, Toluca, and Monterrey. The agency uses an automatic air quality monitoring network, known as Red Automática de Monitoreo Atmosférico in Mexico City, Toluca, and Monterrey to measure concentrations of O_3 and PM_{10}.

Chile has two types of automatic monitoring networks: those run by the local government and those run by private companies (mostly mining companies). The government-run networks comply with strict QC procedures, and provide data of high quality (Koutrakis et al. 2005). All pollution data that were considered for this study came from air monitoring stations that are run by the government. Data from private stations were not available for the period of the analysis.

O_3 (daily 8-hr maximum moving average) and PM were the main pollutants of interest. PM_{10} (daily 24-hr mean average) was used for the PM data because this fraction is most commonly measured in the nine cities. The feasibility of using PM ≤ 2.5 μm in aerodynamic diameter ($PM_{2.5}$) was also assessed, but data availability for this pollutant was not sufficient for our analyses.

Hourly data for PM_{10} and O_3 were obtained from the automatic monitoring networks run by the local government, and data quality was checked using the QA/QC protocol (Appendix C). The following completeness criteria were used to generate daily levels of air pollution for each station in this study:

- To calculate the daily average PM_{10} concentration, at least 75% of the hourly values had to be available on that particular day.
- To compute the 8-hour maximum moving average of O_3 concentration, at least six hourly values had to be

available for each 8-hour average. In addition, at least 16 valid values were required to select the highest 8-hour moving average.

- A station was excluded if more than 25% of the values were missing for the entire period of the analysis.

When these conditions were not met, the corresponding measurement was set to missing. Identification of outlier values was also verified and controlled.

Daily Average of Air Pollution Single monitors are unlikely to be sufficient for assessing the population exposure level in a study area. Most of the cities in the study have more than one monitoring station; therefore, after determining the completeness of the data (Table 4), data from a number of stations were combined to reflect the exposure of the population at risk by following the procedures described in the monitor specification protocol (Appendix D).

On the basis of an analysis of the monitoring stations in Brazilian cities, all were regarded as important for providing a citywide assessment of air pollution levels. None of these stations are directly affected by important local sources such as wood burning or industrial emissions, and the great majority reflect exposures at the micro scale (i.e., pollutant concentrations in the air volume within 100 meters of a monitoring site). Therefore, the average of all stations for São Paulo (14 for PM_{10} and 10 for O_3) were used to characterize the exposure of the population. We also averaged all 6 stations in Rio de Janeiro to obtain a citywide PM_{10} concentration. For O_3 we used the data of the 2 stations that measure this pollutant. The 3 stations in Porto Alegre measured both pollutants, and the average of these stations was used. In Brazil, measurements of PM_{10} are made using beta attenuation monitors (BAM) in São Paulo and Porto Alegre, but some stations in Rio de Janeiro used tapered element oscillating microbalances (TEOM) (see Appendix Table D.1).

For Chile, nine monitors measure PM_{10} and O_3 in Santiago; all are representative of the population exposure. Because measurements among these monitors were highly correlated, we used the average of the data from the nine monitors to characterize population exposure to PM_{10} and O_3. Concepción and Temuco each had one monitor measuring PM_{10} (see Appendix Table D.2).

For Mexican cities, the air pollution data sets were assembled and QC checked by the National Institute of Ecology, however we only considered those monitoring stations that covered the population within a radius of 2 kilometers measured from the monitor. Because the monitor-to-monitor Pearson correlations were high for both O_3 data and PM_{10} data (Appendix J; available on the HEI Web site), the average of all available monitoring stations was computed by city to characterize the population exposure (Table 5). In Mexico City we averaged the data from 16 monitoring stations for PM_{10} and from 21 monitoring stations for O_3; in Monterrey we averaged the data from 5 monitoring stations that measure both pollutants; and in Toluca we averaged the data from 7 monitoring stations that measure both pollutants (Appendix Table D.3).

We compared TEOM measurements with gravimetric methods using data from Santiago, Mexico City, and Toluca. In Santiago we observed that at low PM_{10} concentrations, measurements by TEOM were close to those obtained by the gravimetric method. At higher PM_{10} concentrations TEOM tended to underestimate the concentration of PM_{10} when compared with the gravimetric method ($r = 0.89$). This problem might be difficult to correct and could lead to overestimation of the effect of PM_{10} at concentrations > 75 $\mu g/m^3$. In Mexico City, there was a considerable improvement in the correlations between PM_{10} measurements using the TEOM and gravimetric methods after recalibration of the TEOM equipment ($r = 0.91$). For Toluca, measurements obtained by BAM appeared to slightly overestimate PM_{10} concentrations when compared with gravimetric measurements ($r = 0.81$).

TEOM and BAM were chosen for the analyses because gravimetric measurements were available only in Santiago, Mexico City (every 6 days), and Toluca. However, because there were no concurrent measurements with TEOM and BAM, it is not possible to estimate the magnitude of the bias of one measurement method with respect to the other. In any case, it would also be difficult to make appropriate adjustments, given that the differences in measurements can also be dependent on the volatile content of particles, a quantity that varies among cities.

Climatic Variables Climatic variables may play a role both as confounding factors and as modifiers of the effect of air pollution on mortality, therefore weather factors such as temperature and humidity were considered in the analysis using the same time scale as for air pollution (Appendix Tables G.4–G.6; available on the HEI Web site). Temperature variations between months were used to define warm seasons and cold seasons for each country. Additional analyses of O_3 concentrations were stratified by season to account for the high seasonal variation of this pollutant.

Among the Brazilian cities, temperature and humidity data for São Paulo were collected at the same monitoring stations used for air pollutants. In Porto Alegre, none of the monitoring stations measure meteorologic parameters; temperature and humidity measurements were provided

Table 4. Percentage of Available Air Pollution Data for 2004[a]

Country / City / Station	O_3 (%)	$PM_{2.5}$ (%)	PM_{10} (%)
México			
Mexico City			
Azcapotzalco	95.49		
Chapingo	88.94		
Tlahuac	97.28		
Cuajimalpa	98.13		
Tlanepantla	91.22	96.23	
Tacuba	96.07		
ENEP – Acatlán	97.57		97.34
San Agustín	96.68	92.93	93.27
Xalostoc	96.95		95.71
Merced	92.92	96.60	89.17
Pedregal	98.70		84.52
Cerro de la Estrella	96.30		91.68
Hangares	98.77		96.37
Benito Juárez	96.42		91.31
Plateros	98.49		
UAM-Iztapalapa	94.73	91.12	
Taxqueña	92.81		
Lagunilla	94.18		
Tultitlán			14.71
Villa de las Flores			92.33
Santa Ursula			96.78
La Villa			92.26
San Juan de Aragón			95.32
Perla Reforma			95.66
Camarones			96.64
Brazil			
São Paulo			
P. d. Pedro II	15.91		19.82
Santana	89.69		98.29
Moóca	90.59		95.87
Cambuci			99.30
Ibirapuera	92.58		97.92
N. Sra. do O	51.52		82.71
Congonhas	0.00		98.01
Lapa	0.00		28.20
Cerqueira César			74.06
Centro			74.51
Santo Amaro	94.67		97.11
São Miguel Paulista	94.69		93.52
Pinheiros	48.74		50.14
Penha			100.00
Chile			
Santiago			
La Paz	80.81		100.00
La Florida	77.53	99.95	99.98
Los Condes	77.74	100.00	100.00
Parque O'Higgins	90.99	98.99	98.82
Pudahuel	91.45	99.37	99.73
Cerrillos	89.51		100.00
El Bosque	59.52		99.79
Cerro Navia	99.54		100.00

[a] This detailed information was tabulated only for the major cities with several monitoring stations. The following completeness criteria were used to generate daily levels of air pollution for each station in this study: (1) to calculate the daily average PM_{10} concentration, at least 75% of the hourly values had to be available on that particular day; (2) for the maximum 8-hour value of O_3, at least six hourly values had to be available for each 8-hour average. In addition, at least 16 valid values were required to select the highest 8-hour moving average; (3) if a station had more than 25% of the values missing for the whole period of analysis, it was excluded. When these conditions were not met the corresponding measurement was set to missing. Identification of values outside of the regular patterns followed by the pollutants was controlled and verified using serial plots.

Table 5. Summary of Pearson Correlations Between Monitors[a]

Country / City	PM_{10}[b] (24-hr Daily Mean Average)				O_3[b] (8-hr Maximum Moving Average)			
	Stations (*N*)	Median	Minimum	Maximum	Stations (*N*)	Median	Minimum	Maximum
Brazil								
Porto Alegre	3	−0.094	−0.173	0.085	3	−0.004	−0.022	0.116
Rio de Janeiro	6	0.716	0.579	0.806	2	0.083	NA	NA
São Paulo	14	0.766	0.580	0.919	8[c]	0.850	0.758	0.915
Chile								
Santiago	7	0.879	0.575	0.943	7	0.954	0.909	0.972
Concepción	2	0.476	NA	NA	0	NA	NA	NA
Temuco	1	NA	NA	NA	0	NA	NA	NA
México								
Mexico City	16	0.6915	0.451	0.903	20	0.715	0.328	0.974
Monterrey	5	0.6645	0.642	0.813	5	0.832	0.727	0.870
Toluca	7	0.778	0.588	0.872	7	0.806	0.653	0.939

[a] Source: Appendix J, available on the HEI Web site.

[b] NA indicates not applicable.

[c] Two additional stations were excluded from this analysis because of very sparse data.

by the National Institute of Meteorology. In Rio de Janeiro, we used measurements provided by four meteorologic stations from the military and civilian airports that yield a good coverage of the city.

Among the Chilean cities, a single meteorologic station was used for the whole city of Santiago because an analysis showed very high correlations among nine different meteorologic stations there. Temuco and Concepción each had a single meteorologic station that supplied the data for its city.

In the Mexican cities, information on climatic variables was obtained from the different air quality monitoring stations and was averaged to get the daily mean temperature and humidity values for time-series analyses.

Socioeconomic Data

SES has been identified as a factor that could modify the effects of air pollutants on health, although relatively few studies have examined this in detail (O'Neill et al. 2003). People with low SES may be more susceptible to air pollution than those with high SES, as several factors more prevalent in less advantaged populations may modify the effect of the pollution–mortality relationship. These factors include poor health status, addictions, limited access to health care, closer proximity to exposure sources, and multiple-pollutant exposure. Thus, to analyze the potential modifying effect of SES on the air pollution-mortality relationship we developed a common SES index for the metropolitan cities in the ESCALA project.

To standardize the SES index across countries, we used comparable aggregated *area units* in each country. The cities of São Paulo and Rio de Janeiro are divided into *districts*; the city of Santiago into *comunas*, and Mexico City into *delegaciones* (i.e., municipalities equivalent to county). These area units are fairly comparable. The definition of SES was intended to be applied on a smaller scale (census tracts); however the lack of disaggregated data for all cities led us to construct the SES index at the level of these larger area units.

Another important consideration when constructing the index was that the city needed to comprise several area units to have sufficient variability in SES. Metropolitan areas which comprise a large number of such units are more likely to reflect socioeconomic differences among these units. Therefore, the SES index was calculated only for the largest metropolitan areas, those comprising six or more area units (Mexico City for México, São Paulo and Rio de Janeiro for Brazil, and Santiago for Chile).

The data sources used to construct the SES index were: (1) the Census of Population and Housing 2000 for Mexico City, São Paulo, and Rio de Janeiro; (2) the National Socioeconomic Characterization Survey, which was conducted during 2002 and 2006 (every four years), and the Ministry of Planning and Cooperation for Santiago.

The area-based SES index included variables in three dimensions: education, income, and housing conditions. Because the statistical offices in each country have their own definitions for constructing aggregate-level measures, the specific variables available in each country are not identical. Hence, the comparability of results across countries could not be based on the use of identical variables, but on identifying variables that reflect the same underlying dimensions and indicators within each dimension.

City-Level Meta-Regression Data

The sources of heterogeneity in the effects of air pollution on mortality may be partially attributable to different characteristics of the cities; thus, information relevant to each city was gathered at different levels of aggregation. City characteristics related to the environment, the population, and the exposure characterization were gathered to allow inclusion in meta-regression analyses.

The variables shown in Table 6 were considered for use in the meta-regression analyses: city altitude, average temperature in different seasons, average annual rainfall, pollutant concentrations averaged over the period of the study, air pollutant monitor geographic density, population density, age structure, prevalence of smoking, and lung cancer mortality rates for men and for women.

Data Consistency and Standardization

A series of standard protocols were developed and agreed upon by the ESCALA investigators to ensure that methods for compiling the mortality and air pollution data sets were uniform across the cities.

Mortality data sets were checked for quality and inaccurate data were corrected using a standardized protocol. The distribution of deaths by different causes was compared across cities to assess the consistency of the cause-of-death coding.

Regarding air pollution data, the monitoring network was characterized in the Monitor Specification Protocol (Appendix D) to understand how each monitoring site reflected population exposure. A standard procedure regarding the characteristics required for the selection of monitoring sites was conducted among all participant cities.

The quality of the air pollution data was evaluated, with special attention given to the existence of QA/QC programs in each selected city, as seen in the QA/QC air pollution

Table 6. Meta-Regression Variables

Class / Variables (Unit)	Observations
Environment	
Altitude (meters)	Meters above sea level of each city
Average temperature by season (°C)	During the study period
Rainfall geometric mean (mm)	During the study period
Pollution	
NO_2 geometric mean by season ($\mu g/m^3$)	
PM_{10} geometric mean ($\mu g/m^3$)	
NO_2/PM_{10} ratio	
$PM_{2.5}/PM_{10}$ ratio	
Emissions	
Source distribution (source of PM_{10})	Sector: traffic, industry, natural
Exposure characterization	
Monitor density by pollutant (km^2/monitor)	The area of analysis divided by the number of monitors
Hot spot or background monitor	Proportion of hot spot/background monitors
Population density	Inhabitants per square km
Population	
Age structure (% for each age group)	Age groups
Prevalence of some chronic conditions	
Prevalence of smoking	
Lung cancer and COPD mortality rate (cases/100,000/yr)	Proxy for smoking prevalence.
Proportion of cardiopulmonary mortality	
Human development index	High, medium, and low

protocol (Appendix C). The comparability of measurement methods used in each city for air quality assessment was also evaluated.

WORKSHOPS

During the project we organized four workshops to review databases, define protocols for QA and QC, define analytic strategies, discuss results, and prepare the report. In addition, we took advantage of scientific meetings attended by team researchers to further discuss important issues.

STATISTICAL ANALYSES

In this project, standardized time-series analyses were conducted to provide results that could be compared with those of previous studies conducted in Latin America and with other multicity studies. These analyses were also used to examine long lag periods. An analysis protocol was developed to conduct city-specific analyses to ensure that methods were uniform across the cities (Appendix E). The analysis was conducted in two stages.

In the first stage, time-series data for each of the cities were analyzed separately to obtain city-specific estimates of the effect of air pollution on mortality.

The single-city time-series analyses included the following methods (Appendix H, available on the HEI Web site):

- generalized additive models (GAM) with Poisson error to fit time-series data;
- means of natural splines basis to adjust for time trend and seasonality terms, initially using 3, 6, 9, and 12 *df* per year, and then by using the number of degrees of freedom needed to optimize PACF and the periodogram (spectral density);
- the GLM framework for estimation;
- indicator variables for day-of-week and holidays to account for short-term fluctuations;
- means of natural splines for the mean daily temperature and mean daily humidity indicators, initially using 3 or 6 *df*, each at lags 0, 1, 2, and 3, and then using moving averages. We relied on model diagnostics to make an adequate choice of meteorologic indicator and the number of degrees of freedom, and we checked standardized deviance residuals for each meteorologic indicator before and after its inclusion in the model;
- residual diagnostics:
  - deviance and dispersion parameter estimates for overdispersion,
  - PACF for residual autocorrelation and overfitting,
  - periodogram for residual seasonality,
  - Q-Q plots and simulation for normality of standardized deviance residuals,
  - the Cook distance for influence, and
  - the Akaike Information Criteria (AIC) for model parsimony;
- model specification according to residual diagnostics; and
- estimates of the effect of the exposure, based on DLMs 0–3, 0–5, and 0–10. To assess the association between exposure to air pollutants and risk of mortality, we fit both single-lag models (SLM) and constrained DLMs to PM_{10} and O_3 concentrations. The SLMs evaluated mortality associated with pollutant concentrations on the same day, the previous day, and up to 2 lagged days. The DLMs evaluated mortality associated with pollutant concentrations on the same day and lagged up to 3, 5, or 10 days. However, in the Results section we present estimates only for DLM with a lag of up to 3 days (DLM 0–3).

In the second stage, pooled results were obtained using both meta-analyses and meta-regression analyses. In the meta-analyses, an overall effect (that is, the effect combined across cities) was calculated for each specific pollutant–mortality association using both fixed- and random-effects models. Further, effect estimates for different cities were checked for heterogeneity. In the meta-regression, the set of pollutant–mortality associations (β-coefficients) were assessed, exploring city-level variables that could explain the observed heterogeneity.

Methodology to Develop an SES Index

Complete individual data from the death certificates were not available for all cities, so the SES index was based on the area of residence by using principal components analysis (PCA). This was performed at the level of area units (municipality, district, or neighborhood — depending on the city analyzed). Variables were classified according to the three dimensions — education, income, and housing conditions — but the indicators used to define these categories differed slightly among cities. To explore the feasibility of this approach, the SES index was first developed for Mexico City, São Paulo, and Santiago, with data from the Census of Population and Housing 2000 in México and Brazil, and data from the 2002 and 2006 National Socioeconomic Characterization Surveys in Chile. Later, an SES index was developed for Rio de Janeiro. The census data were obtained from the INEGI for México, from the IBGE in Brazil, and from the INE in Chile.

In Mexico City, the index was constructed by applying PCA to the variables obtained at the municipality level (i.e., the delegation), which were classified according to the three categories, which were defined as: (1) education — average years of education for residents 18 years old or older; (2) income — median per capita household income, and (3) housing conditions — mean of index of precarious floor building materials; mean number of residents per bedroom in each household; mean number of households with car, computer, washing machine, microwave, and telephone. With the exception of the median income, all of the other variables were aggregated by municipality.

The PCA results for Mexico City showed that the percentage of variance explained by education was 82.5%. The distribution of the data from this category was divided into tertiles to provide an estimation of the proportion of data that should fall into each SES. The upper tertile was defined as high SES, the middle tertile as middle SES, and the lower tertile as lower SES.

In São Paulo and Rio de Janeiro the three dimensions were defined as: (1) education — proportion of the population over 10 years old that is literate, proportion of heads of household who are literate, proportion of heads of household with at least 10 years of education; (2) income — proportion of heads of household earning less than half of the minimum wage, proportion of heads of household earning at least 20 times the minimum wage; (3) housing conditions — proportion of households with piped water and sanitation, proportion of households with at least five inhabitants, proportion of households with at least two bathrooms. The PCA produced two factors that explained the variance. The factor with the largest explanatory potential was chosen (in this case the one responsible for nearly all of the total variability in the data). This factor characterized each district or neighborhood in such a way that the higher the factor, the higher the SES of the geographic area. The districts were grouped into tertiles according to this factor to define high, medium, and low SES. In Rio, the proportion of literate head of household was excluded because of the high linear correlation with proportion of head of household with 10 or more years of education, which implied that the covariance matrix was no longer positive-definite.

For Santiago, Chile, an SES index based on municipality-level data was developed. The index was constructed for each municipality using three categories defined as: (1) education — proportion of population with incomplete, basic, secondary, or university education; (2) income — median income by municipality, proportion of households with a washing machine, microwave, refrigerator, car, motorcycle, phone, cable television; and (3) housing conditions — proportion of households with solid floors, solid roof, and appropriate structures. The SES index obtained by PCA was contrasted with the Human Development Index for Chile, which was developed by the UNDP and the Ministry of Planning and Cooperation, and they were found to be in reasonable agreement. The municipalities were assigned to one of three levels based on the value of the SES indices developed for this study.

Once these SES indices had been created for each city, SES levels were assigned to each municipality, district, or neighborhood in each city. The number of deaths was also assigned to the respective SES level according to the area of residence (Appendix F).

In Mexico City, the SES index was created at the municipality or district level and, therefore assumes homogeneity of SES levels within these administrative areas. However, given the large populations in each municipality of Mexico City, misclassification of SES is likely to occur, although it is expected to be nondifferential misclassification with respect to air pollution exposure. Air pollution exposure (O_3 and PM_{10}) was assigned without knowledge of SES, taking into account air pollutant concentrations in the municipality where deaths occurred (all the different municipalities in Mexico City have at least one air pollution monitoring station). Under these circumstances, misclassification of SES would tend to underestimate the real effect of pollutants. São Paulo and Rio de Janeiro have much smaller administrative units (districts), but some degree of misclassification is also expected. Moreover, for São Paulo and Rio de Janeiro we averaged the concentrations of air pollutants for all monitoring stations and used this average in the SES analysis.

After stratifying the mortality database according to SES, time-series analyses were carried out on the number of deaths in each SES stratum. The outcomes with small numbers of death in each stratum (i.e., close to a mean of zero) were excluded from the analysis due to instability in the GLM estimation algorithm.

Time-Series Analyses Library

The Brazilian team developed a library for time-series analyses called ARES (*Ar e Saúde*, i.e., *Air and Health* in Portuguese) using R software. It consists of a set of functions for time-series analyses that explore the relationship between daily air pollutant concentrations and health effects *(http://cran.at.r-project.org/web/packages/ares/index.html)*. The library has routines to fit time trends and seasonality, including the selection of key covariates such as temperature, humidity, and calendar effects (e.g., day-of-week and the public holidays of each country and city). Although these routines allow the inclusion of data

on hospital admissions for pneumonia to control the effect of influenza epidemics, data were not available from all the cities included in ESCALA. Therefore this adjustment was not performed.

Most of the diagnostic tools used in time-series analyses were also included in this library (e.g., periodograms, observed and fitted values by time, standardized residuals by time, standardized residuals by fitted values, Q-Q plots, and Cook influence statistics).

City-Specific Analyses

Initial analyses were conducted to identify data errors and inconsistencies in each city-specific data set. Descriptive statistics of mortality and pollution variables for each city by year and by season were computed. To compare results among cities in the three countries, it was necessary to ensure that the data from the three countries were comparable and were analyzed in the same way. The most critical issues were thought to involve: (1) health outcome categories and air pollutant measurements; (2) the approach for imputing missing data (in the final analysis this procedure was not used given that imputing data did not modify the results); and (3) the criteria used to select air pollution data and aggregate the data across monitoring sites.

All analyses were conducted with the same R software, using the libraries developed for this project.

Time-Series Analysis Approach GAMs with Poisson errors were used to analyze the time-series data according to the analysis plan developed by the team (Appendix H). Time trends and seasonality were adjusted by natural splines with 4 *df* per year as a general rule; however for some outcomes and cities we based the choice of degrees of freedom on the fit of the model. Indicator variables for day-of-week and holidays were used to account for the short-term cyclic fluctuation. The R gam library was used to fit the GAMs using linear terms only. The ns function (natural spline) was used to generate the basis of the spline smoothed terms.

Meteorologic factors were adjusted by using natural splines of same day, 1-day lagged, 2-day lagged or cumulative mean temperature (with 4 *df*) and humidity (with 2 *df*). For different age groups and causes of mortality, the association between exposure and risk of death was assessed by fitting a constrained polynomial DLM with a 2-degree polynomial structure that included the exposure lagged effect from 0–3 days, 0–5 days, and 0–10 days, as well as SLMs to evaluate the single effect of pollutant concentrations (PM_{10} and O_3). The analyses were carried out per cause of death and per SES for each age group. The number of degrees of freedom for seasonal meteorologic factors was chosen by examining the residuals diagnostics as well as by lowering the AIC (Appendix H).

Seasonal Stratification A separate analysis per season was conducted for O_3 to evaluate the potential effect modification on mortality related to O_3 concentration for all cities involved in the ESCALA project. This was important for O_3 because of the seasonal variability of this pollutant (Appendix H).

Single and Distributed Lag Models Constrained DLMs were used to effectively analyze the distributed lag effect between PM_{10} and O_3 on daily mortality considering a 2-degree polynomial structure. We explored the cumulative effects of 0–3, 0–5, 0–10, and 0–15 days lagged. However, due to the consistency and plausibility of the effects, we decided to focus on the distributed lag effects of 0–3 days. In addition, we used SLMs to analyze the single-day effect from air pollution exposure on mortality, exploring the latter effect on the same day and up to 3 days before the event.

Because of the substantial variability in seasonal patterns and weather between cities, different models characterizing the degrees of freedom for time trend could be chosen for each city and cause of death. In addition, for each covariate, it was necessary to choose a smoothing parameter that determined how smooth the function of that covariate should be.

To specify the number of degrees of freedom, sensitivity analyses were conducted considering the minimum AIC, the minimization of the PACF values, and the other criteria described in the sensitivity analyses section.

After the sensitivity analyses were run, two sets of predictor variables were chosen to fit the best models. The first set included natural splines for time to capture seasonal and other long-term trends in data, and natural splines for meteorologic factors (temperature and humidity), which were also optimized separately in each location. The second set included covariates to capture shorter term potential confounding: holiday variables, long weekend terms, and day-of-week.

The purpose of the smooth function of time (natural splines) is to remove seasonal and other long-term patterns in the data. This approach was used because each death is an independent event, and autocorrelation in residuals indicates there are omitted time-independent covariates whose variation may confound air pollution. Autocorrelation was removed so any remaining variation in the omitted covariates would have no systematic temporal pattern, therefore making confounding less likely. Models did not incorporate autoregressive terms because residual

correlations were eliminated by using diagnostic tests to choose the best model.

Sensitivity Analyses In the first stage of the ESCALA project, time-series analyses fit one specific model for each cause of death, age group, and season (warm, cold). Thus, different strategies of sensitivity analysis were conducted for each cause and age group to obtain better model fits. We used several different degrees of freedom per year of analysis as well as different degrees of freedom for natural splines used to control for the dependence of mortality on mean temperature and mean humidity. Also, we considered the minimization of the PACF values and the minimum AIC in evaluating model fit; a lower AIC is generally taken to indicate a better-fitting model.

To better adjust the potential confounding effect of holidays, we fit a first model that considered all holidays (per country) and analyzed its effects (negative, positive, or null). A second (final) model then adjusted the first by creating two new variables: holidays with positive effect and holidays with negative effect.

Goodness-of-fit and residual diagnostics for each model were carried out using the ARES library (Appendix H).

Meta-Analyses and Meta-Regression Analyses

As part of the second stage of the ESCALA project, meta-analyses and meta-regression analyses were conducted to provide a quantitative summary of city-specific results and to investigate potential city features that may act as effect modifiers and explain the heterogeneity in the effect of air pollutants.

Meta-analyses were conducted to get a pooled effect of the magnitude of the relationship between mortality and air pollution among cities. This is normally done by identifying a common measure of effect size, which then can be modeled using meta-regression analyses. In addition, two specific indices were computed to evaluate heterogeneity among cities: The I^2 index and the Cochran Q test of heterogeneity.

Meta-regression analyses were conducted to explore the effect modification by city-level variables. They were also used to identify possible covariates reflecting city characteristics that could explain any heterogeneity in the results. The resulting overall mean effect estimates when controlling for study characteristics can be considered meta-effect sizes, more powerful estimates of the true effect size than those derived in a single study under a given single set of assumptions and conditions.

Meta-Analysis Approach Two potential sources of variation can explain the heterogeneity of effect estimates among cities. One is within-city variability due to sampling errors. This source of variation is a feature of statistical approaches and can be large in many meta-analytic studies, depending on several factors. Even in multicenter studies like ESCALA, which adopt the same methodology and data quality criteria for all centers, there may be some external factors related to the city populations, environmental factors, and quality aspects of the available data that could add noise to the estimation of effects and thus to its precision.

The second source is between-city variability, which occurs when there is heterogeneity among the true effect sizes of the individual cities. The between-city variability is influenced by an indeterminate number of characteristics that vary among the cities, such as those related to the characteristics of the corresponding population profiles (e.g., socioeconomic, demographic, size of susceptible populations), variations in the average concentrations of air pollutants, or even variations in the quality of the monitoring network design.

The assessment of heterogeneity is necessary because presence versus absence of true heterogeneity (between-city variability) determines which meta-analysis model to apply. When the study results differ only by the sampling error (homogeneous case), a fixed-effects model ought to be applied to obtain a combined effect size. By contrast, if the study results differ by more than just sampling errors (indicating the presence of true heterogeneity), then a random-effects model is more appropriate because it can account for both within- and between-study variability. Further, one can explain the heterogeneity from either a fixed- or random-effects model using moderator variables (Appendix H).

As a way to assess heterogeneity across cities, we computed two measures on the R software: (1) the Q statistical test defined by Cochran (1954) and (2) the I^2 percentage (Higgins and Thompson 2002; Higgins et al. 2003).

The Q test is computed by summing the squared deviations of each city's effect estimate from the overall effect estimate, weighting the contribution of each city by its inverse variance. Under the hypothesis of homogeneity, the Q statistic follows a chi-squared distribution with k–1 df, where k is the number of cities.

The I^2 index also measures the extent of heterogeneity and is computed by dividing the difference between the result of the Q test and its degrees of freedom by the Q value itself and multiplying by 100. The I^2 index can be interpreted as the percentage of the total variability in effect sizes among cities that is due to heterogeneity, that is to say, to between-city variability. But the I^2 index has important advantages over the classical Q test. First, it is easily

interpretable because it is a percentage and does not depend on the degrees of freedom. Another advantage is that it provides a way of assessing the magnitude of the heterogeneity in a meta-analysis, whereas the Q test is only testing statistical significance of the homogeneity hypothesis. In addition, the confidence interval for the I^2 index informs on the accuracy of the true heterogeneity estimation.

Because daily mortality for children and infants was low on average, we did not compute meta-effect estimates for infants (< 1 year) or for children (1–4 years). Most of the cities recorded only a small number of daily infant and child deaths, which limited the number of cities that could provide data for the meta-analysis.

Meta-Regression Analyses To investigate potential effect modifiers, univariate meta-regression analyses were applied to sets of effect estimates from the meta-analyses. Meta-regression models were run for each outcome and DLM choice (overall effects for lags 0–3, 0–5, and 0–10) with random effects, using restricted maximum likelihood (REML) as the estimation procedure. REML is a method for fitting linear mixed models; it was first described by Patterson and Thompson (1971). In contrast to conventional maximum likelihood estimation, REML can produce unbiased estimates of variance and covariance parameters. (Morris and Normand 1992) (Appendix H). Meta-regression models were run in STATA software (Version 10; StataCorp, College Station, TX).

Meta-regression analyses were conducted only for PM_{10} and overall effect estimates using DLMs. Because the number of available PM_{10} data sets was limited to nine (from the nine cities), we had few degrees of freedom to estimate the heterogeneity of the PM_{10} effects (Wald statistic). O_3 concentrations were not analyzed because we had even fewer O_3 data sets. Only seven of the nine cities measured O_3 concentration.

The following variables were proposed to be evaluated as possible effect modifiers in the meta-regression analyses: population size, altitude, average temperature, annual rainfall, average PM_{10} during analysis period, average O_3 during analysis period, geographic density of PM_{10} monitors, geographic density of O_3 monitors, population density, age structure of the population, percentage of the population 65 years or older, prevalence of smoking, lung cancer crude mortality in males and in females, and the Gini coefficient (a measure of inequality in which the coefficient varies between 0, complete equality, and 1, complete inequality [World Bank 2011]). Not all the variables were ultimately used in the analyses.

Because of data availability, we used only the following covariates: city altitude, average temperature in different seasons, rainfall annual average, PM_{10} concentrations averaged over the period of the study, geographic density of PM_{10} monitors, population density, age structure, prevalence of smoking, and lung cancer mortality rates for men and for women (Table 6).

Moreover, given multicollinearity in the set of city covariates, the small number of cities, and time restrictions, only univariate meta-regression random-effects models, based on REML, were examined at this stage.

Further, because not all cities had available effect estimates for some of the outcomes (because of low average mortality counts) or not all cities had data for the meta-regression variables (e.g., the Gini coefficient for income has only been made available at the country level), neither the outcome nor the covariate associations were examined for this study. Moreover, the meta-regression analyses had only been conducted for exposures to PM_{10} because of lack of available O_3 data for some cities and therefore the lack of overall effect estimates from DLMs.

The meta-regression models were based on the following equation:

$$10\beta_i = \alpha_0 + \alpha_1\left(x_1 - min\left(x_i, \ldots, x_9\right)\right),$$

where β_i is the effect of PM_{10} for the ith city, estimated via time-series models; x_i is the value of covariate X for the ith city; min $(x_1, \ldots, x_9)$ is the minimum of covariate X over the nine cities; α_0, α_1 are the meta-regression coefficients to be estimated.

β_i is multiplied by 10 because the effects of PM_{10} are always reported for a daily increase of 10 μg/m³. To make the interpretation of the meta-regression results easier, the following transformation was applied:

$$e^{10\beta_i} = e^{\alpha_0 + \alpha_1 x_i} = e^{\alpha_0} e^{\alpha_1 x_i}.$$

Furthermore, because the range of PM_{10} annual values in the nine cities is approximately 40 μg/m³ (four times 10 μg/m³), the latter was the choice of increase in the covariate X reported in the meta-regression tables. That is, instead of reporting e^{α_1} that correspond to an increase of 1 μg/m³ in the annual mean of PM_{10}, the following was reported:

$$e^{\alpha_1 \times 0.25 \times range\left(x_1, \ldots, x_9\right)},$$

where range $(x_1, \ldots, x_9) = \max(x_1, \ldots, x_9) - \min(x_1, \ldots, x_9)$.

Given the above, the results of the meta-regression should be interpreted as:

1. Reference risks (Ref_R) are the expected values of relative risk (RR) = $e^{10\beta}$ corresponding to the minimum, over the ESCALA cities, of the respective covariate where β is the coefficient from each city's time series. In other words, Ref_R is the incremental RR of 10 μg/m^3 daily PM_{10} predicted by the meta-regression model at the city with the lowest value of the covariate (city characteristic) under investigation. For instance, in Table 24 (which appears later in this report) the value 1.0066 (95% CI = 1.0024 to 1.0108) for rainfall should be interpreted as the estimated RR for a city whose rainfall is equal to the minimum of the nine rainfall values observed in the study sample of nine cities.
2. Relative risk ratio (RRR) is the change predicted by the meta-regression in the incremental PM_{10} effect (RR) for an increase of 25% of the full range of the covariate under investigation over the ESCALA cities. For instance, when annual PM_{10} mean was used as a covariate, the range was 40 μg/m^3. So 25% of the range is 10 μg/m^3. The (RRR-1)*100 should be interpreted as the percentage increase or decrease in city-specific PM_{10} effect due to an increase of 10 μg/m^3 in PM_{10} annual mean.

   The advantage of this approach (25% of the range) is that when it comes to the annual mean of PM_{10} as a covariate in the meta-regression, the result quoted in tables for the RRR corresponds to an increase of 10 μg/m^3 in the annual mean (i.e., going from one city to another where the difference between annual mean levels of PM_{10} is 10 μg/m^3).

RESULTS

DESCRIPTION OF DATABASES

Mortality Data

For the Brazilian cities (São Paulo, Rio de Janeiro, and Porto Alegre), Mexican cities (Mexico City, Monterrey, and Toluca), and Chilean cities (Santiago, Concepción, and Temuco), the mortality data sets included data up to the year 2005. Figure 2 provides an overview of the daily counts of death for all-natural-cause, all-age mortality across the nine cities for the period of study. Therefore, for most cities the period of analysis consisted of nine years (1997 to 2005). Data were checked in terms of quality and standardization according to the QA/QC protocol (Appendix B). A summary of cause-specific mortality data for the nine cities appears in Table 7.

Air Pollution Data

The daily PM_{10} concentration exceeded 10 μg/m^3 in all of the cities (Figure 3); the highest concentrations were observed in Santiago, Temuco, Monterrey, and Toluca (Table 8). When the data were stratified by season, the highest concentrations were observed during the cold season (Table 8). Figure 4 describes the daily O_3 concentrations by city across the study period. The highest O_3 concentrations were observed in the Mexican cities and in Santiago. When the data were stratified by season, O_3 concentrations were higher during the warm season than during the cold season in all cities except Mexico City (Table 9).

Based on U.S. Environmental Protection Agency (U.S. EPA) recommendations, we classified the monitoring stations as either *background stations* (medium and local scale) or *hotspot stations* (micro scale). While most of the stations in the Chilean and Mexican cities are background stations (Appendix Tables D.2 and D.3), the large majority in Brazilian cities are considered to be hotspot stations (Appendix Table D.3). Therefore, to standardize measurements across countries and cities, we decided to average air pollutant concentrations over monitoring stations located in populated areas without taking the classification of the station into account.

TIME-SERIES ANALYSES

In this section we present results from the time-series analyses conducted in the nine cities. While we ran several models with different single lags (Appendix I, available on the HEI Web site) and distributed lags, we present the results from the overall effects for lag 0 to lag 3 from DLM 0–3, which appeared to be the most significant for all-natural-cause mortality and for specific causes of deaths.

Results for PM_{10} and O_3 are presented by cause-of-death and age group (all-age, ≥ 65 years, and children) as follows:

1. all seasons (single- and two-pollutant models);
2. stratified by season (single-pollutant models) for the effect of O_3 because of the seasonal variation of this pollutant in some cities;
3. stratified by SES (single-pollutant models); and
4. respiratory mortality in children.

All results are presented as the percentage change in risk associated with a 10-μg/m^3 change in daily pollutant concentration (PM_{10} or O_3).

Because of the low number of infant and child deaths in smaller cities (Porto Alegre, Concepción, Temuco, Toluca,

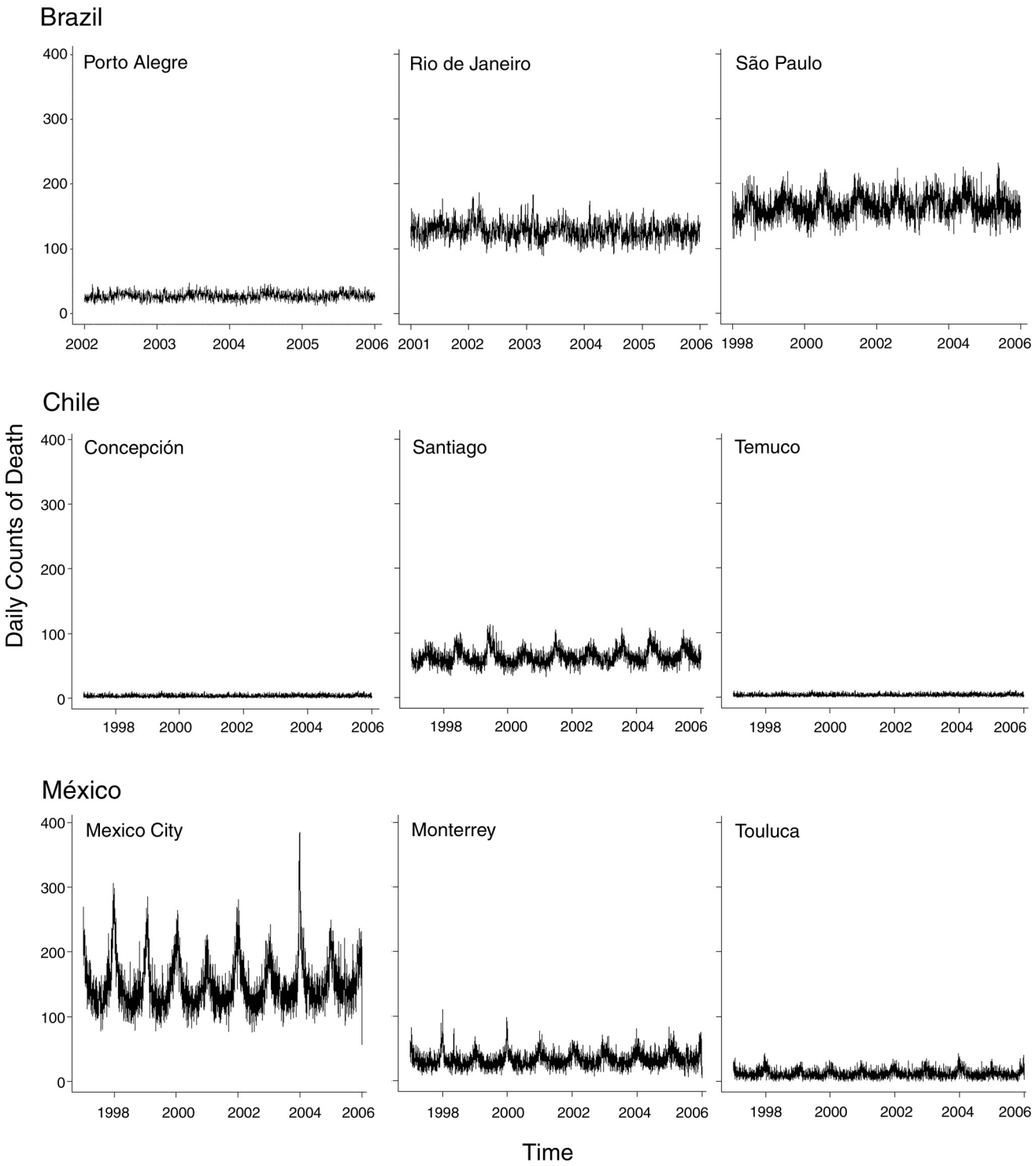


Figure 2. Daily all-natural-cause, all-age mortality, by city. Note: Porto Alegre and Rio de Janeiro have different study years than the other cities, and the *x*-axes for Brazil are scaled differently than those for Chile and México. Source: Appendix Figure G.1, available on the HEI Web site.

Table 7. Summary of Daily Mortality by Cause-of-Death[a]

	Porto Alegre, Brazil Mean (SD)	Rio de Janiero, Brazil Mean (SD)	São Paulo, Brazil Mean (SD)
All-natural-cause	27.36 (5.79)	127.84 (14.08)	165.44 (17.91)
Cardiopulmonary	11.35 (3.90)	53.25 (8.55)	76.86 (12.38)
Cardiopulmonary ≥ 65	8.52 (3.36)	38.41 (7.08)	52.00 (10.00)
Respiratory	2.79 (1.83)	14.79 (4.23)	19.49 (5.58)
Respiratory < 1	0.06 (0.25)	0.20 (0.46)	0.75 (0.94)
Respiratory 1–5	0.01 (0.11)	0.10 (0.32)	0.26 (0.51)
Respiratory ≥ 65	2.13 (1.57)	11.36 (3.66)	13.53 (4.54)
Cardiovascular	8.55 (3.21)	38.46 (6.95)	57.38 (9.71)
Cardiovascular ≥ 65	6.38 (2.79)	27.04 (5.69)	38.15 (7.62)
Cerebrovascular–stroke	2.96 (1.76)	12.19 (3.75)	14.99 (4.17)
Cerebrovascular–stroke ≥ 65	2.28 (1.54)	8.51 (3.06)	9.86 (3.31)
Lower respiratory infection < 1	0.05 (0.23)	0.16 (0.41)	0.62 (0.86)
Lower respiratory infection 1–14	0.01 (0.09)	0.09 (0.31)	0.62 (0.86)
COPD	1.56 (1.34)	3.80 (2.00)	6.36 (2.72)
COPD ≥ 65	1.25 (1.19)	3.11 (1.81)	5.03 (2.36)
	Concepción, Chile Mean (SD)	Santiago, Chile Mean (SD)	Temuco, Chile Mean (SD)
All-natural-cause	5.97 (2.65)	63.16 (11.92)	3.81 (1.99)
Cardiopulmonary	2.45 (1.62)	26.91 (7.97)	1.44 (1.22)
Cardiopulmonary ≥ 65	1.96 (1.45)	21.98 (7.01)	1.13 (1.09)
Respiratory	0.66 (0.84)	7.72 (4.27)	0.41 (0.65)
Respiratory < 1	0.02 (0.14)	0.13 (0.36)	0.01 (0.10)
Respiratory 1–5	0.01 (0.07)	0.03 (0.19)	0.00 (0.07)
Respiratory ≥ 65	0.54 (0.75)	6.50 (3.74)	0.32 (0.58)
Cardiovascular	1.78 (1.35)	19.19 (5.43)	1.03 (1.01)
Cardiovascular ≥ 65	1.42 (1.21)	15.47 (4.78)	0.81 (0.91)
Cerebrovascular–stroke	0.70 (0.84)	5.95 (2.53)	0.42 (0.65)
Cerebrovascular–stroke ≥ 65	0.55 (0.74)	4.78 (2.29)	0.33 (0.56)
Lower respiratory infection < 1	0.02 (0.13)	0.11 (0.35)	0.01 (0.10)
Lower respiratory infection 1–14	0.01 (0.07)	0.04 (0.20)	0.00 (0.07)
COPD	0.15 (0.39)	2.17 (1.68)	0.10 (0.32)
COPD ≥ 65	0.13 (0.36)	1.92 (1.57)	0.09 (0.30)
	Mexico City, México Mean (SD)	Monterrey, México Mean (SD)	Toluca, México Mean (SD)
All-natural-cause	149.8 (37.3)	33.1 (11.9)	12.0 (6.6)
Cardiopulmonary	62.6 (15.1)	14.0 (4.9)	4.8 (2.6)
Cardiopulmonary ≥ 65	45.4 (11.9)	10.1 (4.1)	3.1 (1.9)
Respiratory	16.7 (7.2)	3.1 (2.2)	1.8 (1.6)
Respiratory < 1	1.8 (1.9)	0.1 (0.4)	0.5 (0.8)
Respiratory 1–5	0.3 (0.5)	0.0 (0.2)	0.1 (0.2)
Respiratory ≥ 65	11.5 (5.3)	2.4 (1.8)	1.0 (1.1)
Cardiovascular	45.9 (9.9)	10.8 (3.9)	2.9 (1.8)
Cardiovascular ≥ 65	34.0 (8.3)	7.7 (3.2)	2.2 (1.5)
Cerebrovascular–stroke	10.7 (3.5)	2.6 (1.7)	0.8 (0.9)
Cerebrovascular–stroke ≥ 65	7.9 (3.0)	1.9 (1.4)	0.6 (0.8)
Lower respiratory infection < 1	1.5 (1.6)	0.1 (0.3)	0.5 (0.8)
Lower respiratory infection 1–14	0.2 (0.5)	0.0 (0.1)	0.0 (0.2)
COPD	7.3 (3.7)	1.4 (1.3)	0.6 (0.8)
COPD ≥ 65	6.3 (3.4)	1.3 (1.3)	0.5 (0.8)

[a] The study period was years 1997–2005 except for Porto Alegre (2002–2005) and Rio de Janiero (2001–2005).

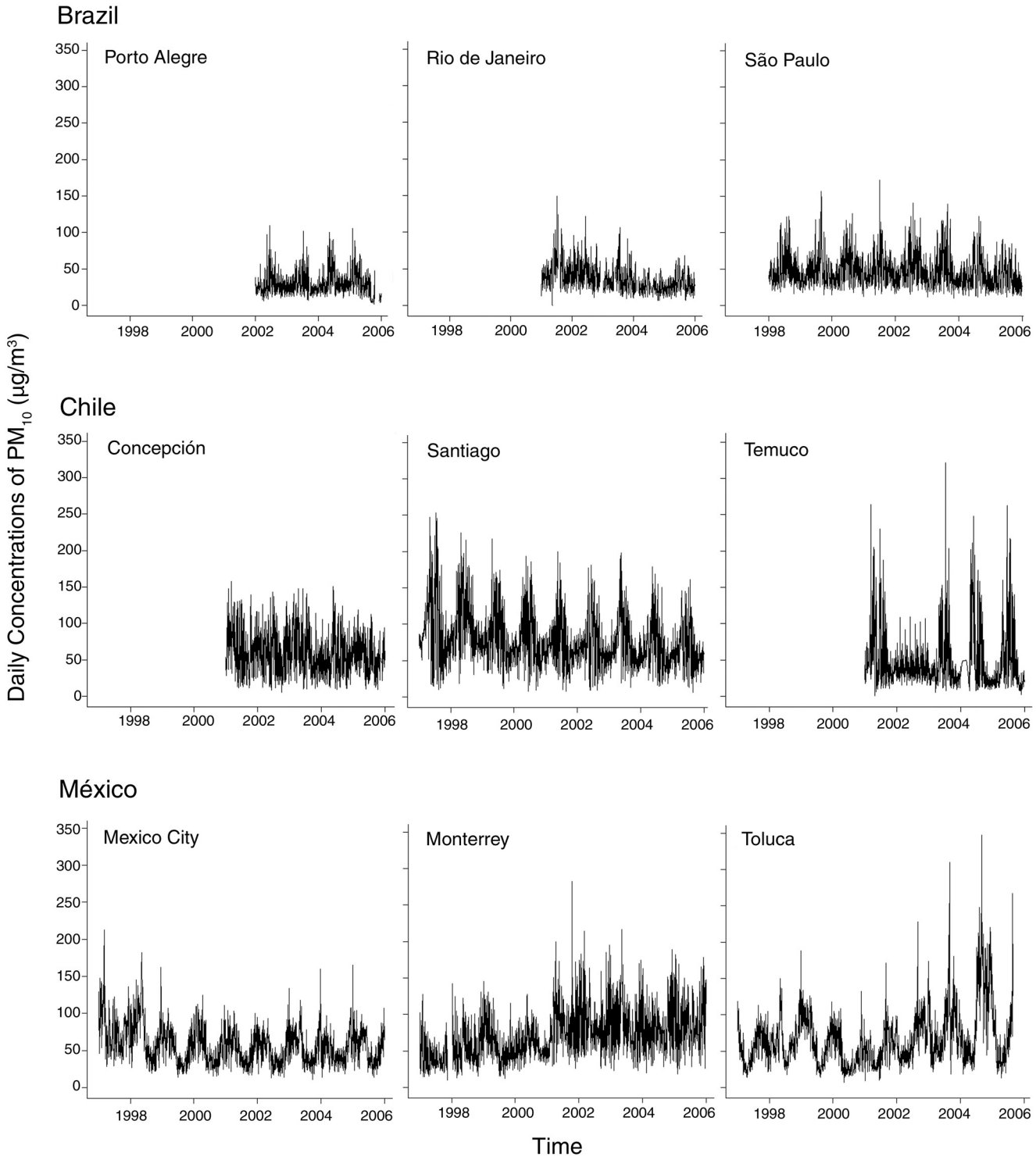


Figure 3. Daily concentrations of PM_{10} ($\mu g/m^3$) by city. All study years. Source: Appendix Figure G.20, available on the HEI Web site.

Table 8. Descriptive Analysis of PM_{10} Concentrations in the Nine Cities

Season / City	Days (*N*)	Mean (μg/m³)	SD	Percentage		
				5	50	95
Whole Period						
São Paulo, Brazil	2921	46.7	21.2	21.5	42.0	89.9
Rio de Janeiro, Brazil	1826	50.9	17.3	29.7	46.9	85.5
Porto Alegre, Brazil	1387	29.6	15.3	11.1	26.5	60.7
Santiago, Chile	3286	78.4	35.7	31.9	71.3	149.2
Temuco, Chile	1826	48.0	37.5	13.8	36.9	130.7
Concepción, Chile	1823	59.1	27.1	19.7	55.9	110.3
Mexico City, México	3287	57.3	24.9	25.0	54.3	101.9
Monterrey, México	3211	71.5	31.7	28.6	67.1	130.9
Toluca, México	3163	66.7	37.0	23.8	58.9	136.4
Warm Season						
São Paulo, Brazil	1457	39.1	13.8	20.8	36.9	65.3
Rio de Janeiro, Brazil	911	47.5	13.9	29.0	45.0	74.0
Porto Alegre, Brazil	671	26.7	12.6	11.8	24.7	49.8
Santiago, Chile	1640	65.7	19.6	36.6	63.8	99.8
Temuco, Chile	911	33.7	18.8	12.8	30.6	61.8
Concepción, Chile	908	60.0	25.7	21.6	56.4	108.7
Mexico City, México	1377	46.5	22.7	22.6	40.4	89.1
Monterrey, México	1367	68.1	26.9	29.6	66.3	113.9
Toluca, México	1345	64.5	42.4	21.7	53.0	154.3
Cold Season						
São Paulo, Brazil	1464	54.2	24.4	23.1	50.5	101.5
Rio de Janeiro, Brazil	915	54.3	19.5	30.4	49.8	90.7
Porto Alegre, Brazil	716	32.4	17.0	9.9	29.1	64.4
Santiago, Chile	1646	91.0	42.9	25.7	87.3	165.6
Temuco, Chile	915	62.2	45.2	15.8	47.3	153.3
Concepción, Chile	915	58.2	28.5	18.0	55.1	111.0
Mexico City, México	1910	65.1	23.4	29.5	63.4	105.9
Monterrey, México	1844	74.0	34.6	28.0	67.7	139.8
Toluca, México	1818	68.4	32.3	27.0	62.4	129.6

and Monterrey), we conducted time-series analyses of air pollutant related childhood mortality only for the large metropolitan cities São Paulo, Rio de Janeiro, Santiago, and Mexico City.

We also were not able to estimate the effects of O_3 for Temuco and Concepción in Chile and for Porto Alegre in Brazil. O_3 was not monitored in the two Chilean cities, and in Porto Alegre the O_3 monitoring data quality was limited, with daily concentrations varying inconsistently across the monitoring sites.

As previously described, diagnostic analyses were conducted to test goodness-of-fit of the models by considering the criteria described earlier in the City-Specific Analyses section (e.g., AIC and PACF). In addition, no significant altered patterns were found in deviance residuals, but for some causes of mortality, such as respiratory conditions and LRI in children, the normality assumption did not hold because of the small number of deaths.

In the following section, we will report results from the single-pollutant models. In general, the effect estimates for PM_{10} in two-pollutant models were similar to those of the single-pollutant models or were slightly increased, while for O_3 the effect estimates decreased. Therefore, to avoid lengthening this report, the two-pollutant models are presented as tables and discussed in the text only if exceptions to these general observations are found.

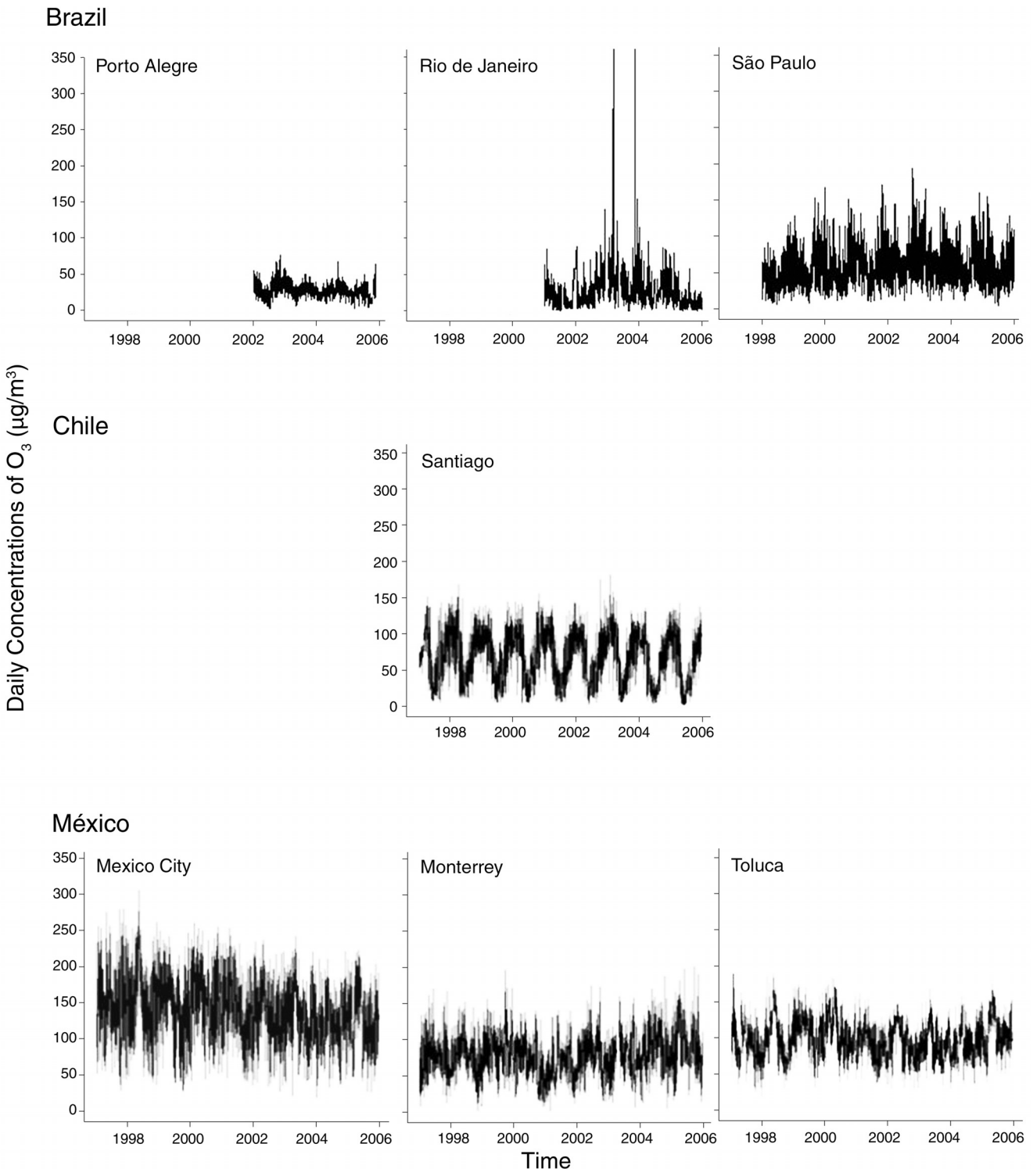


Figure 4. Daily concentrations of O_3 (µg/m³) by city. All study years. Source: Appendix Figure G.21, available on the HEI Web site.

Table 9. Descriptive Analysis of O_3 Concentrations in the Nine Cities[a]

Season / City	Days (*N*)	Mean (μg/m³)[b]	SD	Percentage 5	Percentage 50	Percentage 95
Whole Period						
São Paulo, Brazil	2922	58.2	28.1	21.2	53.4	111.5
Rio de Janeiro, Brazil	1637	28.1	32.8	4.4	21.9	67.4
Porto Alegre, Brazil	1416	27.5	9.9	12.7	26.3	45.2
Santiago, Chile	3264	70.3	34.8	12.9	73.4	123.9
Temuco, Chile	—	—	—	—	—	—
Concepción, Chile	—	—	—	—	—	—
Mexico City, México	3287	138.6	46.8	59.6	138.6	215.2
Monterrey, México	3231	77.8	30.2	29.4	76.6	131.3
Toluca, México	3274	98.4	28.6	52.3	97.6	147.0
Warm Season						
São Paulo, Brazil	1458	64.4	30.4	23.9	60.2	122.0
Rio de Janeiro, Brazil	852	33.2	42.0	5.4	26.5	77.6
Porto Alegre, Brazil	684	29.0	10.7	14.1	27.3	49.3
Santiago, Chile	1640	90.9	24.4	48.2	92.1	129.0
Temuco, Chile	—	—	—	—	—	—
Concepción, Chile	—	—	—	—	—	—
Mexico City, México	1377	134.4	43.5	60.0	134.4	204.9
Monterrey, México	1373	85.4	26.5	45.4	83.9	133.5
Toluca, México	1374	99.8	28.9	51.9	99.6	148.8
Cold Season						
São Paulo, Brazil	1464	52.1	24.0	19.7	48.3	98.4
Rio de Janeiro, Brazil	785	22.6	16.5	3.7	18.4	54.5
Porto Alegre, Brazil	732	26.1	8.9	12.3	25.6	41.1
Santiago, Chile	1624	49.5	31.2	8.6	44.5	106.9
Temuco, Chile	—	—	—	—	—	—
Concepción, Chile	—	—	—	—	—	—
Mexico City, México	1910	141.6	48.9	58.4	142.8	220.9
Monterrey, México	1858	72.2	31.5	24.1	70.2	129.1
Toluca, México	1900	97.4	28.2	53.2	96.4	145.3

[a] — indicates not monitored.

[b] Values are the means of the daily maximum 8-hour moving average O_3 concentrations.

All-Natural-Cause Mortality

PM_{10} The RPCs associated with a 10-μg/m³ increase in PM_{10} concentration showed an increased risk of all-natural-cause, all-age mortality in seven of the nine cities (Table 10). The RPCs for Concepción and Temuco were either negative or not significant. The RPCs ranged from −0.05% in Concepción to 1.26% in Toluca. The RPCs for the largest cities of the ESCALA study, Mexico City and São Paulo, were 1.02% (95% CI = 0.87 to 1.17) and 0.79% (0.64 to 0.94), respectively. The effects of PM_{10} adjusted by O_3 are shown in Table 11.

O_3 The RPCs associated with a 10-μg/m³ increase in O_3 concentration showed an increased risk of all-natural-cause, all-age mortality in Mexico City (0.22% [95% CI = 0.17 to 0.27]), in Monterrey (0.73% [0.56 to 0.90]), in São Paulo (0.18% [0.07 to 0.28]), and Rio de Janeiro (0.13% [0.02 to 0.24]) (Table 12).

Table 10. Nine Cities: Risk Percent Change in Daily Mortality per 10-μg/m^3 Change in PM_{10}, Using DLM 0–3[a]

Cause / Age Group	São Paulo RPC (95% CI)	Rio de Janeiro RPC (95% CI)	Porto Alegre RPC (95% CI)	Santiago RPC (95% CI)	Concepción RPC (95% CI)
All-natural-cause					
All-age	**0.79 (0.64 to 0.94)**	**0.74 (0.49 to 0.99)**	**0.88 (0.28 to 1.48)**	**0.48 (0.35 to 0.61)**	−0.05 (−0.68 to 0.59)
Cardiopulmonary					
All-age	**0.93 (0.71 to 1.15)**	**0.99 (0.61 to 1.38)**	**1.29 (0.37 to 2.22)**	**0.85 (0.66 to 1.05)**	0.09 (−0.9 to 1.10)
≥ 65	**0.88 (0.61 to 1.14)**	**1.66 (1.20 to 2.12)**	**2.53 (1.47 to 3.60)**	**1.06 (0.84 to 1.28)**	0.24 (−0.88 to 1.37)
Respiratory					
All-age	**1.19 (0.77 to 1.62)**	**2.14 (1.41 to 2.87)**	**2.90 (1.03 to 4.81)**	**0.90 (0.56 to 1.25)**	**2.51 (0.58 to 4.48)**
≥ 65	**1.52 (1.00 to 2.03)**	**2.38 (1.56 to 3.20)**	1.69 (−0.41 to 3.84)	**1.01 (0.64 to 1.39)**	**3.78 (1.69 to 5.92)**
Cardiovascular					
All-age	**0.87 (0.63 to 1.11)**	**0.51 (0.06 to 0.96)**	**1.22 (0.16 to 2.29)**	**0.74 (0.51 to 0.97)**	−0.37 (−1.53 to 0.81)
≥ 65	**0.81 (0.50 to 1.12)**	**0.95 (0.43 to 1.48)**	**2.97 (1.75 to 4.21)**	**1.00 (0.75 to 1.25)**	−0.83 (−2.11 to 0.47)
Cerebrovascular–stroke					
All-age	**1.05 (0.55 to 1.55)**	0.73 (−0.05 to 1.51)	**2.63 (0.79 to 4.50)**	**1.20 (0.80 to 1.61)**	0.21 (−1.64 to 2.10)
≥ 65	**0.82 (0.25 to 1.40)**	**1.69 (0.76 to 2.64)**	**3.91 (1.82 to 6.03)**	**0.77 (0.31 to 1.23)**	0.03 (−1.92 to 2.03)
COPD					
All-age	**1.43 (0.69 to 2.18)**	**1.64 (0.19 to 3.12)**	**4.31 (1.81 to 6.87)**	**0.82 (0.15 to 1.50)**	**3.89 (1.12 to 6.75)**
≥ 65	**1.81 (0.97 to 2.65)**	**2.58 (1.00 to 4.19)**	**2.73 (0.00 to 5.54)**	**1.00 (0.27 to 1.74)**	**7.76 (4.80 to 10.8)**

Cause / Age Group	Temuco RPC (95% CI)	Mexico City RPC (95% CI)	Monterrey RPC (95% CI)	Toluca RPC (95% CI)
All-natural-cause				
All-age	0.32 (−0.26 to 0.91)	**1.02 (0.87 to 1.17)**	**1.01 (0.83 to 1.20)**	**1.26 (0.85 to 1.66)**
Cardiopulmonary				
All-age	**1.32 (0.35 to 2.30)**	**0.95 (0.72 to 1.18)**	**1.05 (0.77 to 1.33)**	**1.17 (0.53 to 1.81)**
≥ 65	**1.38 (0.31 to 2.46)**	**1.14 (0.87 to 1.41)**	**1.00 (0.67 to 1.33)**	**1.15 (0.37 to 1.93)**
Respiratory				
All-age	**3.33 (1.73 to 4.96)**	**1.15 (0.72 to 1.58)**	**1.29 (0.70 to 1.88)**	0.15 (−0.84 to 1.14)
≥ 65	**3.74 (1.98 to 5.52)**	**1.49 (0.31 to 2.68)**	0.10 (−0.56 to 0.76)	**1.49 (0.20 to 2.80)**
Cardiovascular				
All-age	0.22 (−0.90 to 1.34)	**0.51 (0.24 to 0.78)**	**0.81 (0.50 to 1.13)**	**1.42 (0.61 to 2.23)**
≥ 65	0.38 (−0.91 to 1.68)	**0.63 (0.31 to 0.95)**	**0.74 (0.37 to 1.11)**	**1.55 (0.62 to 2.50)**
Cerebrovascular–stroke				
All-age	0.94 (−0.68 to 2.59)	**0.22 (0.11 to 0.32)**	**2.28 (1.67 to 2.89)**	0.90 (−0.48 to 2.30)
≥ 65	**2.27 (0.55 to 4.01)**	**1.05 (0.41 to 1.70)**	**1.99 (1.28 to 2.70)**	0.95 (−0.67 to 2.60)
COPD				
All-age	**8.37 (6.22 to 10.56)**	**1.76 (0.54 to 3.00)**	**2.49 (1.66 to 3.33)**	−0.03 (−1.65 to 1.63)
≥ 65	**6.30 (4.13 to 8.53)**	0.28 (−0.42 to 0.99)	−0.80 (−1.69 to 0.10)	−0.16 (−1.91 to 1.62)

[a] **Bolded** values are significant.

In other cities, no significant increased risk was observed. However, in two-pollutant models, where O_3 results are adjusted by PM_{10} concentrations (Table 13), a significant RPC was observed in Santiago (0.60% [0.44 to 0.76]). In stratified analyses by season, RPCs for the warm season were significant for São Paulo (0.64% [0.51 to 0.76]) and Rio de Janeiro (0.31% [0.19 to 0.42]), while in Mexican cities, the effect was higher during the cold season in

Table 11. Risk Percent Change in Daily Mortality per 10-μg/m^3 Change in PM_{10} Adjusted by O_3, Using DLM 0–3[a]

Cause / Age Group	São Paulo RPC (95% CI)	Rio de Janeiro RPC (95% CI)	Santiago RPC (95% CI)
All-natural-cause			
All-age	**0.75 (0.57 to 0.92)**	**0.69 (0.39 to 0.98)**	**0.50 (0.38 to 0.63)**
Cardiopulmonary			
All-age	**0.93 (0.68 to 1.17)**	**0.99 (0.55 to 1.43)**	**0.85 (0.66 to 1.03)**
≥ 65	**0.89 (0.60 to 1.18)**	**1.79 (1.27 to 2.31)**	**1.02 (0.81 to 1.23)**
Respiratory			
All-age	**1.04 (0.57 to 1.50)**	**2.25 (1.41 to 3.08)**	**0.89 (0.55 to 1.22)**
≥ 65	**1.52 (0.97 to 2.07)**	**2.58 (1.66 to 3.52)**	**1.03 (0.66 to 1.39)**
Cardiovascular			
All-age	**0.83 (0.56 to 1.10)**	0.47 (−0.03 to 0.98)	**0.73 (0.51 to 0.96)**
≥ 65	**0.83 (0.49 to 1.16)**	**1.01 (0.43 to 1.60)**	**0.96 (0.71 to 1.21)**
Cerebrovascular–stroke			
All-age	**1.26 (0.74 to 1.79)**	0.59 (−0.27 to 1.47)	**1.24 (0.85 to 1.64)**
≥ 65	**1.11 (0.51 to 1.72)**	**1.78 (0.73 to 2.84)**	**0.81 (0.35 to 1.26)**
COPD			
All-age	**1.27 (0.50 to 2.06)**	**2.26 (0.64 to 3.91)**	**0.99 (0.33 to 1.64)**
≥ 65	**1.76 (0.90 to 2.62)**	**2.92 (1.16 to 4.71)**	**1.15 (0.45 to 1.85)**
	Mexico City RPC (95% CI)	Monterrey RPC (95% CI)	Toluca RPC (95% CI)
All-natural-cause			
All-age	**0.58 (0.42 to 0.74)**	**1.04 (0.86 to 1.22)**	**1.27 (0.86 to 1.67)**
Cardiopulmonary			
All-age	**0.50 (0.24 to 0.75)**	**1.07 (0.79 to 1.35)**	**1.18 (0.54 to 1.82)**
≥ 65	**0.54 (0.24 to 0.83)**	**1.72 (1.19 to 2.25)**	**1.15 (0.38 to 1.94)**
Respiratory			
All-age	**0.61 (0.14 to 1.09)**	0.85 (−0.08 to 1.79)	0.25 (−0.73 to 1.24)
≥ 65	**0.91 (0.33 to 1.49)**	−0.42 (−1.44 to 0.62)	**1.64 (0.35 to 2.95)**
Cardiovascular			
All-age	**0.44 (0.14 to 0.73)**	**0.91 (0.40 to 1.43)**	**1.42 (0.62 to 2.24)**
≥ 65	**0.41 (0.07 to 0.76)**	**1.37 (0.77 to 1.97)**	**1.54 (0.60 to 2.48)**
Cerebrovascular–stroke			
All-age	**0.96 (0.36 to 1.56)**	**2.80 (1.78 to 3.83)**	0.97 (−0.41 to 2.37)
≥ 65	**0.91 (0.21 to 1.61)**	**3.63 (2.44 to 4.83)**	1.03 (−0.59 to 2.68)
COPD			
All-age	0.57 (−0.15 to 1.30)	−0.68 (−1.98 to 0.64)	0.07 (−1.56 to 1.72)
≥ 65	0.32 (−0.46 to 1.11)	−1.62 (−2.98 to −0.24)	−0.02 (−1.77 to 1.76)

[a] **Bolded** values are significant.

Table 12. Risk Percent Change in Daily Mortality per 10-μg/m^3 Change in O_3, Using DLM 0–3[a]

Cause / Age Group	São Paulo RPC (95% CI)	Rio de Janeiro RPC (95% CI)	Santiago RPC (95% CI)
All-natural-cause			
All-age	**0.18 (0.07 to 0.28)**	**0.13 (0.02 to 0.24)**	−0.11 (−0.34 to 0.12)
Cardiopulmonary			
All-age	**0.21 (0.05 to 0.36)**	**0.24 (0.06 to 0.42)**	**0.16 (0.06 to 0.27)**
≥ 65	**0.27 (0.08 to 0.45)**	**0.38 (0.17 to 0.59)**	**0.22 (0.10 to 0.33)**
Respiratory			
All-age	**0.32 (0.00 to 0.63)**	0.15 (−0.20 to 0.49)	0.19 (0.00 to 0.39)
≥ 65	**0.43 (0.05 to 0.81)**	−0.02 (−0.42 to 0.37)	0.13 (−0.08 to 0.34)
Cardiovascular			
All-age	**0.24 (0.08 to 0.41)**	**0.23 (0.03 to 0.44)**	0.10 (−0.01 to 0.21)
≥ 65	**0.30 (0.08 to 0.52)**	**0.28 (0.03 to 0.52)**	**0.14 (0.01 to 0.27)**
Cerebrovascular–stroke			
All-age	−0.02 (−0.36 to 0.33)	−0.35 (−0.74 to 0.04)	−0.10 (−0.27 to 0.07)
≥ 65	−0.02 (−0.41 to 0.38)	**−1.00 (−1.50 to −0.49)**	0.18 (−0.05 to 0.41)
COPD			
All-age	**0.97 (0.42 to 1.53)**	0.31 (−0.33 to 0.95)	0.00 (−0.35 to 0.36)
≥ 65	**1.08 (0.50 to 1.66)**	0.23 (−0.46 to 0.92)	0.21 (−0.19 to 0.61)

Cause / Age Group	Mexico City RPC (95% CI)	Monterrey RPC (95% CI)	Toluca RPC (95% CI)
All-natural-cause			
All-age	**0.22 (0.17 to 0.27)**	**0.73 (0.56 to 0.90)**	−0.47 (−0.80 to −0.13)
Cardiopulmonary			
All-age	**0.22 (0.14 to 0.30)**	**0.69 (0.42 to 0.95)**	−0.49 (−1.02 to 0.04)
≥ 65	**0.31 (0.22 to 0.41)**	**0.79 (0.48 to 1.11)**	−0.20 (−0.85 to 0.46)
Respiratory			
All-age	**0.22 (0.07 to 0.37)**	0.25 (−0.31 to 0.81)	−0.62 (−1.45 to 0.22)
≥ 65	0.11 (−0.07 to 0.29)	−0.09 (−0.73 to 0.55)	−0.93 (−2.05 to 0.21)
Cardiovascular			
All-age	**0.12 (0.03 to 0.22)**	**0.77 (0.46 to 1.07)**	−0.07 (−0.75 to 0.62)
≥ 65	**0.22 (0.11 to 0.32)**	**0.91 (0.56 to 1.27)**	0.06 (−0.74 to 0.85)
Cerebrovascular–stroke			
All-age	**0.29 (0.10 to 0.48)**	0.59 (−0.02 to 1.19)	0.25 (−1.00 to 1.51)
≥ 65	**0.43 (0.21 to 0.65)**	0.68 (−0.01 to 1.39)	0.14 (−1.34 to 1.65)
COPD			
All-age	−0.06 (−0.28 to 0.17)	0.73 (−0.09 to 1.54)	−0.35 (−1.79 to 1.11)
≥ 65	0.01 (−0.23 to 0.26)	−0.26 (−1.14 to 0.62)	−0.22 (−1.78 to 1.36)

[a] **Bolded** values are significant.

Mexico City and during the warm season in Monterrey (Tables 14 and 15).

Cardiopulmonary Mortality

PM_{10} The RPCs associated with a 10-μg/m^3 increase in PM_{10} concentration showed an increased risk of all-age cardiopulmonary mortality in all cities except Concepción (Table 10). RPCs ranged from 0.09% in Concepción to 1.32% in Temuco.

Among people 65 years or older, the RPCs were slightly higher in most cities than those for the all-age group. The greatest cardiopulmonary effect in the older age group was

Table 13. Risk Percent Change in Daily Mortality per 10-μg/m^3 Change in O_3 Adjusted by PM_{10}, Using DLM 0–3[a]

Cause / Age Group	São Paulo RPC (95% CI)	Rio de Janeiro RPC (95% CI)	Santiago RPC (95% CI)
All-natural-cause			
All-age	0.02 (−0.10 to 0.14)	0.10 (−0.02 to 0.22)	**0.60 (0.44 to 0.76)**
Cardiopulmonary			
All-age	0.05 (−0.12 to 0.22)	**0.20 (0.02 to 0.38)**	**0.95 (0.70 to 1.20)**
≥ 65	0.06 (−0.14 to 0.26)	**0.26 (0.05 to 0.48)**	**1.28 (1.00 to 1.56)**
Respiratory			
All-age	0.07 (−0.26 to 0.40)	0.07 (−0.29 to 0.42)	−0.09 (−0.56 to 0.37)
≥ 65	0.02 (−0.38 to 0.41)	−0.11 (−0.52 to 0.30)	−0.49 (−0.99 to 0.01)
Cardiovascular			
All-age	0.13 (−0.05 to 0.31)	0.19 (−0.02 to 0.41)	**1.28 (0.98 to 1.57)**
≥ 65	0.11 (−0.12 to 0.34)	0.22 (−0.03 to 0.46)	**1.48 (1.15 to 1.81)**
Cerebrovascular–stroke			
All-age	−0.27 (−0.62 to 0.09)	−0.40 (−0.79 to 0.00)	**−0.70 (−1.16 to −0.25)**
≥ 65	−0.25 (−0.65 to 0.15)	**−1.08 (−1.59 to −0.57)**	**1.42 (0.84 to 2.01)**
COPD			
All-age	**0.57 (0.01 to 1.14)**	0.24 (−0.41 to 0.88)	0.13 (−0.75 to 1.01)
≥ 65	**0.78 (0.21 to 1.36)**	0.15 (−0.55 to 0.85)	**1.05 (0.10 to 2.00)**
	Mexico City RPC (95% CI)	Monterrey RPC (95% CI)	Toluca RPC (95% CI)
All-natural-cause			
All-age	0.01 (−0.05 to 0.06)	**0.56 (0.38 to 0.73)**	−0.33 (−0.68 to 0.01)
Cardiopulmonary			
All-age	0.01 (−0.08 to 0.10)	**0.53 (0.26 to 0.80)**	−0.35 (−0.89 to 0.20)
≥ 65	**0.12 (0.01 to 0.22)**	0.10 (−0.42 to 0.63)	−0.05 (−0.72 to 0.62)
Respiratory			
All-age	−0.01 (−0.18 to 0.16)	0.22 (−0.73 to 1.19)	−0.61 (−1.45 to 0.25)
≥ 65	0.05 (−0.16 to 0.26)	−0.67 (−1.73 to 0.42)	−1.04 (−2.19 to 0.12)
Cardiovascular			
All-age	0.02 (−0.08 to 0.13)	−0.16 (−0.67 to 0.35)	0.15 (−0.55 to 0.84)
≥ 65	**0.15 (0.03 to 0.27)**	0.15 (−0.44 to 0.75)	0.24 (−0.56 to 1.06)
Cerebrovascular–stroke			
All-age	0.14 (−0.08 to 0.35)	**−1.08 (−2.1 to −0.06)**	0.37 (−0.91 to 1.66)
≥ 65	**0.28 (0.03 to 0.53)**	−0.40 (−1.57 to 0.78)	0.16 (−1.35 to 1.69)
COPD			
All-age	−0.17 (−0.44 to 0.09)	−0.78 (−2.13 to 0.59)	−0.39 (−1.86 to 1.11)
≥ 65	0.01 (−0.28 to 0.29)	**−2.32 (−3.75 to −0.87)**	−0.27 (−1.87 to 1.35)

[a] **Bolded** values are significant.

Table 14. Cold Season: Risk Percent Change in Daily Mortality per 10-μg/m^3 Change in O_3, Using DLM 0–3[a]

Cause / Age Group	São Paulo RPC (95% CI)	Rio de Janeiro RPC (95% CI)	Santiago RPC (95% CI)
All-natural-cause			
All-age	**−0.43 (−0.60 to −0.25)**	**−0.55 (−0.96 to −0.13)**	−0.09 (−0.43 to 0.24)
Cardiopulmonary			
All-age	**−0.88 (−1.13 to −0.62)**	−0.17 (−0.81 to 0.48)	0.09 (−0.06 to 0.24)
≥ 65	**−0.76 (−1.06 to −0.45)**	0.18 (−0.58 to 0.94)	**0.18 (0.01 to 0.34)**
Respiratory			
All-age	−0.18 (−0.67 to 0.32)	0.68 (−0.55 to 1.93)	0.10 (−0.16 to 0.37)
≥ 65	−0.10 (−0.69 to 0.51)	−0.01 (−1.43 to 1.43)	0.07 (−0.21 to 0.34)
Cardiovascular			
All-age	**−1.17 (−1.46 to −0.87)**	−0.47 (−1.21 to 0.28)	0.05 (−0.10 to 0.20)
≥ 65	**−0.85 (−1.20 to −0.48)**	0.15 (−0.75 to 1.04)	0.06 (−0.11 to 0.24)
Cerebrovascular–stroke			
All-age	**−0.59 (−1.17 to −0.02)**	0.55 (−0.83 to 1.95)	0.06 (−0.20 to 0.32)
≥ 65	−0.66 (−1.37 to 0.05)	0.17 (−1.48 to 1.85)	0.09 (−0.24 to 0.42)
COPD			
All-age	0.20 (−0.67 to 1.08)	**3.80 (1.34 to 6.32)**	0.11 (−0.36 to 0.59)
≥ 65	−0.29 (−1.24 to 0.68)	**3.37 (0.72 to 6.09)**	0.16 (−0.36 to 0.69)

Cause / Age Group	Mexico City RPC (95% CI)	Monterrey RPC (95% CI)	Toluca RPC (95% CI)
All-natural-cause			
All-age	**0.21 (0.15 to 0.27)**	**0.60 (0.31 to 0.88)**	**0.44 (0.23 to 0.65)**
Cardiopulmonary			
All-age	**0.17 (0.07 to 0.26)**	**0.36 (0.03 to 0.68)**	−0.39 (−1.05 to 0.28)
≥ 65	**0.19 (0.08 to 0.31)**	**0.47 (0.09 to 0.85)**	−0.36 (−1.18 to 0.47)
Respiratory			
All-age	−0.02 (−0.18 to 0.13)	−0.15 (−0.82 to 0.52)	−0.43 (−1.45 to 0.59)
≥ 65	−0.06 (−0.27 to 0.16)	−0.14 (−0.91 to 0.63)	0.28 (−1.14 to 1.73)
Cardiovascular			
All-age	**0.23 (0.11 to 0.34)**	**0.50 (0.12 to 0.87)**	−0.33 (−1.20 to 0.55)
≥ 65	**0.47 (0.34 to 0.60)**	**0.78 (0.34 to 1.22)**	0.53 (−0.47 to 1.54)
Cerebrovascular–stroke			
All-age	**0.25 (0.02 to 0.49)**	**1.62 (0.86 to 2.38)**	**3.84 (2.17 to 5.54)**
≥ 65	**0.87 (0.60 to 1.14)**	**1.31 (0.44 to 2.19)**	**3.53 (1.55 to 5.56)**
COPD			
All-age	0.10 (−0.16 to 0.37)	0.47 (−0.52 to 1.46)	1.72 (−0.07 to 3.54)
≥ 65	0.18 (−0.11 to 0.46)	−0.01 (−1.05 to 1.04)	−0.28 (−2.23 to 1.70)

[a] **Bolded** values are significant.

Table 15. Warm Season: Risk Percent Change in Daily Mortality per 10-μg/m^3 Change in O_3, Using DLM 0–3[a]

Cause / Age Group	São Paulo RPC (95% CI)	Rio de Janeiro RPC (95% CI)	Santiago RPC (95% CI)
All-natural-cause			
All-age	**0.64 (0.51 to 0.76)**	**0.31 (0.19 to 0.42)**	−0.20 (−0.52 to 0.13)
Cardiopulmonary			
All-age	**0.67 (0.48 to 0.86)**	**0.44 (0.25 to 0.62)**	**0.17 (0.01 to 0.34)**
≥ 65	**0.74 (0.51 to 0.97)**	**0.45 (0.24 to 0.67)**	0.02 (−0.15 to 0.18)
Respiratory			
All-age	**1.45 (1.07 to 1.82)**	0.30 (−0.06 to 0.67)	0.22 (−0.1 to 0.54)
≥ 65	**1.59 (1.15 to 2.04)**	0.12 (−0.30 to 0.54)	−0.19 (−0.5 to 0.13)
Cardiovascular			
All-age	**0.40 (0.19 to 0.62)**	**0.35 (0.15 to 0.55)**	0.16 (−0.03 to 0.35)
≥ 65	**0.41 (0.15 to 0.68)**	**0.56 (0.31 to 0.81)**	0.09 (−0.1 to 0.28)
Cerebrovascular–stroke			
All-age	**0.95 (0.54 to 1.37)**	**−0.51 (−0.91 to −0.12)**	−0.01 (−0.31 to 0.30)
≥ 65	**1.36 (0.85 to 1.87)**	**−0.62 (−1.13 to −0.10)**	0.33 (−0.04 to 0.71)
COPD			
All-age	**2.06 (1.40 to 2.72)**	0.31 (−0.33 to 0.95)	−0.26 (−0.81 to 0.29)
≥ 65	**2.57 (1.89 to 3.26)**	0.12 (−0.59 to 0.83)	−0.26 (−0.84 to 0.32)
	Mexico City RPC (95% CI)	Monterrey RPC (95% CI)	Toluca RPC (95% CI)
All-natural-cause			
All-age	**0.12 (0.03 to 0.22)**	**0.94 (0.63 to 1.24)**	0.09 (−0.47 to 0.65)
Cardiopulmonary			
All-age	**0.23 (0.08 to 0.37)**	**0.95 (0.48 to 1.42)**	0.43 (−0.46 to 1.33)
≥ 65	0.13 (−0.04 to 0.30)	**0.99 (0.42 to 1.55)**	0.86 (−0.27 to 2.00)
Respiratory			
All-age	0.23 (−0.06 to 0.51)	**1.51 (0.47 to 2.56)**	0.25 (−1.30 to 1.83)
≥ 65	**0.45 (0.09 to 0.80)**	0.76 (−0.44 to 1.97)	1.01 (−1.09 to 3.16)
Cardiovascular			
All-age	−0.03 (−0.19 to 0.13)	**1.06 (0.53 to 1.59)**	0.32 (−0.77 to 1.43)
≥ 65	0.09 (−0.1 to 0.29)	**1.91 (1.28 to 2.54)**	0.42 (−0.85 to 1.71)
Cerebrovascular–stroke			
All-age	0.09 (−0.23 to 0.40)	**1.54 (0.46 to 2.62)**	0.52 (−1.52 to 2.61)
≥ 65	0.07 (−0.31 to 0.46)	**1.42 (0.18 to 2.68)**	−0.14 (−2.49 to 2.28)
COPD			
All-age	0.39 (−0.05 to 0.82)	−0.91 (−2.46 to 0.66)	1.53 (−1.03 to 4.15)
≥ 65	**0.61 (0.14 to 1.08)**	**−1.68 (−3.32 to 0.00)**	1.86 (−0.90 to 4.70)

[a] **Bolded** values are significant.

observed in Porto Alegre (2.53% [95% CI = 1.47 to 3.60]). In the two largest cities, Mexico City and São Paulo, the RPCs were 1.14% (0.87 to 1.41) and 0.88% (0.61 to 1.14), respectively.

O_3 The RPCs associated with a 10-μg/m^3 increase in O_3 concentration showed significant increases in all-age cardiopulmonary mortality in all cities except Toluca with RPCs ranging from 0.16% in Santiago to 0.69% in Monterrey (Table 12). The RPCs were slightly higher for people 65 years or older.

In two-pollutant models (Table 13), an increase in O_3 concentration adjusted by PM_{10} was associated with an increased risk of cardiopulmonary mortality in Santiago and Rio de Janeiro in both age groups. The all-age RPC for Santiago was 0.95% (95% CI = 0.70 to 1.20); for Rio de Janeiro it was 0.20% (0.02 to 0.38). In the ≥ 65 age group the RPC for Santiago was 1.28% (1.00 to 1.56) and was 0.26% (0.05 to 0.48) for Rio de Janeiro. Monterrey had a significant RPC for the all-age group (0.53% [0.26 to 0.80]), but not for the ≥ 65 age group. Mexico City had a significant RPC for the ≥ 65 age group (0.12% [0.01 to 0.22]), but not for the all-age group.

When data were stratified by season, higher RPCs were observed during the warm season (Table 15). Significant RPCs were observed in São Paulo (0.67% [95% CI = 0.48 to 0.86]), Rio de Janeiro (0.44% [0.25 to 0.62]), Santiago (0.17% [0.01 to 0.34]), Mexico City (0.23% [0.08 to 0.37]), and Monterrey (0.95% [0.48 to 1.42]). In the older age group, significant and larger RPCs were observed in São Paulo, Rio de Janeiro, and Monterrey. No significant changes were observed in other cities.

Respiratory Mortality

PM_{10} The RPCs associated with a 10-μg/m^3 increase in PM_{10} concentration showed an increased risk of all-age respiratory mortality in all cities except Toluca (Table 10). The RPCs ranged from 0.15% in Toluca to 3.33% in Temuco. In the largest cities, Mexico City and São Paulo, the RPCs were 1.15% (95% CI = 0.72 to 1.58) and 1.19% (0.77 to 1.62), respectively. The effects were generally higher in the ≥ 65 age group than in the all-age group, reaching 3.78% (1.69 to 5.92) in Concepción. However, the effects in the older age group were lower and not significant in Porto Alegre and in Monterrey. In two-pollutant models, the effects of PM_{10} adjusted by O_3 were, in some but not all cases, slightly lower compared with those of PM_{10}, particularly in Mexico City, but the RPCs remained significant in most cases (Table 11).

O_3 The RPCs associated with a 10-μg/m^3 increase in O_3 concentration showed a significant increase in all-age respiratory mortality (Table 12) only in São Paulo (0.32% [95% CI = 0.00 to 0.63]) and Mexico City (0.22% [0.07 to 0.37]); however, in two-pollutant models, for which O_3 concentration was adjusted by PM_{10} (Table 13), the effects lost significance.

In analyses stratified by season (Tables 14 and 15), significant increases in RPC for the all-age group were observed during the warm season for São Paulo (1.45% [95% CI = 1.07 to 1.82]) and Monterrey (1.51% [0.47 to 2.56]). In people 65 years or older, these estimates were slightly higher in São Paulo and the RPC reached significance in Mexico City (0.45% [0.09 to 0.80]).

Cardiovascular Mortality

PM_{10} The RPCs associated with a 10-μg/m^3 increase in PM_{10} concentration showed an increased risk of cardiovascular mortality for both age groups in all cities except Concepción and Temuco (Table 10). The RPCs ranged from −0.37% in Concepción to 1.42% in Toluca. In the largest cities, São Paulo and Mexico City, the RPCs were 0.87% (95% CI = 0.63 to 1.11) and 0.51% (0.24 to 0.78). In the ≥ 65 age group, RPCs changed to 0.63% (0.31 to 0.95) in Mexico City and to 2.97% (1.75 to 4.21) in Porto Alegre. No significant effects were observed in Concepción and Temuco.

O_3 The RPCs associated with a 10-μg/m^3 increase in O_3 concentration showed a significant increase in all-age cardiovascular mortality in São Paulo, Rio de Janeiro, Mexico City and Monterrey, with slightly larger effects among people 65 years or older (Table 12). However, in two-pollutant models, in which O_3 concentration was adjusted by PM_{10} (Table 13), the RPCs lost significance in these cities, but gained significance in Santiago.

After stratification by season, significant RPCs were observed for all-age cardiovascular mortality in Mexico City (0.23% [95% CI = 0.11 to 0.34]) and Monterrey (0.50% [0.12 to 0.87]) during the cold season (Table 14) and in São Paulo, Rio de Janeiro, and Monterrey during the warm season (Table 15). Results for São Paulo in the cold season were negative and statistically significant. Larger effects were observed among people 65 years or older.

Cerebrovascular–Stroke Mortality

PM_{10} The RPCs associated with a 10-μg/m^3 increase in PM_{10} concentration (DLM 0–3) showed an increased risk of all-age cerebrovascular–stroke mortality in all cities

except Rio de Janeiro, Concepción, Temuco, and Toluca (Table 10). RPCs ranged from 0.21% in Concepción to 2.63% in Porto Alegre. In the largest cities, São Paulo and Mexico City, RPCs were 1.05% (95% CI = 0.55 to 1.55) and 0.22% (0.11 to 0.32) respectively. The RPCs were generally higher in the ≥ 65 age group than in the all-age group and reached significance in two additional cities, Rio de Janeiro (1.69 [0.76 to 2.64]) and Temuco (2.27% [0.55 to 4.01]).

O_3 Only in Mexico City did the RPCs associated with a 10-μg/m^3 increase in O_3 concentration show a significant increase in all-age cerebrovascular–stroke mortality (0.29% [95% CI = 0.10 to 0.48]) (Table 12). This effect was slightly larger in people 65 years or older. In Rio de Janeiro the effect was statistically significant in the older age group but the effect was negative. As shown in Table 13, the effect in Mexico City was marginally significant in a two-pollutant model, for which O_3 concentration was adjusted by PM_{10} (0.28% [0.03 to 0.53]), and a larger effect in the older age group appeared for Santiago (1.42% [0.84 to 2.01]).

After stratification by season, significant RPCs were observed for the all-age group in the Mexican cities during the cold season (Table 14): Mexico City (0.25% [95% CI = 0.02 to 0.49]), Monterrey (1.62% [0.86 to 2.38]), and Toluca (3.84% [2.17 to 5.54]). For the ≥ 65 age group, this effect increased in Mexico City (0.87% [0.60 to 1.14]). During the warm season (Table 15), significant RPCs were observed in São Paulo and Monterrey. In Rio de Janeiro it was also significant but the effect was negative.

COPD Mortality

PM_{10} The RPCs associated with a 10-μg/m^3 increase in PM_{10} concentration showed an increased risk of all-age COPD in all cities except Toluca (Table 10). The RPCs ranged from −0.03% in Toluca to 8.37% in Temuco. In the largest cities, São Paulo and Mexico City, the RPCs were 1.43% (95% CI = 0.69 to 2.18) and 1.76% (0.54 to 3.00) respectively.

As with the all-age group, the RPCs for COPD in the older age group were also not elevated for Toluca. However, the RPCs for COPD in the older age group lost significance in Mexico City and Monterrey, were lower in Temuco and Porto Alegre, and were higher in the other four cities.

O_3 The RPCs associated with a 10-μg/m^3 increase in O_3 concentration were not significant for COPD in either of the two age groups in all cities except São Paulo (Table 12). After stratification by season, significant RPCs were observed in Rio de Janeiro during the cold season (Table 14). During the warm season (Table 15), significant RPCs were observed in the all-age group in São Paulo (2.06% [95% CI = 1.40 to 2.72]). In the older age group, RPCs were significant in Mexico City (0.61% [0.14 to 1.08]) and higher in São Paulo (2.57% [1.89 to 3.26]).

Respiratory Mortality in Children

Tables 16–19 present the effects of PM_{10} or O_3 concentration on respiratory mortality for the age groups < 1 year (infants) and children 1–4 years, and on LRI for infants and children 1–14 years in Mexico City, Santiago, and São Paulo.

PM_{10} The RPCs associated with a 10-μg/m^3 increase in PM_{10} concentration (Table 16) showed an increased risk in Santiago for respiratory mortality both in infants (0.64% [95% CI = 0.23 to 1.05]) and in children 1–4 years (0.61% [0.10 to 1.13]). The RPCs for LRI were significantly increased for infants in Mexico City (1.38% [0.09 to 2.69]) and for children 1–14 years in Santiago (1.28% [0.80 to 1.76]).

O_3 The RPCs associated with a 10-μg/m^3 increase in O_3 concentration (Table 17) showed an increased risk of respiratory mortality in Mexico City among children 1–4 years (1.49% [95% CI = 0.31 to 2.68]) and of LRI among infants and children 1–14 years (0.85% [0.37 to 1.33] and 1.76% [0.54 to 3.00], respectively. In Santiago, significant negative results were observed for respiratory mortality in the 1–4 age group and for LRI in the 1–14 age group.

After stratification by season, significantly increased RPCs were observed for respiratory mortality among children 1–4 years and for LRI among both infants and children 1–14 years in Mexico City during the cold season (Table 18). For São Paulo the effect was also statistically significant and positive for LRI in the 1–14 age group (4.73% [95% CI = 0.54 to 9.09]) but negative for LRI in infants (−6.93% [−9.36 to −4.43]). For Santiago, the respiratory mortality effect was statistically significant but negative for infants (−1.11% [−2.09 to −0.13]). During the warm season (Table 19), significantly increased RPCs were observed for respiratory mortality among infants in São Paulo (4.32% [2.36 to 6.32]) and among children 1–4 years (3.31% [0.51 to 6.18]) in Mexico City. In Santiago, statistically significant but negative results were observed for respiratory mortality in the 1–4 age group and for LRI in the 1–14 age group.

Table 16. São Paulo, Santiago, and Mexico City: Risk Percent Change in Daily Mortality for Children per 10-μg/m^3 Change in PM_{10}, Using DLM 0–3[a]

Cause / Age Group	São Paulo RPC (95% CI)	Santiago RPC (95% CI)	Mexico City RPC (95% CI)
Respiratory			
< 1	**−3.96 (−5.83 to −2.05)**	**0.64 (0.23 to 1.05)**	0.69 (−0.49 to 1.88)
1–4	−3.03 (−6.01 to 0.03)	**0.61 (0.10 to 1.13)**	−0.24 (−3.42 to 3.05)
Lower respiratory infection			
< 1	**−2.53 (−4.65 to −0.36)**	−1.54 (−3.10 to 0.04)	**1.38 (0.09 to 2.69)**
1–14	1.40 (−2.05 to 4.98)	**1.28 (0.80 to 1.76)**	3.10 (−0.20 to 6.51)

[a] **Bolded** values are significant.

Table 17. São Paulo, Santiago, and Mexico City: Risk Percent Change in Daily Mortality for Children per 10-μg/m^3 Change in O_3, Using DLM 0–3[a]

Cause / Age Group	São Paulo RPC (95% CI)	Santiago RPC (95% CI)	Mexico City RPC (95% CI)
Respiratory			
< 1	−0.26 (−1.73 to 1.23)	−0.62 (−1.37 to 0.13)	0.11 (−0.33 to 0.55)
1–4	0.63 (−1.65 to 2.95)	**−1.50 (−2.45 to −0.55)**	**1.49 (0.31 to 2.68)**
Lower respiratory infection			
< 1	1.52 (−0.16 to 3.23)	−0.51 (−1.33 to 0.31)	**0.85 (0.37 to 1.33)**
1–14	−1.00 (−3.37 to 1.41)	**−1.17 (−2.1 to −0.23)**	**1.76 (0.54 to 3.00)**

[a] **Bolded** values are significant.

Table 18. Cold Season São Paulo, Santiago, and Mexico City: Risk Percent Change in Daily Mortality for Children per 10-μg/m^3 Change in O_3, Using DLM 0–3[a]

Cause / Age Group	São Paulo RPC (95% CI)	Santiago RPC (95% CI)	Mexico City RPC (95% CI)
Respiratory			
< 1	−8.75 (−16.95 to 0.25)	**−1.11 (−2.09 to −0.13)**	0.36 (−0.13 to 0.86)
1–4	2.23 (−1.95 to 6.60)	0.06 (−1.22 to 1.35)	**2.02 (0.67 to 3.40)**
Lower respiratory infection			
< 1	**−6.93 (−9.36 to −4.43)**	−0.88 (−2.06 to 0.32)	**0.78 (0.25 to 1.32)**
1–14	**4.73 (0.54 to 9.09)**	−0.42 (−1.64 to 0.83)	**2.53 (1.12 to 3.96)**

[a] **Bolded** values are significant.

RESULTS STRATIFIED BY SES

In this section we present the results of the time-series analyses stratified by SES conducted in Mexico City, São Paulo, Rio de Janeiro, and Santiago. PM_{10} and O_3 effects on mortality for different causes of death and age groups were analyzed. Three SES strata (low, medium, and high) were compared within each pollutant, cause, and age group. We did not conduct formal tests for interaction, but evaluated effect modification by considering whether CIs for differing strata enclosed the point estimates of the other strata; therefore, we are presenting the RPCs in each SES stratum. Only results for adults were explored in this analysis. We did not

Table 19. Warm Season São Paulo, Santiago, and Mexico City: Risk Percent Change in Daily Mortality for Children per 10-μg/m^3 change in O_3, Using DLM 0–3[a]

Cause / Age Group	São Paulo RPC (95% CI)	Santiago RPC (95% CI)	Mexico City RPC (95% CI)
Respiratory			
< 1	**4.32 (2.36 to 6.32)**	0.71 (−0.74 to 2.18)	−0.16 (−1.13 to 0.82)
1–4	2.69 (−0.29 to 5.77)	**−5.42 (−7.09 to −3.72)**	**3.31 (0.51 to 6.18)**
Lower respiratory infection			
< 1	2.24 (−0.15 to 4.69)	0.45 (−1.28 to 2.21)	0.27 (−0.86 to 1.40)
1–14	0.94 (−2.36 to 4.37)	**−3.11 (−4.75 to −1.44)**	−0.42 (−2.95 to 2.17)

[a] **Bolded** values are significant.

stratify by SES for children's mortality because the number of daily events was too low when divided among the three SES strata. Percentage changes by cause for a 10-μg/m^3 increase of PM_{10} or O_3 using DLM 0–3 for low-, medium-, and high-SES groups are shown in Figures 5 to 10 for Mexico City, São Paulo, Rio de Janeiro, and Santiago. The corresponding data are in Appendix Tables I.9–I.12, available on the HEI Web site.

PM_{10}

In Mexico City, all-natural-cause, all-age mortality (Figure 5) was significantly related to PM_{10} in both medium- and high-SES groups (1.09% [95% CI = 0.86 to 1.33] and 0.30% [0.04 to 0.56], respectively), with a higher RPC in the medium-SES group. No significant increase was observed in the low-SES group. In contrast, all-age respiratory mortality (Figure 6) and all-age COPD mortality (Figure 7) were significantly related to PM_{10} in the low-SES group (1.69% [1.11 to 2.28] and 1.71% [0.82 to 2.62], respectively). A smaller increase was observed in the medium-SES group for respiratory mortality and no effect was observed in the high-SES group. Mortality for COPD was not associated with PM_{10}, either in the medium- or in the high-SES group. All-age cardiovascular and cerebrovascular–stroke mortality were significantly associated with PM_{10} in the medium- and high-SES groups, while no effect was observed in the low-SES group (Figures 8 and 9). Of particular interest is the high RPC observed for cerebrovascular–stroke mortality in people 65 years or older (Figure 9) in both the medium- and high-SES groups (2.88% [1.88 to 3.89] and 2.02% [0.93 to 3.13]).

For São Paulo, the pattern was distinct. All-natural-cause, all-age mortality (Figure 5) was significantly related to PM_{10} in low-, medium-, and high-SES groups, with the high-SES group having the highest RPC (1.40% [95% CI = 1.14 to 1.67]). All-age respiratory mortality was significantly related to PM_{10} in all three SES groups (Figure 6), but effects in people 65 years or older showed a trend with higher effects in the high-SES group. For all-age COPD, cardiovascular, and cardiopulmonary mortality, the RPCs were also higher in the high-SES group (Figures 7, 8, and 10). For all-age cardiovascular mortality (Figure 8) these estimates were 0.94% (0.55 to 1.33) (low SES), 1.03% (0.61 to 1.45) (medium SES), and 1.36% (0.93 to 1.80) (high SES).

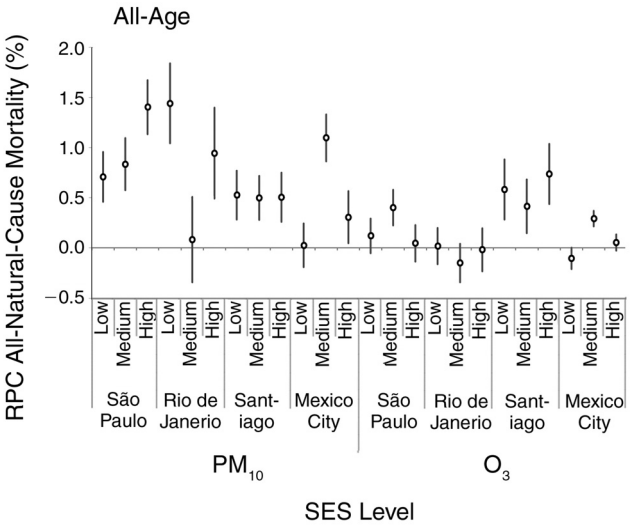


Figure 5. All-natural-cause, all-age mortality. Risk percent changes (95% CI) per 10-μg/m^3 increase of PM_{10} and O_3, using DLM 0–3 for low, medium, and high SES levels, in São Paulo and Rio de Janeiro, Brazil; Santiago, Chile; and Mexico City, México (1997–2005). Note: the *y*-axes of Figures 5–10 are scaled differently. Sources: Appendix Tables I.9–I.12, available on the HEI Web site.

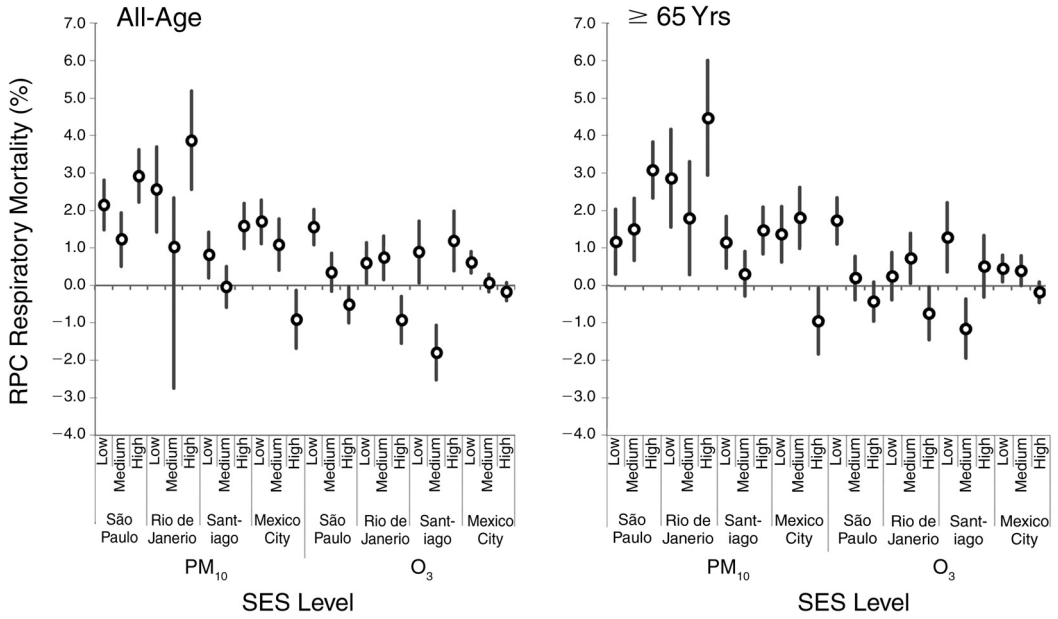


Figure 6. Respiratory mortality. Risk percent changes (95% CI) per 10-µg/m³ increase of PM_{10} and O_3, using DLM 0–3 for low, medium, and high SES levels, in São Paulo and Rio de Janeiro, Brazil; Santiago, Chile; and Mexico City, México (1998–2005). Note: the *y*-axes of Figures 5–10 are scaled differently. Sources: Appendix Tables I.9–I.12, available on the HEI Web site.

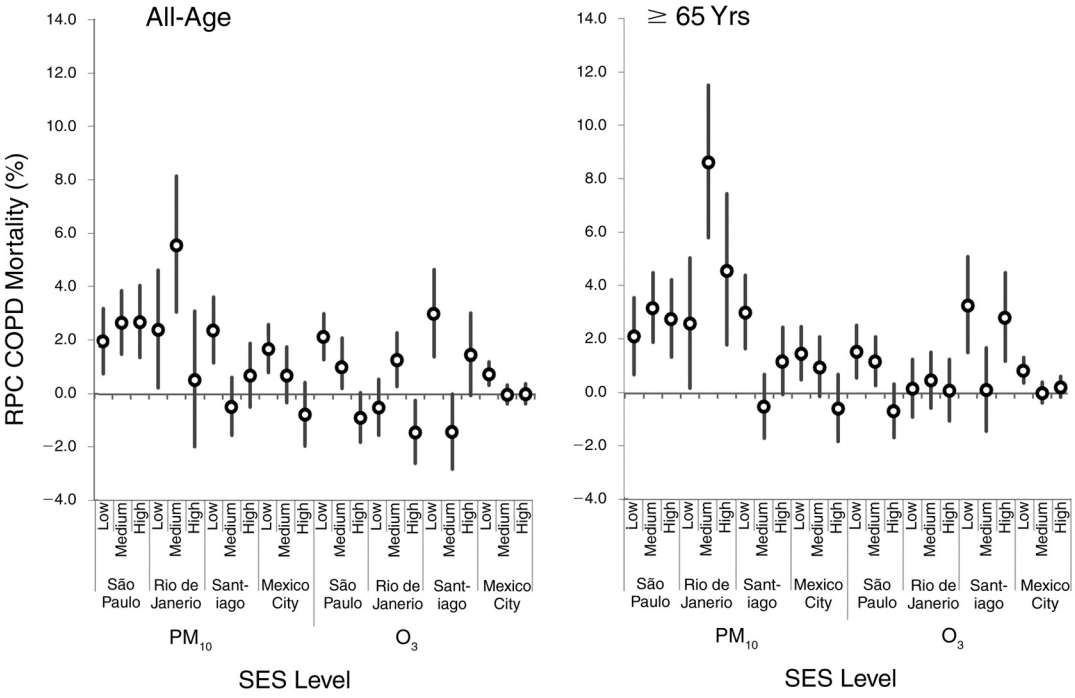


Figure 7. COPD mortality. Risk percent changes (95% CI) per 10-µg/m³ increase of PM_{10} and O_3, using DLM 0–3 for low, medium, and high SES levels, in São Paulo and Rio de Janeiro, Brazil; Santiago, Chile; and Mexico City, México (1998–2005). Note: the *y*-axes of Figures 5–10 are scaled differently. Sources: Appendix Tables I.9–I.12, available on the HEI Web site.

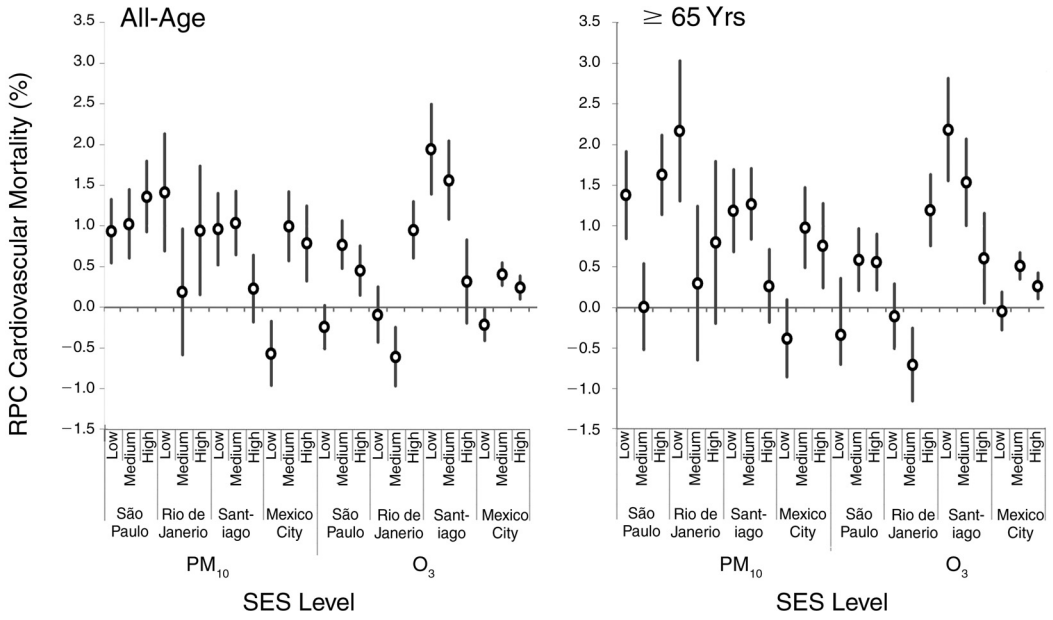


Figure 8. Cardiovascular mortality. Risk percent changes (95% CI) per 10-μg/m^3 increase of PM_{10} and O_3 for distributed lag models for low, medium, and high SES levels, in São Paulo and Rio de Janeiro, Brazil; Santiago, Chile; and Mexico City, México (1997–2005). Note: the *y*-axes of Figures 5–10 are scaled differently. Sources: Appendix Tables I.9–I.12, available on the HEI Web site.

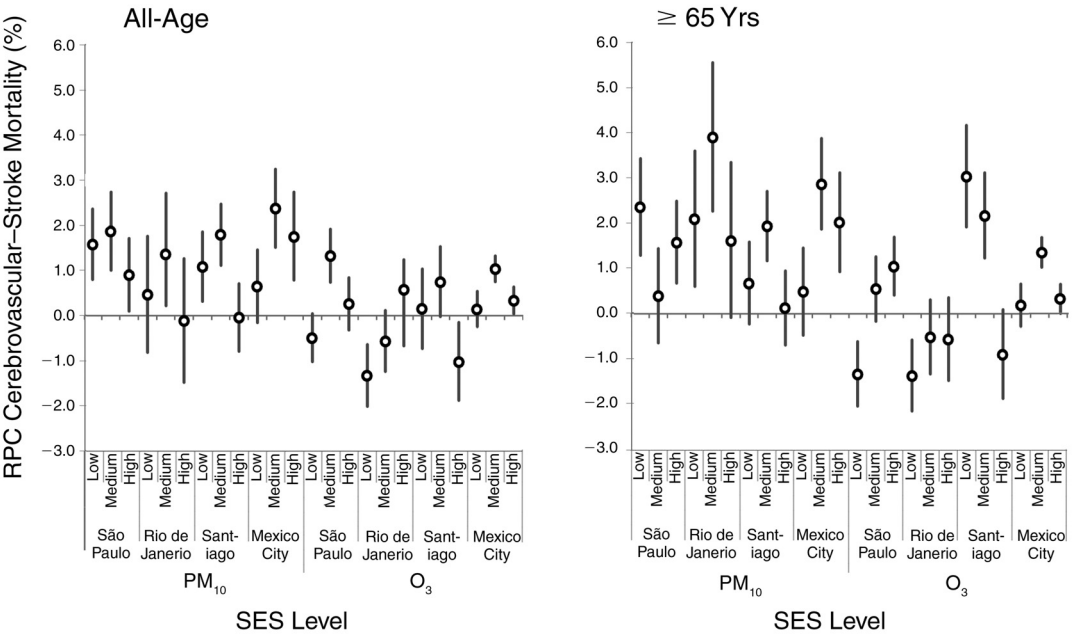


Figure 9. Cerebrovascular–stroke mortality. Risk percent changes (95% CI) per 10-μg/m^3 increase of PM_{10} and O_3, using DLM 0–3 for low, medium, and high SES levels, in São Paulo and Rio de Janeiro, Brazil; Santiago, Chile; and Mexico City, México (1998–2005). Note: the *y*-axes of Figures 5–10 are scaled differently. Sources: Appendix Tables I.9–I.12, available on the HEI Web site.

In Rio de Janeiro, all-natural-cause, all-age mortality (Figure 5) was significantly related to PM_{10} in the low- and high-SES groups with RPCs of 1.44% (95% CI = 1.04 to 1.84) and 0.94% (0.49 to 1.40) respectively, with a higher RPC in the low-SES group. All-age respiratory, cardiovascular, and cardiopulmonary mortality were significantly related to PM_{10} in the low- and high-SES groups (Figures 6, 8, and 10). For all-age respiratory mortality, the RPCs were 2.56% (1.42 to 3.71) and 3.87% (2.56 to 5.20) for the low- and high-SES groups, respectively. PM_{10} was significantly related to all-age cerebrovascular–stroke and to all-age COPD mortality in the medium-SES group, 1.36% (0.02 to 2.72) and 5.63% (3.11 to 8.22), respectively (Figures 7 and 9). Effects for these two outcomes were substantially larger for people 65 years or older.

In Santiago, all-age, all-natural-cause (Figure 5) and cardiopulmonary mortality (Figure 10) were significantly related to PM_{10} in the low-, medium-, and high-SES groups with very similar estimates across SES groups. All-age cardiovascular mortality (Figure 8) was significantly related to PM_{10} in the low- and medium-SES groups with RPCs of 0.96% (95% CI = 0.53 to 1.40) and 1.04% (0.65 to 1.43), respectively, while no significant effect was observed in the high-SES group. In the high-SES group, the highest RPC was observed for respiratory mortality (1.58% [0.98 to 2.19]). In the low-SES group, all-age COPD mortality had the highest RPC (2.41% [1.18 to 3.65]). In the medium-SES group, all-age cerebrovascular–stroke mortality had the highest RPC (1.80% [1.12 to 2.47]).

O_3

In Mexico City, all-natural-cause, all-age mortality related to O_3 concentrations presented a similar pattern as for PM_{10} but with lower estimates (Figure 5). All-natural-cause, all-age mortality was significantly increased only in the medium-SES group. In the low-SES group, significant RPCs were observed for all-age respiratory mortality (Figure 6) and all-age COPD mortality (Figure 7), while in

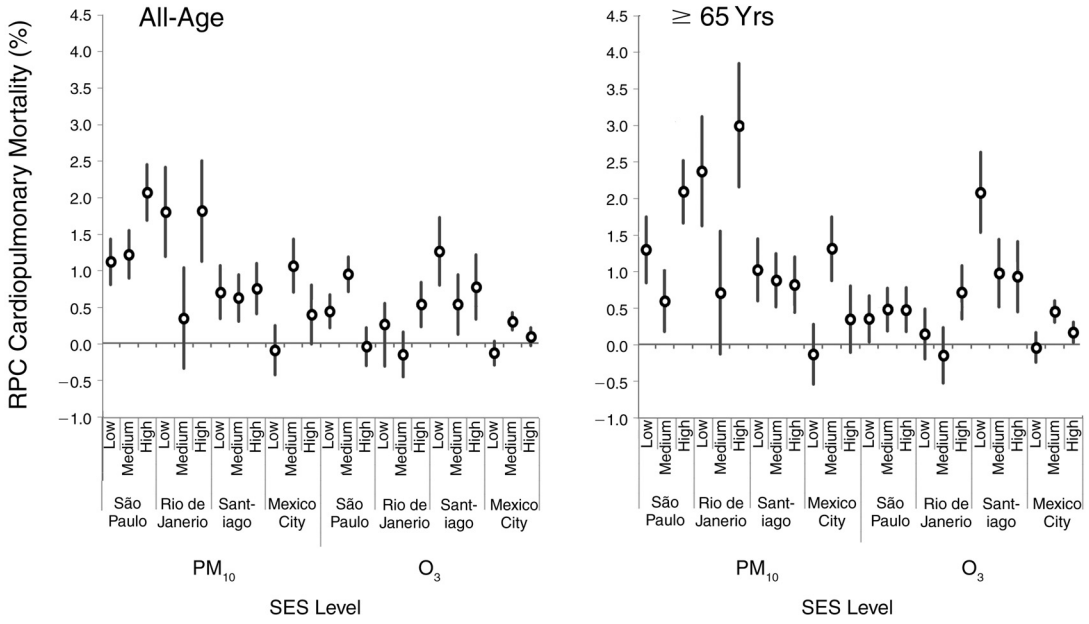


Figure 10. Cardiopulmonary mortality. Risk percent changes (95% CI) per 10-μg/m^3 increase of PM_{10} and O_3, using DLM 0–3 for low, medium, and high SES levels, in São Paulo and Rio de Janeiro, Brazil; Santiago, Chile; and Mexico City, México (1997–2005). Note: the *y*-axes of Figures 5–10 are scaled differently. Sources: Appendix Tables I.9–I.12, available on the HEI Web site.

the medium- and high-SES groups, significant RPCs were observed for all-age cardiovascular mortality (Figure 8) and all-age cerebrovascular–stroke mortality (Figure 9), with higher estimates in the medium-SES group.

As in Mexico City, São Paulo all-natural-cause, all-age mortality related to O_3 concentrations was significantly increased only in the medium-SES group but not in the other SES groups (Figure 5). In the low-SES group, significant RPCs were observed for all-age respiratory mortality (Figure 6) and all-age COPD mortality (Figure 7), and they decreased in the medium- and high-SES groups. RPCs for cardiopulmonary mortality in the all-age group were significant in the low- and medium-SES groups, but in the ≥ 65 age group it was significant in all SES groups.

In Rio de Janeiro, several RPCs were negative and statistically significant and we could not observe a clear trend among the three SES levels.

In Santiago, for the all-age group, all-natural-cause mortality (Figure 5) and cardiopulmonary mortality (Figure 10) were significantly related to O_3 in all three SES groups. We observed higher RPCs in the low-SES group compared with the medium- and high-SES groups for most causes of death examined except for all-natural-cause, respiratory, and cerebrovascular mortality in the all-age group. The highest effects related to O_3 were observed in the low-SES group for COPD in the older group (RPC = 3.31% [95% CI = 1.52 to 5.13]), COPD in the all-age group (RPC = 3.03% [1.39 to 4.70]), and cerebrovascular–stroke mortality in the older group (RPC = 3.05% [1.93 to 4.18]).

Summary

In Mexico City, higher respiratory and COPD mortality associated with an increase of PM_{10} was observed in the low-SES group, while for the other causes of mortality the RPCs were higher in the medium-SES group. For O_3 the RPCs were higher in the low-SES group for respiratory and COPD (in the all-age and the ≥ 65 age groups). In both São Paulo and Rio de Janeiro, the impact of PM_{10} was more related to respiratory mortality than to cardiovascular mortality, with larger effects in people 65 years or older. In Santiago, no SES gradient was observed in all-natural-cause mortality for either pollutant. However, in the low-SES group, mortality from respiratory causes, in particular COPD, and from cardiovascular mortality, were significantly increased. There was a declining trend along the other SES categories (see Appendix I).

META-ANALYSES AND META-REGRESSION ANALYSES

Meta-Analyses

As part of the ESCALA study we conducted a meta-analysis on pooled data from single-city models. Meta-analyses of independently published results may be limited by the differences in study design, outcome definition, exposure assessment, and data analysis. In ESCALA, these second-stage pooled results came from standardized first-stage analyses that had the same design. This analytic approach addressed most of the issues raised by combining independent studies.

To provide a quantitative summary of all city-specific results, we first combined estimations from the fixed- and random-effects univariate analyses (for one-pollutant models) that were described earlier. Figures 11–16 display the individual city and meta-analytic results for all-natural-cause and cause-specific mortality for the nine cities with PM_{10} measurements. Figures 17–22 display similar results for the six cities with O_3 measurements. The corresponding values for the meta-analytic results in those figures can be found in Table 20 for PM_{10} results and Table 21 for O_3 results. In the fixed- and random-effects models, the mean or combined effect is estimated by weighted regression of city-specific estimates from the distributed lag models (overall effect for lags 0–3, 0–5, and 0–10) with weights inversely proportional to their city-specific variances. We also computed the I^2 index (Higgins and Thompson 2002) as well as the Cochran Q test as measures of the extent of heterogeneity among cities.

The number of events was low for infants and children, so we did not compute pooled effects for the following causes of death: LRI in the < 1 year and the 1–14 year age groups; and respiratory mortality in the < 1 year and the 1–4 year age groups. The implications of basing analyses on a small number of events have been described earlier.

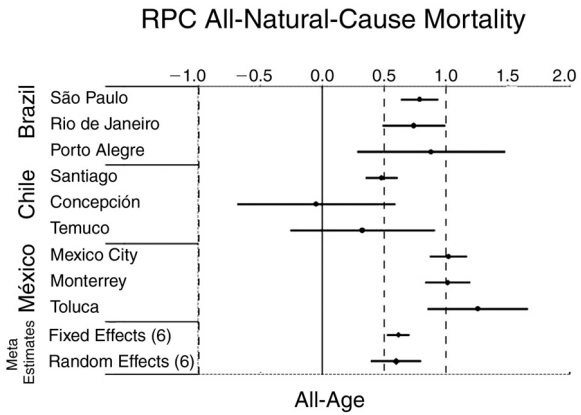


Figure 11. PM_{10} — All-natural-cause, all-age mortality. Risk percent changes (%) by city and by fixed and random combined effects of PM_{10}, using DLM 0–3, per 10-µg/m^3 increase of ambient PM_{10} concentrations. Note: The *x*-axes of Figures 11–16 are scaled differently. Sources: Table 20 and Appendix Table I.13, available on the HEI Web site.

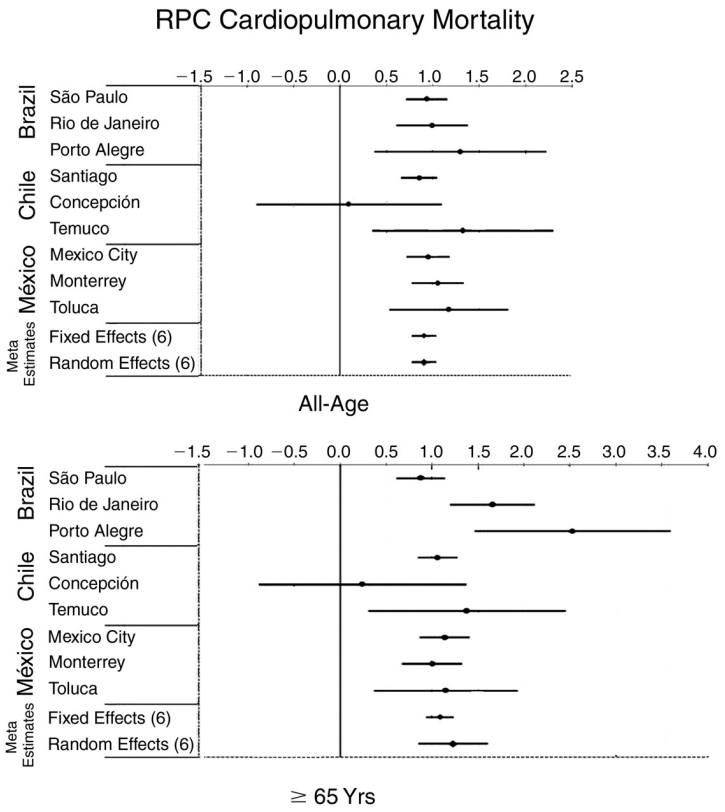


Figure 12. PM_{10} — Cardiopulmonary mortality. Risk percent changes (%) by city and by fixed and random combined effects of PM_{10}, using DLM 0–3, per 10-µg/m^3 increase of ambient PM_{10} concentrations. Note: The *x*-axes of Figures 11–16 are scaled differently. Sources: Table 20; Appendix Table I.14 and I.15, available on the HEI Web site.

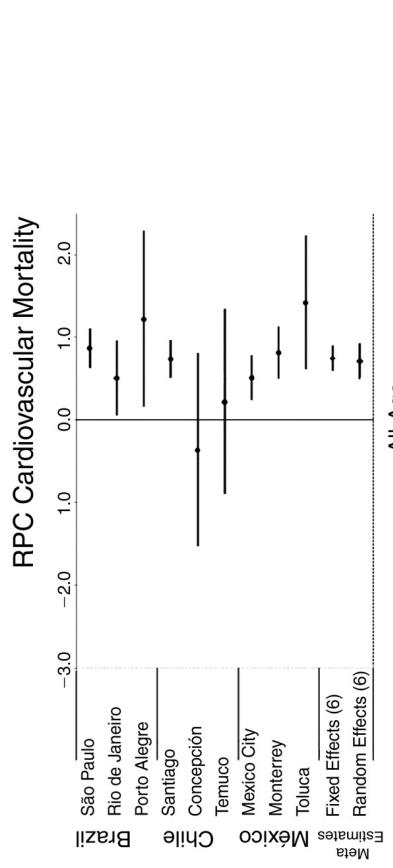


Figure 14. PM_{10} — Cardiovascular mortality. Risk percent changes (%) by city and by fixed and random combined effects of PM_{10}, using DLM 0–3, per 10-µg/m^3 increase of ambient PM_{10} concentrations. Note: The x-axes of Figures 11–16 are scaled differently. Sources: Table 20; Appendix Table I.18 and I.19, available on the HEI Web site.

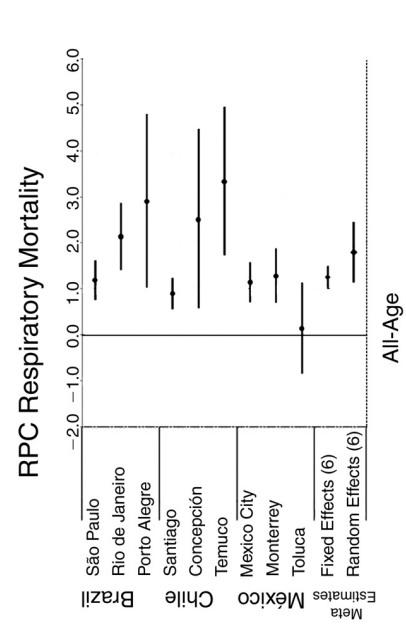


Figure 13. PM_{10} — Respiratory mortality. Risk percent changes (%) by city and by fixed and random combined effects of PM_{10}, using DLM 0–3, per 10-µg/m^3 increase of ambient PM_{10} concentrations. Note: The x-axes of Figures 11–16 are scaled differently. Sources: Table 20; Appendix Table I.16 and I.17, available on the HEI Web site.

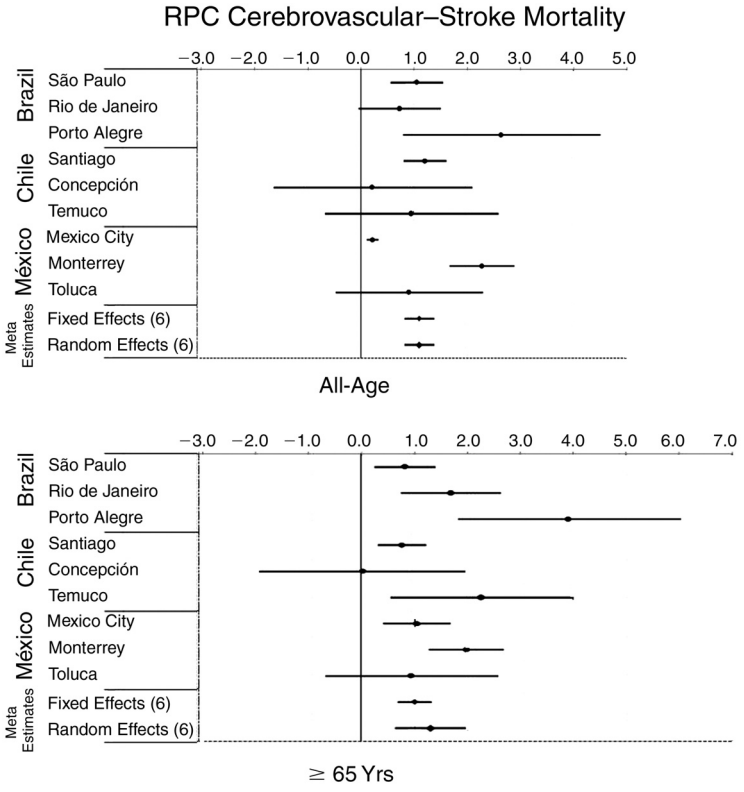


Figure 15. PM_{10} — Cerebrovascular–stroke mortality. Risk percent changes (%) by city and by fixed and random combined effects of PM_{10}, using DLM 0–3, per 10-µg/m^3 increase of ambient PM_{10} concentrations. Note: The *x*-axes of Figures 11–16 are scaled differently. Sources: Table 20; Appendix Table I.20 and I.21, available on the HEI Web site.

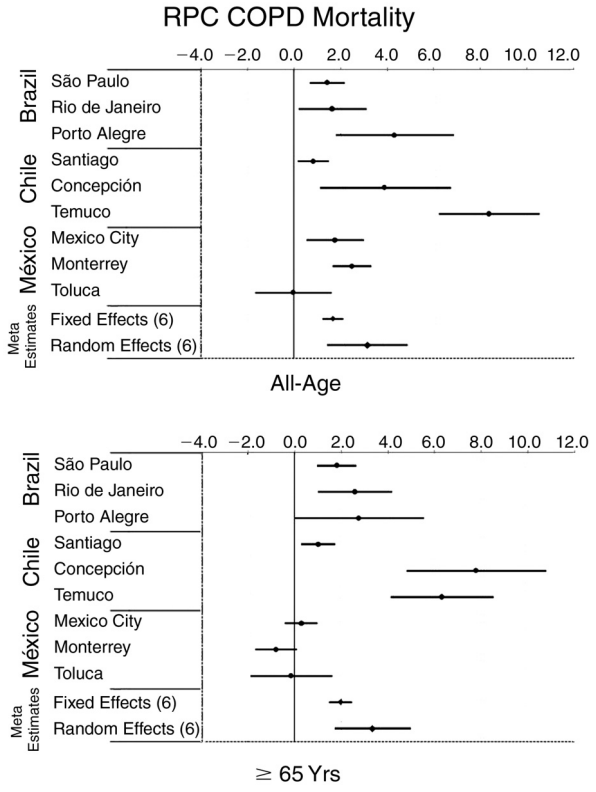


Figure 16. PM_{10} — COPD mortality. Risk percent changes (%) by city and by fixed and random combined effects of PM_{10}, using DLM 0–3, per 10-µg/m^3 increase of ambient PM_{10} concentrations. Note: The *x*-axes of Figures 11–16 are scaled differently. Sources: Table 20; Appendix Table I.22 and I.23, available on the HEI Web site.

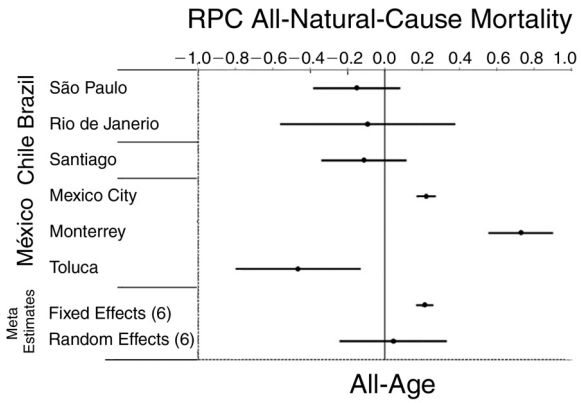


Figure 17. O_3 — All-natural-cause, all-age mortality. Risk percent changes (%) by city and by fixed and random combined effects of O_3, using DLM 0–3, per 10-μg/m^3 increase of ambient O_3 concentrations. Sources: Table 21 and Appendix Table I.24, available on the HEI Web site.

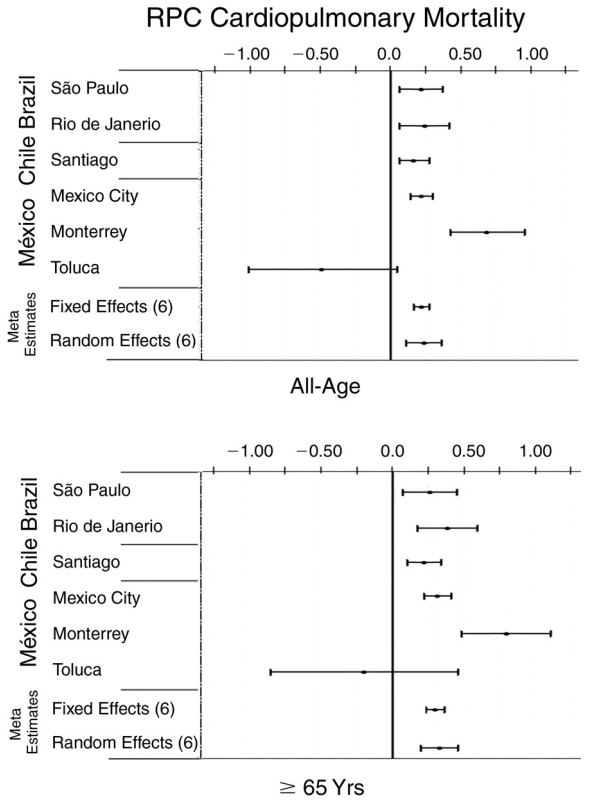
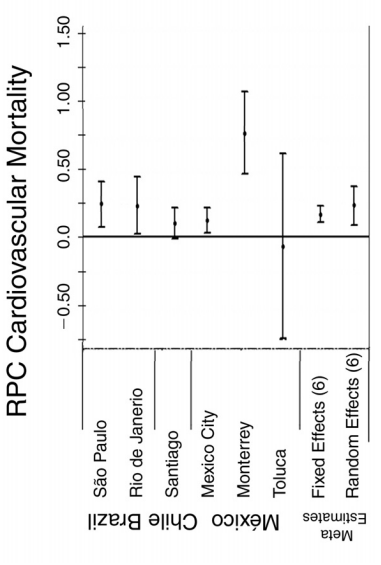


Figure 18. O_3 — Cardiopulmonary mortality. Risk percent changes (%) by city and by fixed and random combined effects of O_3, using DLM 0–3, per 10-μg/m^3 increase of ambient O_3 concentrations. Sources: Table 21; Appendix Table I.25 and I.26, available on the HEI Web site.



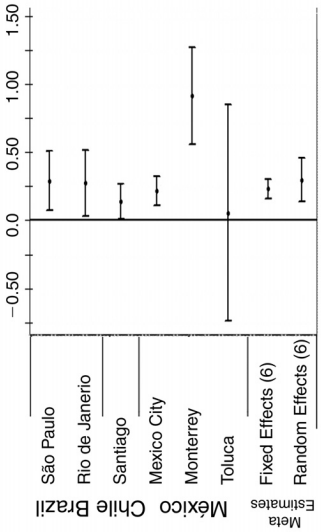
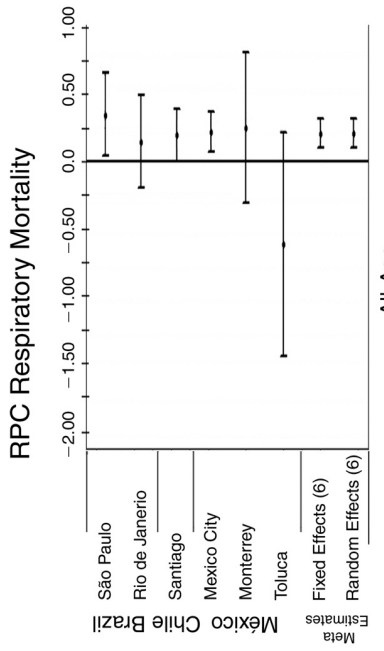


Figure 20. O_3 — Cardiovascular mortality. Risk percent changes (%) by city and by fixed and random combined effects of O_3, using DLM 0–3, per 10-µg/m^3 increase of ambient O_3 concentrations. Sources: Table 21; Appendix Table I.29 and I.30, available on the HEI Web site.



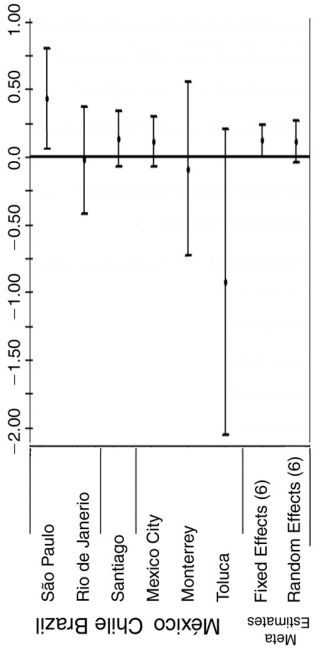


Figure 19. O_3 — Respiratory mortality. Risk percent changes (%) by city and by fixed and random combined effects of O_3, using DLM 0–3, per 10-µg/m^3 increase of ambient O_3 concentrations. Sources: Table 21; Appendix Table I.27 and I.28, available on the HEI Web site.

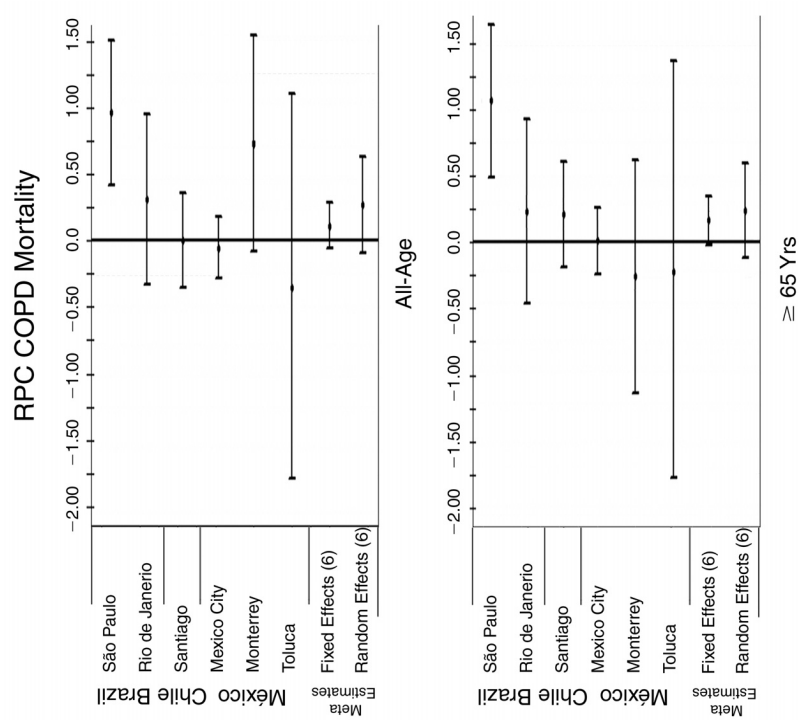


Figure 22. O_3 — COPD mortality. Risk percent changes (%) by city and by fixed and random combined effects of O_3, using DLM 0–3, per 10-µg/m^3 increase of ambient O_3 concentrations. Sources: Table 21; Appendix Table I.33 and I.34, available on the HEI Web site.

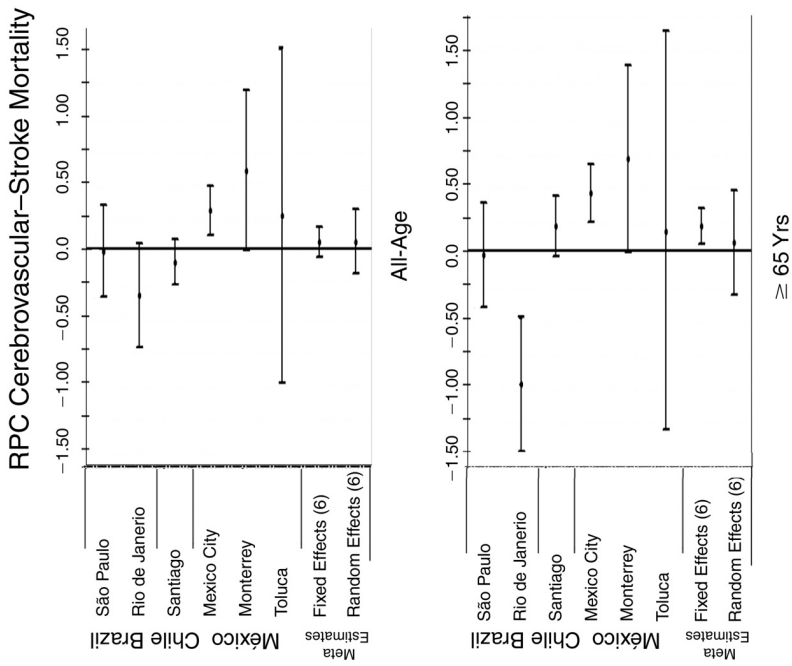


Figure 21. O_3 — Cerebrovascular–stroke mortality. Risk percent changes (%) by city and by fixed and random combined effects of O_3, using DLM 0–3, per 10-µg/m^3 increase of ambient O_3 concentrations. Sources: Table 21; Appendix Table I.31 and I.32, available on the HEI Web site.

Results for DLM 0–3 The following estimates are from the single-city analyses using DLM 0–3 for both fixed- and random-effects models. Estimates are expressed for a change of 10-μg/m^3 per daily concentration of PM_{10} or O_3.

PM_{10} Santiago provided the largest weights for pooled effects both in fixed- and random-effects models, for most causes of death except for cerebrovascular–stroke in the all-age group and COPD in the ≥ 65 group. Concepción and Porto Alegre showed the lowest weights with both fixed- and random-effects models (Appendix Tables I.13–I.23, available on the HEI Web site). For all-natural-cause mortality and for specific causes of death, random-effects estimates were slightly higher than those for fixed-effect estimates (Table 20) and appeared more adequate, given the significant tests for heterogeneity across cities (Table 22). Random-effect RPCs were significantly increased for all mortality, whether for all natural causes or for specific causes. The RPCs ranged from 0.77% (95% CI = 0.60 to 1.00) for all-natural-cause, all-age mortality to 2.44% (1.36 to 3.59) for all-age COPD mortality. Among people 65 years or older, the RPCs ranged from 0.72% (0.54 to 0.89) for respiratory mortality to 1.98% (0.78 to 3.23) for COPD mortality. Of interest was the 1.32% RPC increase (95% CI = 0.84 to 1.81) observed for cerebrovascular–stroke mortality in this older age group.

Table 20. PM_{10}: Summary Estimates for Fixed- and Random-Effects Meta-Analyses

	Fixed Effects				Random Effects			
Cause / Age Group	β (× 1000)	SE (× 1000)	RPC[a] (%)	(95% CI)	β (× 1000)	SE (× 1000)	RPC[a] (%)	(95% CI)
All-natural-cause								
All-age	0.78	0.04	**0.78**	**(0.70 to 0.80)**	0.77	0.10	**0.77**	**(0.60 to 1.00)**
Cardiopulmonary								
All-age	0.94	0.05	**0.94**	**(0.84 to 1.05)**	0.94	0.05	**0.94**	**(0.84 to 1.05)**
≥ 65	1.08	0.06	**1.09**	**(0.97 to 1.21)**	1.14	0.11	**1.15**	**(0.93 to 1.37)**
Respiratory								
All-age	1.19	0.10	**1.19**	**(1.00 to 1.39)**	1.39	0.21	**1.39**	**(0.98 to 1.81)**
≥ 65	1.26	0.12	**1.26**	**(1.02 to 1.51)**	0.71	0.09	**0.72**	**(0.54 to 0.89)**
Cardiovascular								
All-age	0.72	0.06	**0.72**	**(0.61 to 0.85)**	0.71	0.09	**0.72**	**(0.54 to 0.89)**
≥ 65	0.85	0.07	**0.85**	**(0.71 to 1.00)**	0.88	0.15	**0.88**	**(0.59 to 1.18)**
Cerebrovascular–stroke								
All-age	0.39	0.05	**0.39**	**(0.29 to 0.48)**	1.09	0.31	**1.10**	**(0.48 to 1.71)**
≥ 65	1.14	0.13	**1.15**	**(0.89 to 1.41)**	1.32	0.24	**1.32**	**(0.84 to 1.81)**
COPD								
All-age	1.74	0.18	**1.74**	**(1.39 to 2.12)**	2.44	0.56	**2.44**	**(1.36 to 3.59)**
≥ 65.	1.00	0.18	**1.01**	**(0.65 to 1.37)**	1.98	0.61	**1.98**	**(0.78 to 3.23)**

[a] RPC per 10 μg/m^3 increase in pollutant concentration. **Bolded** values are significant.

Table 21. O_3: Summary Estimates for Fixed- and Random-Effects Meta-Analyses

	Fixed Effects				Random Effects			
Cause / Age Group	β (× 1000)	SE (× 1000)	RPC[a] (%)	(95% CI)	β (× 1000)	SE (× 1000)	RPC[a] (%)	(95% CI)
All-natural-cause								
All-age	0.22	0.02	**0.22**	**(0.18 to 0.26)**	0.16	0.09	0.16	(−0.02 to 0.33)
Cardiopulmonary								
All-age	0.22	0.03	**0.22**	**(0.16 to 0.27)**	0.23	0.07	**0.23**	**(0.11 to 0.36)**
≥ 65	0.30	0.03	**0.30**	**(0.24 to 0.36)**	0.33	0.07	**0.33**	**(0.20 to 0.46)**
Respiratory								
All-age	0.21	0.05	**0.21**	**(0.10 to 0.31)**	0.21	0.05	**0.21**	**(0.10 to 0.31)**
≥ 65	0.12	0.06	**0.12**	**(0.00 to 0.24)**	0.11	0.08	0.11	(−0.04 to 0.27)
Cardiovascular								
All-age	0.17	0.03	**0.17**	**(0.11 to 0.23)**	0.23	0.07	**0.23**	**(0.09 to 0.37)**
≥ 65	0.23	0.04	**0.23**	**(0.16 to 0.30)**	0.30	0.08	**0.30**	**(0.14 to 0.46)**
Cerebrovascular–stroke								
All-age	0.05	0.06	0.05	(−0.06 to 0.16)	0.05	0.13	0.05	(−0.19 to 0.30)
≥ 65	0.18	0.07	**0.18**	**(0.05 to 0.32)**	0.06	0.20	0.06	(−0.33 to 0.45)
COPD								
All-age	0.11	0.09	0.11	(−0.06 to 0.28)	0.27	0.18	0.27	(−0.09 to 0.63)
≥ 65	0.16	0.09	0.16	(−0.02 to 0.35)	0.24	0.18	0.24	(−0.12 to 0.59)

[a] RPC per 10 μg/m^3 increase in pollutant concentration. **Bolded** values are significant.

Table 22. The Cochran Q test of Heterogeneity and Percentage of the Total Variability (I^2) resulting from Heterogeneity Among the Nine Cities, for Cause of Death and Pollutant, Using DLM 0–3

	PM_{10}		O_3		PM_{10}	O_3
Cause / Age Group	Q[a]	*P* Value	Q[a]	*P* Value	I^2 (%)[b]	I^2 (%)[b]
All-natural-cause, all-age	37.88	< 0.0001	64.51	< 0.0001	78.9	92.2
Cardiopulmonary, all-age	14.97	0.061	72.23	< 0.0001	46.3	93.1
Cardiopulmonary, ≥ 65	31.82	0.001	77.93	< 0.0001	74.9	93.6
Respiratory, all-age	28.29	< 0.0001	6.79	0.2364	71.7	26.4
Respiratory, ≥ 65	30.80	0.002	7.74	0.1713	74.0	35.4
Cardiovascular, all-age	13.58	0.093	67.78	< 0.0001	41.1	92.6
Cardiovascular, ≥ 65	27.81	0.005	78.56	< 0.0001	71.2	93.6
Cerebrovascular–stroke, all-age	22.66	0.004	16.27	0.0061	64.7	69.3
Cerebrovascular–stroke, ≥ 65	31.39	0.000	46.09	< 0.0001	74.5	89.2
COPD, all-age	45.81	< 0.0001	13.34	0.0204	82.5	62.5
COPD, ≥ 65	50.73	< 0.0001	24.43	0.0002	84.2	79.5

[a] Under the hypothesis of homogeneity among cities, the Cochran Q statistic follows a chi-square distribution with k - 1 degrees of freedom, with k being the number of cities involved in meta-analysis, per pollutant. The Q test only informs about the presence versus the absence of heterogeneity.

[b] The I^2 index informs about the percentage of the variability due to heterogeneity and not to chance.

O_3 In the O_3 analyses, Concepción and Temuco were not included because this pollutant is not monitored in these cities. Data from Porto Alegre were also not included because of the limited quality of the monitoring data.

Mexico City provided the largest weights for pooled effects in both fixed- and random-effects models for most causes of death; however, Santiago provided the largest weights for cerebrovascular–stroke in the all-age group (Appendix Table I.24–I.34, available on the HEI Web site). Monterrey and Toluca showed the lowest weights in both fixed- and random-effects models. Fixed- and random-effects models provide similar point estimates of RPC for most of the pooled estimates (Table 21). In random-effects models, significantly increased RPCs were observed for cardiopulmonary mortality (both age groups), respiratory mortality (all-age), and cardiovascular mortality (both age groups). The combined random-effects RPC for all-natural-cause mortality was 0.16% (95% CI = -0.02 to 0.33). The RPCs ranged from 0.05% (-0.19 to 0.30) for cerebrovascular–stroke mortality to 0.33% (0.20 to 0.46) for cardiovascular mortality in people 65 years or older. In general, both fixed- and random-effects estimates were higher in older people (Table 21).

These results suggest that a certain level of heterogeneity was observed for most causes of death, mainly in the O_3 effects. However, the pooled results do not by themselves prove the presence of heterogeneity. To complement these findings, we present measures of the extent of heterogeneity as described earlier: the Cochran Q test and the I^2 percentage of true variability.

Heterogeneity In this section we present the results obtained with the Cochran Q test of heterogeneity and the I^2 percentage of total variability for both pollutants and all outcomes with combined effects DLM 0–3 (Table 22**)**.

PM_{10} The results of the Cochran Q test and the I^2 test suggest that some unexplained heterogeneity may exist in the long-term effects of PM_{10} across cities for some particular outcomes.

Results for PM_{10} showed that the I^2 percentage ranged from 63.4% (cerebrovascular–stroke mortality) to 83% (cardiopulmonary deaths) when single-lag effects were taken into account. I^2 for O_3 ranged from 74.1% (for cerebrovascular–stroke mortality) up to 96% for all-natural-cause mortality (data not shown).

When DLM 0–3 effects were analyzed, a substantial level of heterogeneity for PM_{10} was also observed, ranging from 41.1% (all-age cardiovascular mortality) to 84.2% for COPD in people 65 years or older (Table 22).

Table 23. 25% of the Range, Minimum, and the City Where the Minimum is Achieved, for the Covariates Considered in the Meta-Regression

Covariate (Units)	25% of Range	Minimum	City (Minimum)
Altitude (m)	665.5	10	Porto Alegre, Brazil
Temperature (°C)			
Summer	3.3	14	Temuco, Chile
Winter	3.5	9	Temuco, Chile
Rainfall (mm)	278.8	340	Santiago, Chile
PM_{10} mean ($\mu g/m^3$)	10.5	29.58	Porto Alegre, Brazil
PM_{10} monitor density (km^2/monitor)	2359.5	86.54	Santiago, Chile
Population density (people/km^2)	1550.6	648.9	Temuco, Chile
Population age groups (%)			
< 1	0.33	1.36	Concepción, Chile
1–4	1.85	7.2	Concepción, Chile
5–14	1.29	13.41	Rio de Janeiro, Brazil
15–64	2.53	58.61	Monterrey, México
≥ 65	0.95	5.32	Toluca, México
Prevalence of smoking (%)	6.85	17.5	Rio de Janeiro, Brazil
Lung cancer mortality (cases/100k)			
Male	8.28	8.7	Temuco, Chile
Female	1.68	4.8	Temuco, Chile

O_3 We also observed significant variability among cities for most causes of death for O_3 and important heterogeneity for DLM 0–3.

Q tests were statistically significant (null hypothesis is homogeneity) and percentages of total variability due to heterogeneity (I^2) were higher than for PM_{10} percentages. With a 0-day lag (data not shown), the extent of heterogeneity varied from 2.4% (all-age respiratory mortality) to 83.1% (all-age cardiopulmonary mortality). With effects estimated using DLM 0–3, the extent of heterogeneity observed was higher for O_3 than for PM_{10} for all but respiratory mortality, all-age cerebrovascular–stroke, and COPD (Table 22). Having demonstrated significant variability and heterogeneity among cities, exploration of effect modification was conducted via meta-regression analyses, accounting for different city-level variables potentially considered as important explanatory factors for the health outcomes studied.

Meta-Regression

In ESCALA the time-series analyses results are reported for a standard increase in PM_{10} of 10 μg/m^3, a range that corresponds to 25% of the actual range of PM_{10} annual average concentrations in the nine cities of the study. Therefore, we also used 25% of the full range of each of the other covariates included in the meta-regression (Table 23), to report the results for each cause of death (Tables 24–34). Although we conducted analyses for DLM 0–3, DLM 0–5 and DLM 0–10, only the results for DLM 0–3 are presented in this report.

Table 24. All-Natural-Cause Mortality, All-Age: Reference Risks for PM_{10} Adjusted by the Contribution of Each Covariate (Univariate Models) and Relative Risk Ratios of Meta-Regression Covariates

	Reference Risks[a]		Relative Risk Ratios[b]	
Covariate (Unit)	Ref_R	(95% CI)	RRR	(95% CI)
Altitude (m)	1.0059	(1.0031 to 1.0088)	1.0009	(0.9994 to 1.0024)
Temperature (°C)				
Summer	1.0054	(1.0018 to 1.0159)	1.0009	(0.9994 to 1.0024)
Winter	1.0048	(1.0007 to 1.0090)	1.0011	(0.9993 to 1.0029)
Rainfall (mm)	1.0066	(1.0024 to 1.0108)	1.0002	(0.9985 to 1.0019)
PM_{10} mean (μg/m^3)	1.0064	(1.0013 to 1.0114)	1.0003	(0.9984 to 1.0022)
PM_{10} monitor density (km^2/monitor)	1.0074	(1.0051 to 1.0098)	0.9991	(0.9969 to 1.0013)
Population density (people/km^2)	1.0058	(1.0027 to 1.0089)	1.0007	(0.9994 to 1.0020)
Population age groups (%)				
< 1	1.0051	(1.0035 to 1.0067)	1.0015	(1.0006 to 1.0023)
1–4	1.0055	(1.0038 to 1.0071)	1.0013	(1.0005 to 1.0022)
5–14	1.0058	(1.0022 to 1.0095)	1.0007	(0.9990 to 1.0024)
15–64	1.0106	(1.0074 to 1.0138)	0.9988	(0.9978 to 0.9998)
≥ 65	1.0082	(1.0041 to 1.0123)	0.9995	(0.9978 to 1.0011)
Prevalence of smoking (%)	1.0092	(1.0066 to 1.0118)	0.9987	(0.9976 to 0.9999)
Lung cancer mortality (cases/100k)				
Male	1.0032	(1.0003 to 1.0062)	1.004	(1.0005 to 1.0076)
Female	1.0065	(1.0019 to 1.0112)	1.0003	(0.9983 to 1.0023)

[a] Reference risks (Ref_R) are the expected values of relative risk (RR) = $e^{10\beta}$ corresponding to the minimum, over the ESCALA cities, of the respective covariate where β is the coefficient from each city's time series. In other words, Ref_R is the incremental relative risk (RR) of 10 μg/m^3 daily PM_{10} predicted by the meta-regression model at the city with the lowest value of the covariate (city characteristic) under investigation. For instance, in Table 24 the value 1.0066 (95% CI = 1.0024 to 1.0108) for rainfall should be interpreted as the estimated RR for a city whose rainfall is equal to the minimum of the 9 rainfall values observed in the study sample of 9 cities.

[b] Relative risk ratio (RRR) is the change predicted by the meta-regression in the incremental PM_{10} effect (RR) for an increase of 25% of the full range of the covariate under investigation over the ESCALA cities. For instance, when annual PM_{10} mean was used as a covariate, the range was 40 μg/m^3. So 25% of the range is 10 μg/m^3. The (RRR-1)*100 should be interpreted as the percentage increase or decrease in city-specific PM_{10} effect due to an increase of 10 μg/m^3 in PM_{10} annual mean.

Table 25. Cardiopulmonary Mortality, All-Age Results: Reference Risks for PM_{10} Adjusted by the Contribution of Each Covariate (Univariate Models) and Relative Risk Ratios of Meta-Regression Covariates

	Reference Risks[a]		Relative Risk Ratios[b]	
Covariate (Unit)	Ref_R	(95% CI)	RRR	(95% CI)
Altitude (m)	1.0093	(1.0058 to 1.0129)	0.9999	(0.9979 to 1.0018)
Temperature (°C)				
Summer	1.0081	(1.0038 to 1.0240)	1.0006	(0.9987 to 1.0025)
Winter	1.0084	(1.0034 to 1.0134)	1.0004	(0.9981 to 1.0028)
Rainfall (mm)	1.0075	(1.0020 to 1.0130)	1.0007	(0.9986 to 1.0028)
PM_{10} mean ($\mu g/m^3$)	1.0111	(1.0056 to 1.0167)	0.9991	(0.9970 to 1.0013)
PM_{10} monitor density (km^2/monitor)	1.0085	(1.0057 to 1.0113)	1.0011	(0.9991 to 1.0032)
Population density (people/km^2)	1.0089	(1.0050 to 1.0129)	1.0002	(0.9983 to 1.0020)
Population age groups (%)				
< 1	1.0081	(1.0050 to 1.0111)	1.0007	(0.9991 to 1.0023)
1–4	1.0084	(1.0050 to 1.0119)	1.0006	(0.9988 to 1.0025)
5–14	1.0095	(1.0049 to 1.0142)	0.9998	(0.9976 to 1.0020)
15–64	1.0107	(1.0047 to 1.0167)	0.9995	(0.9977 to 1.0013)
≥ 65	1.0087	(1.0035 to 1.0140)	1.0002	(0.9981 to 1.0024)
Prevalence of smoking (%)	1.01	(1.0056 to 1.0145)	0.9995	(0.9976 to 1.0015)
Lung cancer mortality (cases/100k)				
Male	1.0076	(1.0024 to 1.0127)	1.0025	(0.9970 to 1.0080)
Female	1.0086	(1.0037 to 1.0134)	1.0003	(0.9982 to 1.0024)

[a] Reference risks (Ref_R) are the expected values of relative risk (RR) = $e^{10\beta}$ corresponding to the minimum, over the ESCALA cities, of the respective covariate where β is the coefficient from each city's time series. In other words, Ref_R is the incremental relative risk (RR) of 10 $\mu g/m^3$ daily PM_{10} predicted by the meta-regression model at the city with the lowest value of the covariate (city characteristic) under investigation. For instance, in Table 24 the value 1.0066 (95% CI = 1.0024 to 1.0108) for rainfall should be interpreted as the estimated RR for a city whose rainfall is equal to the minimum of the 9 rainfall values observed in the study sample of 9 cities.

[b] Relative risk ratio (RRR) is the change predicted by the meta-regression in the incremental PM_{10} effect (RR) for an increase of 25% of the full range of the covariate under investigation over the ESCALA cities. For instance, when annual PM_{10} mean was used as a covariate, the range was 40 $\mu g/m^3$. So 25% of the range is 10 $\mu g/m^3$. The (RRR-1)*100 should be interpreted as the percentage increase or decrease in city-specific PM_{10} effect due to an increase of 10 $\mu g/m^3$ in PM_{10} annual mean.

Table 26. Cardiopulmonary Mortality, ≥ 65 years: Reference Risks for PM_{10} Adjusted by the Contribution of Each Covariate (Univariate Models) and Relative Risk Ratios of Meta-Regression Covariates

	Reference Risks[a]		Relative Risk Ratios[b]	
Covariate (Unit)	Ref_R	(95% CI)	RRR	(95% CI)
Altitude (m)	1.0144	(1.0086 to 1.0201)	0.9985	(0.9954 to 1.0016)
Temperature (°C)				
Summer	1.0078	(1.0019 to 1.0233)	1.0027	(1.0001 to 1.0053)
Winter	1.0084	(1.0008 to 1.0161)	1.0023	(0.9988 to 1.0059)
Rainfall (mm)	1.0107	(1.0013 to 1.0202)	1.0008	(0.9972 to 1.0045)
PM_{10} mean (μg/m^3)	1.0184	(1.0099 to 1.0269)	0.9975	(0.9943 to 1.0007)
PM_{10} monitor density (km^2/monitor)	1.0124	(1.0073 to 1.0176)	1.0003	(0.9966 to 1.0041)
Population density (people/km^2)	1.0111	(1.0046 to 1.0176)	1.0010	(0.9980 to 1.0040)
Population age groups (%)				
< 1	1.0112	(1.0052 to 1.0173)	1.0010	(0.9978 to 1.0043)
1–4	1.0119	(1.0060 to 1.0178)	1.0007	(0.9975 to 1.0039)
5–14	1.0159	(1.0085 to 1.0233)	0.9981	(0.9948 to 1.0015)
15–64	1.0142	(1.0039 to 1.0246)	0.9995	(0.9963 to 1.0026)
≥ 65	1.0077	(0.9999 to 1.0156)	1.0024	(0.9991 to 1.0056)
Prevalence of smoking (%)	1.0152	(1.0080 to 1.0225)	0.9986	(0.9954 to 1.0017)
Lung cancer mortality (cases/100k)				
Male	1.0077	(1.0016 to 1.0138)	1.0079	(1.0014 to 1.0145)
Female	1.0075	(1.0008 to 1.0144)	1.0027	(0.9997 to 1.0056)

[a] Reference risks (Ref_R) are the expected values of relative risk (RR) = $e^{10\beta}$ corresponding to the minimum, over the ESCALA cities, of the respective covariate where β is the coefficient from each city's time series. In other words, Ref_R is the incremental relative risk (RR) of 10 μg/m^3 daily PM_{10} predicted by the meta-regression model at the city with the lowest value of the covariate (city characteristic) under investigation. For instance, in Table 24 the value 1.0066 (95% CI = 1.0024 to 1.0108) for rainfall should be interpreted as the estimated RR for a city whose rainfall is equal to the minimum of the 9 rainfall values observed in the study sample of 9 cities.

[b] Relative risk ratio (RRR) is the change predicted by the meta-regression in the incremental PM_{10} effect (RR) for an increase of 25% of the full range of the covariate under investigation over the ESCALA cities. For instance, when annual PM_{10} mean was used as a covariate, the range was 40 μg/m^3. So 25% of the range is 10 μg/m^3. The (RRR-1)*100 should be interpreted as the percentage increase or decrease in city-specific PM_{10} effect due to an increase of 10 μg/m^3 in PM_{10} annual mean.

Table 27. Cardiovascular Mortality, All-Age: Reference Risks for PM_{10} Adjusted by the Contribution of Each Covariate (Univariate Models) and Relative Risk Ratios of Meta-Regression Covariates

	Reference Risks[a]		Relative Risk Ratios[b]	
Covariate (Unit)	Ref_R	(95% CI)	RRR	(95% CI)
Altitude (m)	1.0052	(1.0009 to 1.0095)	1.0014	(0.9990 to 1.0037)
Temperature (°C)				
Summer	1.0047	(0.9993 to 1.0140)	1.0012	(0.9988 to 1.0036)
Winter	1.0044	(0.9982 to 1.0107)	1.0014	(0.9985 to 1.0043)
Rainfall (mm)	1.0065	(0.9991 to 1.0140)	1.0001	(0.9973 to 1.0030)
PM_{10} mean ($\mu g/m^3$)	1.0072	(0.9997 to 1.0147)	0.9999	(0.9970 to 1.0028)
PM_{10} monitor density (km^2/monitor)	1.0077	(1.0039 to 1.0114)	0.9986	(0.9959 to 1.0013)
Population density (people/km^2)	1.0058	(1.0008 to 1.0109)	1.0006	(0.9983 to 1.0030)
Population age groups (%)				
< 1	1.0045	(1.0011 to 1.0080)	1.0019	(1.0001 to 1.0038)
1–4	1.0046	(1.0009 to 1.0084)	1.0019	(0.9999 to 1.0040)
5–14	1.0059	(0.9999 to 1.0120)	1.0005	(0.9977 to 1.0034)
15–64	1.0116	(1.0046 to 1.0187)	0.9984	(0.9963 to 1.0005)
≥ 65	1.0081	(1.0013 to 1.0150)	0.9994	(0.9966 to 1.0022)
Prevalence of smoking (%)	1.0099	(1.0048 to 1.0151)	0.9983	(0.9960 to 1.0005)
Lung cancer mortality (cases/100k)				
Male	1.0016	(0.9982 to 1.0050)	1.0060	(1.0024 to 1.0097)
Female	1.0043	(0.9984 to 1.0103)	1.0013	(0.9987 to 1.0039)

[a] Reference risks (Ref_R) are the expected values of relative risk (RR) = $e^{10\beta}$ corresponding to the minimum, over the ESCALA cities, of the respective covariate where β is the coefficient from each city's time series. In other words, Ref_R is the incremental relative risk (RR) of 10 $\mu g/m^3$ daily PM_{10} predicted by the meta-regression model at the city with the lowest value of the covariate (city characteristic) under investigation. For instance, in Table 24 the value 1.0066 (95% CI = 1.0024 to 1.0108) for rainfall should be interpreted as the estimated RR for a city whose rainfall is equal to the minimum of the 9 rainfall values observed in the study sample of 9 cities.

[b] Relative risk ratio (RRR) is the change predicted by the meta-regression in the incremental PM_{10} effect (RR) for an increase of 25% of the full range of the covariate under investigation over the ESCALA cities. For instance, when annual PM_{10} mean was used as a covariate, the range was 40 $\mu g/m^3$. So 25% of the range is 10 $\mu g/m^3$. The (RRR-1)*100 should be interpreted as the percentage increase or decrease in city-specific PM_{10} effect due to an increase of 10 $\mu g/m^3$ in PM_{10} annual mean.

Table 28. Cardiovascular Mortality, ≥ 65 years: Reference Risks for PM_{10} Adjusted by the Contribution of Each Covariate (Univariate Models) and Relative Risk Ratios of Meta-Regression Covariates

	Reference Risks[a]		Relative Risk Ratios[b]	
Covariate (Unit)	Ref_R	(95% CI)	RRR	(95% CI)
Altitude (m)	1.0095	(1.0004 to 1.0185)	1.0004	(0.9955 to 1.0053)
Temperature (°C)				
Summer	1.0041	(0.9944 to 1.0122)	1.0033	(0.9990 to 1.0076)
Winter	1.0042	(0.9925 to 1.0159)	1.0032	(0.9978 to 1.0086)
Rainfall (mm)	1.0077	(0.9936 to 1.0221)	1.0010	(0.9955 to 1.0064)
PM_{10} mean (μg/m^3)	1.0165	(1.0030 to 1.0302)	0.9972	(0.9920 to 1.0023)
PM_{10} monitor density (km^2/monitor)	1.0111	(1.0037 to 1.0185)	0.9980	(0.9926 to 1.0035)
Population density (people/km^2)	1.0083	(0.9984 to 1.0182)	1.0011	(0.9965 to 1.0056)
Population age groups (%)				
< 1	1.0069	(0.9981 to 1.0157)	1.0024	(0.9977 to 1.0071)
1–4	1.0078	(0.9993 to 1.0164)	1.0019	(0.9972 to 1.0065)
5–14	1.0121	(1.0005 to 1.0239)	0.9987	(0.9933 to 1.0042)
15–64	1.0142	(0.9990 to 1.0296)	0.9986	(0.9940 to 1.0032)
≥ 65	1.0072	(0.9942 to 1.0205)	1.0013	(0.9959 to 1.0067)
Prevalence of smoking (%)	1.0151	(1.0048 to 1.0255)	0.9971	(0.9927 to 1.0017)
Lung cancer mortality (cases/100k)				
Male	0.9995	(0.9929 to 1.0061)	1.0147	(1.0075 to 1.0218)
Female	1.0015	(0.9919 to 1.0112)	1.0045	(1.0003 to 1.0087)

[a] Reference risks (Ref_R) are the expected values of relative risk (RR) = $e^{10\beta}$ corresponding to the minimum, over the ESCALA cities, of the respective covariate where β is the coefficient from each city's time series. In other words, Ref_R is the incremental relative risk (RR) of 10 μg/m^3 daily PM_{10} predicted by the meta-regression model at the city with the lowest value of the covariate (city characteristic) under investigation. For instance, in Table 24 the value 1.0066 (95% CI = 1.0024 to 1.0108) for rainfall should be interpreted as the estimated RR for a city whose rainfall is equal to the minimum of the 9 rainfall values observed in the study sample of 9 cities.

[b] Relative risk ratio (RRR) is the change predicted by the meta-regression in the incremental PM_{10} effect (RR) for an increase of 25% of the full range of the covariate under investigation over the ESCALA cities. For instance, when annual PM_{10} mean was used as a covariate, the range was 40 μg/m^3. So 25% of the range is 10 μg/m^3. The (RRR-1)*100 should be interpreted as the percentage increase or decrease in city-specific PM_{10} effect due to an increase of 10 μg/m^3 in PM_{10} annual mean.

Table 29. Cerebrovascular–stroke Mortality, All-Age: Reference Risks for PM_{10} Adjusted by the Contribution of Each Covariate (Univariate Models) and Relative Risk Ratios of Meta-Regression Covariates

	Reference Risks[a]		Relative Risk Ratios[b]	
Covariate (Unit)	Ref_R	(95% CI)	RRR	(95% CI)
Altitude (m)	1.0114	(1.0007 to 1.0223)	0.9997	(0.9938 to 1.0055)
Temperature (°C)				
Summer	1.0027	(0.9921 to 1.0081)	1.0047	(0.9999 to 1.0094)
Winter	1.0046	(0.9906 to 1.0187)	1.0036	(0.9971 to 1.0101)
Rainfall (mm)	1.0135	(0.9966 to 1.0307)	0.9989	(0.9925 to 1.0054)
PM_{10} mean (μg/m^3)	1.0138	(0.9967 to 1.0312)	0.9988	(0.9923 to 1.0054)
PM_{10} monitor density (km^2/monitor)	1.0110	(1.0019 to 1.0202)	1.0001	(0.9934 to 1.0068)
Population density (people/km^2)	1.0070	(0.9959 to 1.0181)	1.0026	(0.9975 to 1.0078)
Population age groups (%)				
< 1	1.0061	(0.9963 to 1.0160)	1.0040	(0.9986 to 1.0093)
1–4	1.0074	(0.9978 to 1.0171)	1.0032	(0.9980 to 1.0085)
5–14	1.0126	(0.9986 to 1.0267)	0.9991	(0.9926 to 1.0056)
15–64	1.0193	(1.0020 to 1.0369)	0.9972	(0.9920 to 1.0025)
≥ 65	1.0078	(0.9923 to 1.0235)	1.0016	(0.9952 to 1.0080)
Prevalence of smoking (%)	1.0146	(1.0015 to 1.0279)	0.9980	(0.9923 to 1.0038)
Lung cancer mortality (cases/100k)				
Male	1.0011	(0.9901 to 1.0123)	1.0122	(1.0002 to 1.0243)
Female	1.0014	(0.9898 to 1.0132)	1.0051	(0.9999 to 1.0102)

[a] Reference risks (Ref_R) are the expected values of relative risk (RR) = $e^{10\beta}$ corresponding to the minimum, over the ESCALA cities, of the respective covariate where β is the coefficient from each city's time series. In other words, Ref_R is the incremental relative risk (RR) of 10 μg/m^3 daily PM_{10} predicted by the meta-regression model at the city with the lowest value of the covariate (city characteristic) under investigation. For instance, in Table 24 the value 1.0066 (95% CI = 1.0024 to 1.0108) for rainfall should be interpreted as the estimated RR for a city whose rainfall is equal to the minimum of the 9 rainfall values observed in the study sample of 9 cities.

[b] Relative risk ratio (RRR) is the change predicted by the meta-regression in the incremental PM_{10} effect (RR) for an increase of 25% of the full range of the covariate under investigation over the ESCALA cities. For instance, when annual PM_{10} mean was used as a covariate, the range was 40 μg/m^3. So 25% of the range is 10 μg/m^3. The (RRR-1)*100 should be interpreted as the percentage increase or decrease in city-specific PM_{10} effect due to an increase of 10 μg/m^3 in PM_{10} annual mean.

Table 30. Cerebrovascular–Stroke Mortality, ≥ 65 years: Reference Risks for PM_{10} Adjusted by the Contribution of Each Covariate (Univariate Models) and Relative Risk Ratios of Meta-Regression Covariates

	Reference Risks[a]		Relative Risk Ratios[b]	
Covariate (Unit)	Ref_R	(95% CI)	RRR	(95% CI)
Altitude (m)	1.0203	(1.0089 to 1.0318)	0.9970	(0.9909 to 1.0032)
Temperature (°C)				
Summer	1.0081	(0.9958 to 1.0241)	1.0048	(0.9994 to 1.0103)
Winter	1.0110	(0.9949 to 1.0274)	1.0031	(0.9957 to 1.0107)
Rainfall (mm)	1.0150	(0.9960 to 1.0344)	1.0007	(0.9935 to 1.0080)
PM_{10} mean (μg/m^3)	1.0237	(1.0052 to 1.0426)	0.9970	(0.9900 to 1.0041)
PM_{10} monitor density (km^2/monitor)	1.0153	(1.0054 to 1.0253)	1.0026	(0.9953 to 1.0099)
Population density (people/km^2)	1.0131	(1.0004 to 1.0260)	1.0023	(0.9965 to 1.0082)
Population age groups (%)				
< 1	1.0130	(1.0010 to 1.0251)	1.0029	(0.9964 to 1.0095)
1–4	1.0141	(1.0027 to 1.0256)	1.0023	(0.9961 to 1.0085)
5–14	1.0201	(1.0047 to 1.0358)	0.9981	(0.9910 to 1.0053)
15–64	1.0232	(1.0031 to 1.0437)	0.9978	(0.9918 to 1.0039)
≥ 65	1.0097	(0.9932 to 1.0265)	1.0034	(0.9966 to 1.0103)
Prevalence of smoking (%)	1.0197	(1.0048 to 1.0348)	0.9984	(0.9919 to 1.0049)
Lung cancer mortality (cases/100k)				
Male	1.0089	(0.9949 to 1.0232)	1.0108	(0.9957 to 1.0262)
Female	1.0083	(0.9940 to 1.0229)	1.0044	(0.9981 to 1.0108)

[a] Reference risks (Ref_R) are the expected values of relative risk (RR) = $e^{10\beta}$ corresponding to the minimum, over the ESCALA cities, of the respective covariate where β is the coefficient from each city's time series. In other words, Ref_R is the incremental relative risk (RR) of 10 μg/m^3 daily PM_{10} predicted by the meta-regression model at the city with the lowest value of the covariate (city characteristic) under investigation. For instance, in Table 24 the value 1.0066 (95% CI = 1.0024 to 1.0108) for rainfall should be interpreted as the estimated RR for a city whose rainfall is equal to the minimum of the 9 rainfall values observed in the study sample of 9 cities.

[b] Relative risk ratio (RRR) is the change predicted by the meta-regression in the incremental PM_{10} effect (RR) for an increase of 25% of the full range of the covariate under investigation over the ESCALA cities. For instance, when annual PM_{10} mean was used as a covariate, the range was 40 μg/m^3. So 25% of the range is 10 μg/m^3. The (RRR-1)*100 should be interpreted as the percentage increase or decrease in city-specific PM_{10} effect due to an increase of 10 μg/m^3 in PM_{10} annual mean.

Table 31. COPD, All-Age: Reference Risks for PM_{10} Adjusted by the Contribution of Each Covariate (Univariate Models) and Relative Risk Ratios of Meta-Regression Covariates

	Reference Risks[a]		Relative Risk Ratios[b]	
Covariate (Unit)	Ref_R	(95% CI)	RRR	(95% CI)
Altitude (m)	1.0344	(1.0129 to 1.0564)	0.9900	(0.9787 to 1.0015)
Temperature (°C)				
Summer	1.0365	(1.0078 to 1.1119)	0.9923	(0.9801 to 1.0047)
Winter	1.0432	(1.0119 to 1.0755)	0.9889	(0.9749 to 1.0030)
Rainfall (mm)	1.0010	(0.9662 to 1.0371)	1.0094	(0.9957 to 1.0232)
PM_{10} mean ($\mu g/m^3$)	1.0423	(1.0047 to 1.0812)	0.9916	(0.9776 to 1.0058)
PM_{10} monitor density (km^2/monitor)	1.0127	(0.9997 to 1.0258)	1.0170	(1.0073 to 1.0268)
Population density (people/km^2)	1.0335	(1.0078 to 1.0599)	0.9930	(0.9815 to 1.0047)
Population age groups (%)				
< 1	1.0371	(1.0152 to 1.0595)	0.9887	(0.9772 to 1.0002)
1–4	1.0347	(1.0141 to 1.0557)	0.9896	(0.9788 to 1.0005)
5–14	1.0309	(0.9987 to 1.0642)	0.9952	(0.9805 to 1.0102)
15–64	0.9946	(0.9590 to 1.0315)	1.0095	(0.9983 to 1.0208)
≥ 65	1.0157	(0.9794 to 1.0533)	1.0032	(0.9882 to 1.0185)
Prevalence of smoking (%)	1.0060	(0.9788 to 1.0339)	1.0091	(0.9970 to 1.0215)
Lung cancer mortality (cases/100k)				
Male	1.0450	(1.0139 to 1.0771)	0.9836	(0.9522 to 1.0161)
Female	1.0349	(1.0023 to 1.0687)	0.9936	(0.9797 to 1.0076)

[a] Reference risks (Ref_R) are the expected values of relative risk (RR) = $e^{10\beta}$ corresponding to the minimum, over the ESCALA cities, of the respective covariate where β is the coefficient from each city's time series. In other words, Ref_R is the incremental relative risk (RR) of 10 $\mu g/m^3$ daily PM_{10} predicted by the meta-regression model at the city with the lowest value of the covariate (city characteristic) under investigation. For instance, in Table 24 the value 1.0066 (95% CI = 1.0024 to 1.0108) for rainfall should be interpreted as the estimated RR for a city whose rainfall is equal to the minimum of the 9 rainfall values observed in the study sample of 9 cities.

[b] Relative risk ratio (RRR) is the change predicted by the meta-regression in the incremental PM_{10} effect (RR) for an increase of 25% of the full range of the covariate under investigation over the ESCALA cities. For instance, when annual PM_{10} mean was used as a covariate, the range was 40 $\mu g/m^3$. So 25% of the range is 10 $\mu g/m^3$. The (RRR-1)*100 should be interpreted as the percentage increase or decrease in city-specific PM_{10} effect due to an increase of 10 $\mu g/m^3$ in PM_{10} annual mean.

Table 32. COPD, ≥ 65 years: Reference Risks for PM_{10} Adjusted by the Contribution of Each Covariate (Univariate Models) and Relative Risk Ratios of Meta-Regression Covariates

	Reference Risks[a]		Relative Risk Ratios[b]	
Covariate (Unit)	Ref_R	(95% CI)	RRR	(95% CI)
Altitude (m)	1.0360	(1.0132 to 1.0593)	0.9891	(0.9771 to 1.0012)
Temperature (°C)				
Summer	1.0403	(1.0107 to 1.1242)	0.9905	(0.9780 to 1.0032)
Winter	1.0443	(1.0104 to 1.0793)	0.9886	(0.9735 to 1.0039)
Rainfall (mm)	1.0020	(0.9640 to 1.0415)	1.0091	(0.9942 to 1.0242)
PM_{10} mean (μg/m^3)	1.0387	(0.9971 to 1.0821)	0.9933	(0.9777 to 1.0091)
PM_{10} monitor density (km^2/monitor)	1.0161	(0.9965 to 1.0361)	1.0117	(0.9972 to 1.0264)
Population density (people/km^2)	1.0342	(1.0064 to 1.0627)	0.9929	(0.9805 to 1.0055)
Population age groups (%)				
< 1	1.0423	(1.0223 to 1.0627)	0.9851	(0.9747 to 0.9955)
1–4	1.0387	(1.0192 to 1.0585)	0.9866	(0.9764 to 0.9969)
5–14	1.0339	(0.9998 to 1.0691)	0.9938	(0.9783 to 1.0096)
15–64	0.9870	(0.9529 to 1.0224)	1.0123	(1.0014 to 1.0232)
≥ 65	1.0141	(0.9756 to 1.0541)	1.0042	(0.9882 to 1.0204)
Prevalence of smoking (%)	1.0062	(0.9767 to 1.0365)	1.0093	(0.9961 to 1.0227)
Lung cancer mortality (cases/100k)				
Male	1.0537	(1.0299 to 1.0781)	0.9753	(0.9517 to 0.9996)
Female	1.0411	(1.0077 to 1.0755)	0.9907	(0.9766 to 1.0049)

[a] Reference risks (Ref_R) are the expected values of relative risk (RR) = $e^{10\beta}$ corresponding to the minimum, over the ESCALA cities, of the respective covariate where β is the coefficient from each city's time series. In other words, Ref_R is the incremental relative risk (RR) of 10 μg/m^3 daily PM_{10} predicted by the meta-regression model at the city with the lowest value of the covariate (city characteristic) under investigation. For instance, in Table 24 the value 1.0066 (95% CI = 1.0024 to 1.0108) for rainfall should be interpreted as the estimated RR for a city whose rainfall is equal to the minimum of the 9 rainfall values observed in the study sample of 9 cities.

[b] Relative risk ratio (RRR) is the change predicted by the meta-regression in the incremental PM_{10} effect (RR) for an increase of 25% of the full range of the covariate under investigation over the ESCALA cities. For instance, when annual PM_{10} mean was used as a covariate, the range was 40 μg/m^3. So 25% of the range is 10 μg/m^3. The (RRR-1)*100 should be interpreted as the percentage increase or decrease in city-specific PM_{10} effect due to an increase of 10 μg/m^3 in PM_{10} annual mean.

Table 33. Respiratory Mortality, All-Age: Reference Risks for PM_{10} Adjusted by the Contribution of Each Covariate (Univariate Models) and Relative Risk Ratios of Meta-Regression Covariates

	Reference Risks[a]		Relative Risk Ratios[b]	
Covariate (Unit)	Ref_R	(95% CI)	RRR	(95% CI)
Altitude (m)	1.0228	(1.0167 to 1.0290)	0.9944	(0.9911 to 0.9976)
Temperature (°C)				
Summer	1.0165	(1.0044 to 1.0496)	0.9998	(0.9945 to 1.0051)
Winter	1.0185	(1.0048 to 1.0324)	0.9987	(0.9924 to 1.0050)
Rainfall (mm)	1.0076	(0.9939 to 1.0214)	1.0037	(0.9985 to 1.0090)
PM_{10} mean (μg/m³)	1.0276	(1.0149 to 1.0404)	0.9951	(0.9903 to 0.9999)
PM_{10} monitor density (km²/monitor)	1.0133	(1.0067 to 1.0199)	1.0050	(1.0001 to 1.0099)
Population density (people/km²)	1.0176	(1.0068 to 1.0284)	0.9991	(0.9942 to 1.0040)
Population age groups (%)				
< 1	1.0215	(1.0132 to 1.0300)	0.9956	(0.9912 to 1.0001)
1–4	1.0211	(1.0133 to 1.0289)	0.9958	(0.9916 to 0.9999)
5–14	1.0236	(1.0126 to 1.0347)	0.9958	(0.9908 to 1.0008)
15–64	1.0045	(0.9908 to 1.0184)	1.0039	(0.9998 to 1.0082)
≥ 65	1.0079	(0.9954 to 1.0204)	1.0040	(0.9988 to 1.0092)
Prevalence of smoking (%)	1.0126	(1.0008 to 1.0245)	1.0020	(0.9968 to 1.0072)
Lung cancer mortality (cases/100k)				
Male	1.0222	(1.0105 to 1.0340)	0.9985	(0.9863 to 1.0109)
Female	1.0164	(1.0032 to 1.0299)	0.9998	(0.9941 to 1.0056)

[a] Reference risks (Ref_R) are the expected values of relative risk (RR) = $e^{10\beta}$ corresponding to the minimum, over the ESCALA cities, of the respective covariate where β is the coefficient from each city's time series. In other words, Ref_R is the incremental relative risk (RR) of 10 μg/m³ daily PM_{10} predicted by the meta-regression model at the city with the lowest value of the covariate (city characteristic) under investigation. For instance, in Table 24 the value 1.0066 (95% CI = 1.0024 to 1.0108) for rainfall should be interpreted as the estimated RR for a city whose rainfall is equal to the minimum of the 9 rainfall values observed in the study sample of 9 cities.

[b] Relative risk ratio (RRR) is the change predicted by the meta-regression in the incremental PM_{10} effect (RR) for an increase of 25% of the full range of the covariate under investigation over the ESCALA cities. For instance, when annual PM_{10} mean was used as a covariate, the range was 40 μg/m³. So 25% of the range is 10 μg/m³. The (RRR-1)*100 should be interpreted as the percentage increase or decrease in city-specific PM_{10} effect due to an increase of 10 μg/m³ in PM_{10} annual mean.

Table 34. Respiratory Mortality, ≥ 65 years: Reference Risks for PM_{10} Adjusted by the Contribution of Each Covariate (Univariate Models) and Relative Risk Ratios of Meta-Regression Covariates

	Reference Risks[a]		Relative Risk Ratios[b]	
Covariate (Unit)	Ref_R	(95% CI)	RRR	(95% CI)
Altitude (m)	1.0217	(1.0110 to 1.0325)	0.9968	(0.9911 to 1.0026)
Temperature (°C)				
Summer	1.0265	(1.0147 to 1.0805)	0.9953	(0.9902 to 1.0004)
Winter	1.0266	(1.0122 to 1.0413)	0.9953	(0.9887 to 1.0019)
Rainfall (mm)	1.0069	(0.9914 to 1.0226)	1.0048	(0.9988 to 1.0108)
PM_{10} mean (μg/m^3)	1.0251	(1.0076 to 1.0430)	0.9969	(0.9903 to 1.0036)
PM_{10} monitor density (km^2/monitor)	1.0147	(1.0067 to 1.0228)	1.0055	(0.9996 to 1.0115)
Population density (people/km^2)	1.0236	(1.0123 to 1.0351)	0.9964	(0.9913 to 1.0016)
Population age groups (%)				
< 1	1.0252	(1.0160 to 1.0344)	0.9942	(0.9894 to 0.9990)
1–4	1.0239	(1.0150 to 1.0329)	0.9948	(0.9901 to 0.9996)
5–14	1.0206	(1.0058 to 1.0357)	0.9985	(0.9916 to 1.0054)
15–64	1.0041	(0.9882 to 1.0203)	1.0047	(0.9998 to 1.0096)
≥ 65	1.0167	(0.9998 to 1.0338)	1.0006	(0.9937 to 1.0076)
Prevalence of smoking (%)	1.0125	(0.9990 to 1.0261)	1.0030	(0.9971 to 1.0090)
Lung cancer mortality (cases/100k)				
Male	1.0302	(1.0203 to 1.0403)	0.9894	(0.9791 to 0.9998)
Female	1.0280	(1.0152 to 1.0411)	0.9947	(0.9893 to 1.0002)

[a] Reference risks (Ref_R) are the expected values of relative risk (RR) = $e^{10\beta}$ corresponding to the minimum, over the ESCALA cities, of the respective covariate where β is the coefficient from each city's time series. In other words, Ref_R is the incremental relative risk (RR) of 10 μg/m^3 daily PM_{10} predicted by the meta-regression model at the city with the lowest value of the covariate (city characteristic) under investigation. For instance, in Table 24 the value 1.0066 (95% CI = 1.0024 to 1.0108) for rainfall should be interpreted as the estimated RR for a city whose rainfall is equal to the minimum of the 9 rainfall values observed in the study sample of 9 cities.

[b] Relative risk ratio (RRR) is the change predicted by the meta-regression in the incremental PM_{10} effect (RR) for an increase of 25% of the full range of the covariate under investigation over the ESCALA cities. For instance, when annual PM_{10} mean was used as a covariate, the range was 40 μg/m^3. So 25% of the range is 10 μg/m^3. The (RRR-1)*100 should be interpreted as the percentage increase or decrease in city-specific PM_{10} effect due to an increase of 10 μg/m^3 in PM_{10} annual mean.

A meta-regression analysis was conducted to make the following estimates: (1) the combined effect (Ref_R) of the set of effect estimates [e^{α_0}, 95% CI], adjusted by the contributions of each covariate, one at a time, in explaining heterogeneity of the set of effect estimates; and (2) The RRR [$e^{\alpha_1 R_{25}}$, 95% CI] for an increase of 25% in the range of each covariate.

The approach to univariate meta-regression models consisted of modeling 10β, where β is the effect of PM_{10} in a specific outcome for one unit of variation of PM_{10} (i.e., the univariate meta-regression model is simply $10\beta = \alpha_0 + \alpha_1 X$, where X is the meta-regression covariate, centered on its minimum over the nine cities). The fit of this regression model was followed by an exponential transformation applied to the meta-regression results (i.e., $e^{10\beta} = e^{\alpha_0} e^{\alpha_1 X}$. Thus, Ref_Rs are the value of e^{α_0} corresponding to a city where the value of covariate X is the minimum over the ESCALA cities. The RRRs reported are defined as,

$$e^{\alpha_1\left(x + range(X)/4\right)} / e^{\alpha_1 X} = e^{\alpha_1 range(X)/4},$$

so they represent the change in $e^{10\beta}$ for an increase of 25% in the range of covariate X. The results of these analyses are presented in Tables 24 through 34.

For all-natural-cause, all-age mortality, the Ref_Rs for all the covariates explored in this analysis were statistically significant. Taking altitude as an example, we can infer that the risk of all-natural-cause mortality due to exposure to PM_{10} in the cities at the minimum altitude (sea level), Porto Alegre or Rio de Janeiro, is statistically significant. Examining the RRR corresponding to altitude, we conclude that the picture depicted for Porto Alegre and Rio de Janeiro does not change in other ESCALA cities, that is, exposure to PM_{10} is significant for all-natural-cause, all-age mortality. Similar interpretations can be made for the other covariates in relation to this outcome. Changing the focus to the mortality rate due to lung cancer in males, we conclude that the RRR of PM_{10} (RRR for an increase of 10 μg/m^3) on all-natural-cause, all-age mortality is significant in the city where the minimum of this covariate is observed, Temuco, Chile (see Table 23). However, this specific RRR increases by 0.40% (95% CI = 0.05 to 0.76) for an increase of 8.28 (25% of the covariate range) in mortality rate due to lung cancer for males.

For cardiopulmonary mortality we observed the same, all the Ref_Rs were significant, but for the remaining outcomes explored in this analysis different sets of covariates were statistically significant as far as Ref_R is concerned.

Examining the RRRs we noticed that, overall, the lung cancer mortality rate in males was the covariate that explained part of the heterogeneity in the effect estimates for more outcomes. Besides all-natural-cause, all-age mortality, the lung cancer mortality rate was also statistically significant for cardiovascular diseases (all-age and ≥ 65), cardiopulmonary diseases (≥ 65), and for cerebrovascular–stroke mortality (all-age). We can infer that for an increase in the mortality rate for lung cancer in males by 25% of the range observed among the nine cities, we will have an increase in the effect of PM_{10} for these outcomes.

It should also be noted that for respiratory mortality (all-age and ≥ 65) and COPD mortality (≥ 65) some *protective* statistically significant effects were observed. The proportion of the population in specific age-groups, lung cancer mortality rate in males, altitude, and PM_{10} annual mean were the covariates for which an increase of 25% of the range observed among the nine cities is associated with a decrease in the effect estimate of PM_{10}.

For all-natural-cause, all-age mortality this was also observed for the proportion of the population 15–64 years old and the prevalence of smoking.

We had only nine observations for each specific outcome with which to conduct the meta-regression analyses of the associations between PM_{10} and mortality. This has limited the inclusion of several covariates together in the regression models, especially because some of the covariates were multicollinear. Therefore, we ran only univariate meta-regression models; this can explain why we obtained several significant covariates for the 11 individual outcomes.

DISCUSSION

Several studies conducted in Latin America in the past few years have examined the association between air pollution and adverse health effects, such as mortality and hospital admissions (Pan American Health Organization 2005). However, it is difficult to compare and summarize results across the region or even across a single country because of the variety of analytic approaches and definitions used in each city-specific study. These differences include: the fraction of PM available for measurement (total suspended particles [TSP], PM_{10}, or $PM_{2.5}$), the age groups selected, and the health outcomes examined.

A recent trend in study design is to use standardized methodologies and multicity approaches to gain precision and to explore variations in estimates of the effects of air pollution across locations. Examples of such studies

include Air Pollution and Health: A European Approach (APHEA) (Katsouyanni et al. 1996); Air Pollution and Health: A European and North American Approach (APHENA) (Katsouyanni et al. 2009); the National Morbidity, Mortality, and Air Pollution Study (NMMAPS) (Samet et al. 2000); and the HEI Public Health and Air Pollution in Asia (PAPA) study (HEI PAPA 2010). For example, the APHEA study, the first of such initiatives, included a large number of European cities, but the time-series models were developed and fit to each individual city's data according to a common protocol, although to accommodate potential local differences, the models were not required to be identical (Katsouyanni et al. 1996; Touloumi et al. 2004). NMMAPS benefited from the availability of uniformly collected and reported data for many cities in the United States. The same model was applied in each city, and sensitivity analyses were carried out by varying the degrees of freedom used in the models. Through these studies, a consensus was reached to use GAMs to evaluate the association between air pollution and health effects in time-series studies, which led to a reanalysis of the original data sets from APHEA, NMMAPS, and some Canadian studies. The APHENA project was motivated by the need to compare findings among these major time-series studies of air pollution and health effects and to explore the possible basis for any heterogeneity among the risk estimates in the three data sets (Katsouyanni et al. 2009). More recently, HEI supported a multicity study in Asia to evaluate the impact of air pollution on mortality in four Asian cities: Bangkok in Thailand, and Shanghai, Wuhan and Hong Kong in China (HEI PAPA 2010). In that study a common protocol was established to evaluate the quality of data and analyses and GAMs were used to evaluate single-city as well as combined estimates of increased mortality risk using random-effects models.

The ESCALA project shares the same purpose as previous multicity studies. We used common protocols to evaluate the association between air pollutants, PM_{10} and O_3, in nine Latin American cities from three large countries: São Paulo, Rio de Janeiro, and Porto Alegre from Brazil; Santiago, Temuco, and Concepción from Chile; and Mexico City, Monterrey, and Toluca from México. The study included up to nine years (1997 to 2005) of daily data on mortality and air pollution levels. For the analyses we relied on a common library (ARES), developed in R software by researchers from the Brazilian team, to conduct single-city and combined-city analyses. ARES is a set of functions for time-series analyses whose purpose is to support the analysis of the effects of air pollution on health. By using these common protocols throughout the study we avoided the problem of having different analytic approaches when comparing results among cities.

SUMMARY OF RESULTS

In the ESCALA project we concentrated the analysis on the effects of PM_{10} and O_3 on mortality. The most common and consistent association reported in the literature has been with PM (Pope and Dockery 2006; Dockery 2009). Although the fine fraction has shown greater association with mortality, PM_{10} is the fraction available for most cities in Latin America. Gaseous pollutants, especially O_3, have also been associated with adverse health effects, and measurements of O_3 concentrations were available for most of the cities included in this study. Our analysis strategy involved the examination of single- and distributed-lag models for each individual city and the combined effects obtained by meta-analysis.

PM_{10} was associated with increased mortality in most cities and for all natural causes and for specific causes of death. Larger effects were observed in older people ($\geq$ 65 years) and for respiratory causes compared with cardiovascular causes (Table 10). The random-effects estimate from the meta-analysis of the results from the nine cities showed that a 10-$\mu g/m^3$ increase in PM_{10} was associated with an increased risk for all-natural-cause, all-age mortality of 0.77% (95% CI = 0.57 to 0.97) when using DLM 0–3. These effects are somewhat higher than those reported in other multicity studies. For example, as part of the HEI PAPA study, Wong and colleagues (2008) found a 10-$\mu g/m^3$ increase in PM_{10} was associated with a 0.55% increase in all-natural-cause, all-age mortality. NMMAPS reported an increase of 0.5% in all-natural-cause, all-age mortality for the United States (Samet et al. 2000), while results from the APHENA study ranged from 0.18% to 0.42%, depending on the model specification (Katsouyanni et al. 2009).

The results for O_3 in individual cities were more variable than the PM_{10} results but did show increases in risk of mortality with increases in O_3 (Table 12). Most of the combined fixed- and random-effects estimates were positive and about half were also significant (Table 21). The increased risk using DLM 0–3 for all-natural-cause, all-age mortality was 0.22% (95% CI = 0.18 to 0.26) using fixed effects and 0.16% (−0.02 to 0.33) using random effects for an increase of 10 $\mu g/m^3$ in O_3 concentrations. Effect estimates, with the exception of respiratory outcomes and COPD in the random effects, were higher for the $\geq$ 65 age group compared with the all-age group, especially for cardiopulmonary and cerebrovascular–stroke causes. In the PAPA study,

investigators found an increase of 0.38% (0.23 to 0.53) for the combined effect of O_3 on mortality (Wong et al. 2008).

We also carried out analyses by season (warm and cold) for O_3. This approach is particularly important for this pollutant given that its formation in the atmosphere is related to temperature and radiation. In studies conducted in the United States and Europe, statistical control of temperature has been shown to affect the association of O_3 with mortality because of the strong temporal correlation between O_3 concentration and temperature (Bell et al. 2004; Gryparis et al. 2004; Medina-Ramón et al. 2006). In fact, results for O_3 were seasonally dependent, with effect estimates greater in the warm season for some of the cities (Tables 14 and 15). The larger effect during warm months may reflect the higher concentrations of O_3 during that period, greater personal exposure, and differing characteristics of the air pollution mixture by season. However, the larger effects of O_3 in the cold season observed in México might be explained by the peculiar pattern of the climate in that country. O_3 concentrations are higher during the cold season in México, because pollutants are trapped by a seasonal atmospheric inversion layer and because the warm season usually has higher rainfall, which lowers pollutant concentrations.

We also observed an effect of air pollution on infant and child mortality in the largest cities of each country (Tables 16–19). However, because the daily mortality for these age groups was low in most of the cities, we did not calculate combined estimates. Individual city analyses revealed that, with the exception of LRI in infants, effect estimates for mortality in children are much higher for O_3 than for PM_{10} in Mexico City, especially in the cold season. In Santiago, with the exception of LRI in infants, significant effects were observed for PM_{10} for respiratory causes and LRI in children. Regarding O_3, no significant effects were observed. In São Paulo during the warm season, O_3 was strongly related with an increased risk of respiratory mortality in infants.

Results of two-pollutant analyses (PM_{10} and O_3) were similar to those of single pollutant analyses for most of the outcomes. O_3 effects on all-natural-cause, cardiopulmonary, respiratory (≥ 65), cardiovascular, cerebrovascular–stroke, and COPD mortality did not show a significant change when data were adjusted by PM_{10}, but PM_{10} effects adjusting for O_3 were slightly higher than those not adjusted by O_3. This could suggest an interaction between pollutants.

One of the main objectives of the ESCALA project was to evaluate the effect of SES as a modifying factor of the association of air pollution and mortality. However, a major challenge was to assure that SES levels were defined in a comparable way across the three countries. Thus we developed a protocol to obtain similar indices using three different categories: education, income, and housing conditions. Because of statistical power issues, we conducted this analysis only in the larger cities of each country (Mexico City, São Paulo, Rio de Janeiro, and Santiago).

Our results indicate that people with the lowest SES have a higher risk of death, especially from respiratory causes. On the other hand, there was some evidence that the risk of mortality from cardiovascular causes related to air pollution was larger among people from the medium- and high-SES groups.

A few studies have explored the role of SES in the association of air pollution with health effects (Gouveia and Fletcher 2000, Gouveia et al. 2003; O'Neill et al. 2003). These studies indicate that the SES might interact with air pollution through different and complementary pathways. Conditions more likely to be found among low-SES populations, such as less access to health care and higher exposure to air pollution, may act synergistically to produce ill health.

Similar analyses should be performed in other locations. If our findings are corroborated, these could have important public health implications for the region.

Finally, univariate meta-regression models were applied to the ESCALA data to find potential effect modifiers. Our results suggest that several variables modify the effects of air pollution: percentage of the population < 1 year, 1 to 4 years, 15 to 64 years, and ≥ 65 years; as well as annual average PM_{10} concentrations, temperature in the warm season, and mortality rates for lung cancer. These variables played an important role in explaining the heterogeneity across cities in the ESCALA project.

METHODOLOGIC ISSUES

Overview

In the ESCALA project we were faced with several decisions regarding the specification of the models to be applied to single-city analyses, such as the definition of season, the selection of adequate degrees of freedom for smoothing of temporal and meteorologic confounders, and the adequate choice of smoothing functions and estimation framework. We built on the experience of previous work in this area by considering both natural and penalized splines; however, we decided to use natural splines as a proxy for any time-dependent outcome predictors or confounders with long-term trends and seasonal patterns not explicitly included in the model. Core model goodness-of-fit was obtained by varying the amount of smoothing (number of degrees of freedom) and assessed using the following diagnostic approaches: PACF, periodogram pattern, AIC, the Cook distance, deviance residuals, and normal probability plots.

We explored several single-lag periods and observed that most of the effects occurred within the first three days for the different outcomes. Therefore we focused our report on the results of analyses using cumulative mortality effects over lags 1–3. The reasons for conducting single-lag analyses were to evaluate the single-day pollutant effect and also to allow the results to be compared with other published studies (results of single-lag analyses are shown in Appendix Tables I.5 to I.8, available on the HEI Web site).

One strength of our study was the ability to explore the cumulative associations between air pollution and daily mortality using constrained DLMs. This was possible because we had daily data on air pollution for all nine cities.

Recent evidence (Schwartz 2000b; Schwartz et al. 2003) shows that the relationship between air pollution and health effects may be best described by a distributed lag (i.e., the incidence of the health effect on day n is influenced by the pollutant concentration on day n, on the previous day, on the 2 previous days, and so on). Under these assumptions, SLMs are likely to underestimate the total impact of air pollution. Because of this, a DLM may be preferable to SLMs.

In the ESCALA project, DLMs were fitted as a systematic approach to specifying the long-term lag association between mortality and pollution. It also allowed a better comparison among sites. In addition, DLMs have the advantage of estimating the distributed lag function, which describes the change over time in the risk associated with a given day's air pollution. The distributed lag coefficients give insight into the total effect of air pollution on a particular day, as that day's exposure contributes to the effect of air pollution on multiple subsequent days. Information about the shape of the distributed lag function provides useful evidence concerning the time course of risk for the outcome and may give clues about mechanisms by which air pollution causes disease (Katsouyanni et al. 2009). DLMs can also give insights with regard to mortality displacement (Zeger et al. 1999; Schwartz 2000a, 2001; Dominici et al. 2002b; Zanobetti et al. 2002).

In our analysis we explored DLMs spanning up to 60 days to estimate the time course of all-natural-cause and specific-cause mortality in response to air pollution, as proposed by Zanobetti and colleagues (2003). While we explored relatively long term effects to evaluate a potential displacement of mortality, we did not observe a clear pattern. We therefore calculated increased risk by fixing constrained DLMs with 0–3, 0–5, and 0–10 days lagged. This report focuses on the DLM 0–3 approach.

Second Stage Analyses

One feature of the multisite time-series design is the possibility of combining information across locations and of exploring effect modification. As conducted in previous multicity time-series studies (Katsouyanni et al. 2001, Dominici et al. 2002a, Touloumi et al. 2004, Le Tertre et al. 2005, Wong et al. 2008), we combined information across cities to obtain summary estimates by using a meta-analysis approach.

There can be two sources of variability that explain the heterogeneity in a set of studies in a meta-analysis. One of them is the variability due to sampling error, also known as within-study variability. The sampling error variability is always present in a meta-analysis, because every single study uses different samples. The other source of heterogeneity is the between-study variability, which can appear in a meta-analysis when there is true heterogeneity among the effect sizes estimated by the individual studies. The between-study variability is influenced by an undetermined number of characteristics that vary among the cities, such as those related to the characteristics of the populations and variations in the study design quality (Hunter and Schmidt 2000; Brockwell and Gordon 2001).

As part of the objectives of the ESCALA project, we conducted a meta-analysis aimed to:

- Integrate the results of the nine cities to obtain a global index on the effect of air pollution exposure on mortality. We combined the effects using both fixed- and random-effects models.
- Test whether the effects of air pollution in the studies (cities) are homogeneous (i.e., evaluate the between-study variability).

To conduct the meta-analysis, we took into account the set of nine coefficients from the GLMs (one per city). However, because the between-city variability for some causes of death and specific age groups was not constant when the number of lags varied, we decided to focus the meta-analysis on the effects from the DLM 0–3.

Heterogeneity among cities was assessed mainly with two parameters:

- The Cochran Q test (Cochran 1954). Under the null hypothesis of homogeneity among cities, the Q statistics follows a chi-squared distribution with $k - 1$ df, with k being the number of studies (cities).
- The I^2 percentage of variability. This measures the extent of true heterogeneity and represents the percentage of the total variability in the set of effects due to true heterogeneity, that is, the between-city variability (Higgins and Thomson 2002).

The Q and the I^2 tests are both useful because both assess the presence of heterogeneity, but the I^2 index also provides a measure of the extent of it. I^2 should be better than the Q test in assessing whether there is true heterogeneity among the studies in a meta-analysis (Huedo-Medina et al. 2006).

In addition we conducted meta-regression analyses as an extension to the meta-analyses to investigate heterogeneity of mortality effects across cities. Meta-regression examines the relationship between observed effect sizes and city-level characteristics (e.g., aspects of geographic location, meteorologic or socioeconomic factors, or air pollution levels).

In summary, the sizes of the combined effects across cities are the usual measures available for a meta-analysis (such as odds ratios or increased risks), and the meta-regression analyses aim to compare, explain, and contrast the heterogeneity in these effect measures among cities in relation to the city-level characteristics.

The meta-regression analyses were fitted using REML as the estimation procedure. The REML is a method for fitting linear mixed models that was first described by Patterson and Thompson (1971). In contrast to conventional maximum likelihood estimation, REML can produce unbiased estimates of variance and covariance parameters.

We applied univariate models (including only one covariate per model) for each of the 15 covariates available for this analysis (city altitude, population density, prevalence of smoking, lung cancer mortality rates, age structure, temperature in different seasons, rainfall annual average, pollutant concentrations averaged over the period of the study, and geographic density of air pollutant monitors). Then we explored the inclusion of more than one covariate at a time, as well as shapes of association other than linear. Finally, the meta-regression models were applied for all outcomes regardless of the issue of heterogeneity or homogeneity. The meta-regression analyses used the nine β-coefficients obtained in the single-city analysis for each outcome and DLM choice. We did not consider carrying out the meta-regression analyses using the increased risks, since the meta-regression model assumes normality for both the between-study and the within-study variations.

Our approach is similar to that of the APHENA multicity study that used univariate (for one-pollutant models) or multivariate (for multiple-pollutant models) meta-regression models to pool the city-specific estimates and to explore determinants of heterogeneity. However, we ran only univariate meta-regression models. In such models, random-effects pooled regression coefficients were estimated by the weighted regression of city-specific estimates on potential effect modifiers (at the city level), with weights inversely proportional to their city-specific variances. The results for both approaches of combining data were similar. However, the power to detect heterogeneity was greater in the APHENA project than in the ESCALA project because APHENA had a larger number of cities (30 in Europe [APHEA2], 90 in the United States [NMMAPS], and 11 in Canada).

HETEROGENEITY

One of the objectives of ESCALA was to explore effect modification across study locations. The first step was to test for the existence and extent of heterogeneity in the effect estimates (DLM 0–3) among cities using the Cochran Q test and the I^2 index for each pollutant. A large and significant variability in the DLM 0–3 effects was found for most of the health outcomes for each of the pollutants.

Another way to detect between-city variability is to use the results from the meta-analysis that also provided single-city weights and global effects estimations. For O_3, the highest combined effects were observed at DLM 0–3 and were higher using the random-effects model than the fixed-effects model.

These results suggest different patterns for PM_{10} and O_3. While there was not substantial heterogeneity among cities in the association of PM_{10} with mortality, some levels of heterogeneity were present for most of the causes of death with respect to O_3 effects.

Because of the variability observed and the likely heterogeneity among cities, exploration of effect modification was conducted via meta-regression analyses that accounted for variables that could potentially explain a relative percentage of heterogeneity among cities. Variables selected to conduct the meta-regression analyses are shown in Table 23. Our results showed different significant variables for different causes of death over the nine cities, but the most important among those selected were the mean average temperature in the warm season, the percentage of the population less than 1 year old, the percentage of the population between 1 and 5 years, the percentage of the population 65 years or older, geographic density of PM_{10} monitors, annual average concentration of PM_{10}, and mortality rates for lung cancer in men and in women.

LIMITATIONS

We intended to have standardized data sets and analyses and to use a common statistical program to run all analyses (R software Version 2.9.2. Copyright 2009, the R Foundation for Statistical Computing ISBN 3-900051-07-0). R codes and routines were also standardized for all cities. The

differences in modeling resided only in the adjustment for some covariates such as holidays, long-weekend indicator variables, and the number of degrees of freedom for controlling time trend and seasonality, as well as for adjusting humidity and temperature via natural splines. Nevertheless, we were faced with limitations inherent to the analysis of secondary data and the fact that the data sources and the information provided differed by country.

Lack of Information

Some limitations are related to the type of information that is on the death certificates or that is provided by the national authorities. The information that is available differs among countries, in particular the information about SES. For infants and children, the only possibility was to assign SES based on the place of residence. In addition, SES based on years of schooling is highly dependent on age because of cohort effects. These points are discussed in more detail in Appendix F.

Exposure Measurements (PM_{10} and O_3)

As in previous time-series studies, we used city monitoring networks to determine pollutant exposure for different populations. While we applied a strict QC protocol to all data, we were dependent on existing data. Rio de Janeiro changed its monitoring network during the study period. The O_3 data measurements were incomplete in Porto Alegre; Concepción and Temuco had no O_3 measurements at all. We sought to improve the exposure assessment in large cities by looking at clusters of pollution by geographic units. We were able to do this with Mexico City, dividing it into three areas. However this procedure could not be conducted in other large cities, so we decided to drop this approach. PM_{10} concentration was monitored with different equipment in different cities (TEOM or BAM). Although we planned to adjust the measurements from one method to compare them gravimetrically with the other, the data were not available for all of the cities, so we could not account for this difference. Finally, we were not able to assess only background monitoring stations because most of the monitoring stations in the Brazilian cities were located in places that might be considered hot spots.

Measurement error is inevitable in air pollution studies, particularly when using a monitoring network to estimate population exposure. In general, bias toward the null would be anticipated, but the degree of bias could vary because of differences in activity pattern, type of housing, and other factors affecting exposure among populations. We did not have enough information to account for these factors.

In addition, the SES indexes were created at the municipality or district level, so the homogeneity of SES classification within these area units can be assumed; however, each unit has a large population, so some SES misclassification is likely. Nevertheless, air pollution exposures were assigned to populations without knowledge of SES status, taking into account air pollution levels in the area unit where the deaths occurred. Thus, misclassification of SES would tend to underestimate the real effect of pollutants.

Relatively Small Number of Cities for the Meta-Analyses

A limitation of our study is the small number of cities available for calculating combined estimates. There is a trade-off between including more cities with poorer quality data, in particular with respect to air pollution monitoring, or including fewer cities with better data. This was a point of discussion we had at the start of this project, and we decided that the quality of the air pollution data was of major importance. Therefore, we included only the three Mexican cities with the best air pollution data as confirmed by the Mexican Environmental Agency. Similarly, the federal agency in Chile and the appropriate state agencies in Brazil identified the cities with the best air pollution data in those countries. In the future, as monitoring networks expand in the Latin American region and the quality of monitoring improves, we plan to include a longer time series and more cities in the analyses to obtain more precise combined estimates.

Lack of Variables for Meta-Regression Analyses

We planned to include a greater number of variables that could possibly explain the between-city variability in the effects of air pollution on mortality. These included variables in five different categories:

1. population characteristics and structure (population density, age structure, prevalence of some chronic conditions such as diabetes, prevalence of smoking, lung cancer and COPD mortality rates, percentage of mortality from cardiopulmonary causes, and socioeconomic indicators such as the Gini coefficient and the Human Development Index);
2. exposure characterization (geographic density of monitors by pollutant, relation between hotspot and background monitor stations);
3. emissions (the percentage of fuel consumed by season, the percentage of PM_{10} concentrations emitted by sector);
4. air pollution profile (nitrogen dioxide [NO_2] mean by season, PM_{10} mean, NO_2/PM_{10} ratio, $PM_{2.5}/PM_{10}$ ratio); and

5. general environmental conditions (altitude, average temperature by season, rainfall).

However, much of this information was not available at the city level.

We had only nine observations for running meta-regression analyses, which limited the number of covariates that could be considered together in the regression models, especially because some of the covariates are rather multicollinear (e.g., the percentages of different age brackets [pairs of those covariates are highly significant], temperature in the warm and in the cold, mortality rates of COPD and lung cancer). This could explain why we sometimes got many significant covariates for a single outcome. Also, because not all cities had available effect estimates for some of the outcomes (because of low average numbers) or not all cities had data for the meta-regression variables (e.g., Gini coefficients have been available only at the country level), neither the outcome nor the covariate associations could be examined. Moreover, the meta-regression analyses have so far only been applied to PM_{10} and to combined effect estimates from DLM.

Finally, restricted to the outcomes for which effects were available in all cities, to the city covariates with complete data, and to DLM 0–3, all meta-regression analyses were fitted for PM_{10} without regard for heterogeneity. This strategy can be justified by the fact that, even for homogeneous or for low heterogeneity sets of effect estimates, there may be one or more city covariates that are so strongly associated with these effects that they would explain the limited amount of heterogeneity in the sets of effect estimates.

SUMMARY AND FUTURE RESEARCH

The ESCALA project was developed to obtain information on the effects of air pollutants on mortality in nine Latin American cities where large populations are exposed to relatively high pollutant concentrations. Information about the health outcomes for the population of children was particularly desired. An important goal was to provide evidence to support air pollution control policies in Latin America. Within this project, our team developed standardized protocols and analytic statistical programs in R to ensure that results could be compared among cities. The analytic approach and statistical programming developed within this project should be valuable for researchers carrying out single-city analyses, and could facilitate the inclusion of additional Latin American cities within the ESCALA multicity project.

Our data confirms what was observed in other parts of the world concerning the relationships between PM_{10} and O_3 concentrations and mortality. It also suggests that SES plays a role in susceptibility to air pollution. Lower SES was associated with a higher risk of respiratory-related mortality; medium and high SES were associated with a higher risk of cardiovascular and cerebrovascular–stroke mortality. However, these results on effect modification by SES need to be evaluated in the other cities, and robust combined estimates need to be calculated.

Future research under the ESCALA project will include the following:

1. *Inclusion of other air pollutants.* We plan to evaluate the single and combined effects of other routinely collected air pollutants such as carbon monoxide, NO_2, and sulfur dioxide. Most of the nine cities included in ESCALA already monitor for other criteria pollutants.
2. *Addition of other cities from Latin America.* As part of this project we plan to include other Latin American cities by sharing our protocols and providing analytic support. This process has already begun with Bogota, Colombia, and we hope to add other cities based on the availability of air pollution data for time series.
3. *SES index for metropolitan cities.* While we could define an SES index and carry out stratified analyses for Mexico City, São Paulo, Rio de Janeiro, and Santiago, this type of analysis was not possible for the rest of the cities in this study. We also plan to develop an R-routine to formally test for interaction in the SES analyses.
4. *Meta-analysis with different approaches.* Different meta-analysis strategies, such as hierarchical models, could be applied to the ESCALA data to compare the results. Hierarchical models provide a unified and flexible framework for making estimates of pollutant effects for particular cities or countries, overall and covariate effects, and components of variation. This approach facilitates more precise RPC estimation within each city than can be accomplished by analyzing each city's data individually without consideration of the data from other cities. In addition, the hierarchical approach allows the estimation of city-specific, country-specific, and overall pooled effects of air pollution for a region, while accounting for variability in the increased risks of mortality associated with air pollution across cities, within a country, and across countries. The estimation of the city-specific, country-specific, overall pooled effect of air pollution, and of between-city and between-country variability can be also carried out with Monte Carlo Markov chain methods. One useful feature of these methods is that they provide, in addition to the point estimate and CI, an approximation of the entire distribution of the unknown parameters.

5. *Effect of temperature.* An interesting issue is the effect of temperature on mortality, adjusting for pollutant concentrations. Several studies have suggested that extreme (low and high) temperatures had an effect on increasing the risk of mortality independent of that from air pollution. Considering the large amount of data gathered for the ESCALA project, we would have good statistical power for studying this association. We intend to develop a standardized protocol to carry out this research.

In conclusion, the ESCALA project has yielded very interesting results on the effect of PM_{10} and O_3 concentrations on the risk of mortality in Latin American populations. It has confirmed previous findings from other multicity projects such as APHEA, NMMAPS, APHENA, and PAPA. This information is very valuable for the region. Results from the Mexican part of the ESCALA project have already been used for risk assessments of air pollution in Mexico City, and are also being used to review the air pollution standards of the countries. Data will continue to be collected and analyzed under the ESCALA project; its approach provides more informative analyses than can be achieved with a meta-analytic summary. Also, this ESCALA study led to the development of a standardized protocol for analyses of daily time-series data on air pollution and mortality comparable with other studies like APHENA or APHEA2.

Our results are relevant for decision makers in Latin America because of their robustness and comparability of the underlying data. Although we found some differences in data availability and comparability among cities, in the future it should be possible to build a larger set of time-series data in such a way that similar analyses and estimation approaches can be conducted with additional Latin American cities.

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APPENDIX A. HEI Quality Assurance Statement

The conduct of this study was subjected to independent audits by Mr. David Bush of T&B Systems, Inc. Mr. Bush is an expert in quality assurance for air quality monitoring studies and data management. The audits included an on-site review of study activities for conformance to the study protocol and operating procedures. The dates of the audit activities are given below, along with a brief summary of the audit effort and findings.

JANUARY 21–22, 2009

Mr. David Gemmill of Quality Assurance Consulting, Inc. assisted with an onsite audit at the National Institute of Public Health (INSP) in Cuernavaca, Mexico. The audit concentrated on the study's analytical and data management activities, and included an audit of the study's database. Several data points were traced through the entire data processing sequence to verify the integrity of the database. Recommendations resulting from the audit primarily concentrated on issues assuring the comparability of data among the three centers.

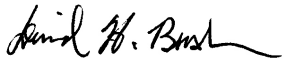
APRIL 2011

Mr. David Gemmill assisted in an audit of the study's final report. Several data and data presentation related issues were identified — most notably an inconsistency in the O_3 metrics used by one of the centers. This issue resulted in the reanalysis of some of the data and a revision of the final report.

AUGUST 21, 2012

The revised final report was reviewed to verify that issues identified during the April 2011 audit had been addressed. All issues were addressed by the authors.

Written reports of each inspection were provided to the HEI project manager, who transmitted the findings to the Principle Investigator. These quality assurance audits demonstrated that the study was conducted by an experienced team with a high concern for data quality. Study personnel were very responsive to audit recommendations, providing formal responses that adequately addressed all issues. The report appears to be an accurate representation of the study.



David H. Bush, Quality Assurance Officer

APPENDIX B. QA/QC Mortality Data Protocol

Quality assurance (QA) and Quality control (QC) steps were followed for the analysis of mortality data.

Descriptive analyses of the mortality data sets, with individual-level information for each city in order to assess the quality of the information. These include:

- period of the mortality data to be analyzed;
- ICD version used;
- frequency distributions and/or univariate distributions for the categorical or continuous variables in the data set to be used;
- examination of the distribution of the primary causes of death according to ICD;
- examination of the distribution of causes by ICD-group to check the percentage of causes assigned to the "ill-defined" group. This can be used as an indicator of the quality of the mortality data;
- examination of the education variable according to age groups (< 1, 1–4, 5–44, 45–64, 65–74, ≥ 75);
- examination of mother's education for children < 1 and 1–4 years old;
- examination of the distributions for miscoded, missing, and out-of-range data;
- examination of possible errors, questions, or concerns regarding specific data points.

For the data in México and Chile, because the ICD-9 coding was still in use in 1997, a program has been developed to convert the classification to the ICD-10 coding. Special attention needs to be given to the distribution of causes of death between 1997 and 1998, when the codification changed from ICD-9 to ICD-10, to verify if there are any unexpected changes.

APPENDIX C. QA/QC Air Pollution Data Protocol

Data on air pollutant concentrations for each city in the ESCALA project were provided by different environmental agencies. Though each country has its own QA/QC procedures, preliminary assessments revealed that they are very similar to each other and comply with the norms and methods established by the U.S. EPA, particularly with respect to criteria for completeness of measurements.

In México, the QC of air pollution monitoring is the responsibility of the SEMARNAT, Secretary of Environment and Natural Resources. Similar operational procedures and QC measures are followed in each city with a monitoring network.

While monitoring networks in cities in Brazil are run by local environmental agencies, they all have to report to the Ministry of Environment, and thus must comply with a defined QC protocol.

Chile has two types of automatic monitoring networks: those run by the local government and those run by private companies (mostly mining companies). The government-run networks comply with strict QC procedures, and provide data of high quality (Koutrakis et al. 2005). All pollution data that was considered for this study came from air monitoring stations that are run by the government. Data from private stations were not available for the period of the analysis.

For all three countries (and their respective cities), data from automatic monitoring systems are validated on an hourly basis using the following criteria:

1. Data collected every minute with potential estimation problems are marked automatically, and hourly means are based on at least 75% valid 1-minute measurements per hour, otherwise the hourly value is set to missing.
2. Identification of the values outside the regular patterns of the pollutants are controlled and verified.

In this study, we will consider daily concentrations (24-hr averages) of PM_{10}, as well as daily 8-hour maximum moving average for O_3, from all available monitoring stations.

COMPLETENESS CRITERIA

Hourly data provided for this study from the automatic network of monitoring stations has been assembled at a server at the INSP-México. The following criteria for data completeness will be used to generate daily air pollutant concentrations to be used in the analyses proposed by the ESCALA project:

- for the calculation of daily average concentrations of PM_{10}, it is required to have at least 75% of the 1-hour values on that particular day;
- for the maximum 8-hour value of O_3, at least 6 hourly values for each 8-hour average must be available, and at least 16 valid values were required to select the highest 8-hour moving average;
- for the maximum 1-hour value of O_3, 75% of the 1-hour values in a day must be available; and
- if a station has more than 25% of the values missing for the entire period of analysis, it will be excluded.

When these conditions are not met, the corresponding measurements will be set to missing. Identification of the values outside the regular patterns of the pollutants will be controlled and verified.

MEASUREMENT METHODS

The methods used to measure pollutants differ among the nine cities in the ESCALA study. This is particularly important for PM_{10}, which has been measured using gravimetric, TEOM, and BAM. The comparability of the measurement methods used for air quality assessment was also evaluated.

O_3 concentrations were measured with ultraviolet photometry in Brazil and Chile and with ultraviolet fluorescence in Mexico.

APPENDIX D. Monitor Specification Protocol

For each city, the locations of the monitors are evaluated to determine if they reflect the urban background air pollution level, if they are not influenced by local sources (e.g., traffic, industrial sources, or waste burning and incinerators), and if they are located in flat spaces with no major influence from city buildings or wind speed and direction. Thus, preference is given to background monitoring stations, when available. In addition, only urban air pollution is measured; monitoring stations located outside urban areas are not used.

The different scales for the more commonly used monitoring objectives are:

- Micro scale: defines pollutant concentrations in the air volume within 100 meters of a monitoring site;
- Medium scale: defines pollutant concentrations in air volumes of typical areas (several blocks), with a radius between 100 and 500 meters;
- Local scale: defines pollutant concentrations within a city area containing relatively similar land usage, a radius between 500 meters and 4 kilometers;
- Urban scale: defines pollutant concentrations for an entire urban area, with a radius between 4 and 50 kilometers. This scale normally requires more than one monitoring station to be defined;
- Regional scale: defines pollutant concentrations for a reasonably homogeneous rural area, geographically covering between tens and hundreds of kilometers;
- National or global scale: these measuring scales represent pollutant concentrations that characterize an entire country or the planet, in general.

To determine the classification to which a monitoring station belongs in the Mexican, Chilean, or Brazilian cities studied, each aspect of the physical surroundings of each monitoring station must be evaluated with respect to each contaminant. It is likely that the same station could be considered representative of one scale for PM_{10} and another for O_3.

DEFINITION OF THE SPATIAL RELEVANCE OF THE MONITORING STATIONS

The surroundings and relevance of the monitoring stations included in the ESCALA project shall be evaluated based on the Code of Federal Regulations (2004) and shall comply with the following site selection criteria:

- the sites shall reflect the urban background level of air pollution, thereby excluding those in the direct vicinity of traffic or 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 site shall be large enough to ensure the availability of space for monitoring, located in a flat space and elevated between 1 m and 14 m above ground level;
- the sites should be located 5 m upwind of building exhausts and at least 2 m from walls;

To facilitate the characterization of the monitoring networks in each location and to help the selection of those that provided information for this project, the major attributes of each station will be documented, such as:

- identification number, name and address;
- latitude and longitude for georeferencing;
- site elevation;
- inlet description, placement, and height above ground;
- land-use classification (residential, commercial, industrial, mixed-use, or suburban);
- information on emission sources in the vicinity of the station (around 1 km).

To better characterize population exposure, the latitude and longitude or the station address is geocoded to obtain estimates of the population density around each station.

CHARACTERISTICS OF THE ESCALA MONITORING STATIONS

The monitoring stations for each city are listed in Tables D.1–D.3.

Appendix Table D.1. Brazil: Characteristics of PM_{10} Monitoring Stations

City	Monitoring Station	Type of Equipment	Site[a]	Scale[b]	Classification[c]
São Paulo	P. d. Pedro II	BAM	Urban	Micro	Commercial
	Santana	BAM	Urban	Micro	Commercial/residential
	Moóca	BAM	Urban	Micro	Commercial/residential
	Cambuci	BAM	Urban	Micro	Commercial/residential
	Ibirapuera	BAM	Urban background	Local	Residential
	N. Sra. do O	BAM	Urban	Micro	Commercial/residential
	Congonhas	BAM	Urban	Micro	Commercial/residential
	Lapa	BAM	Urban	Medium	Commercial/residential/ industrial
	Cerqueira César	BAM	Urban	Micro	Commercial/residential
	Centro	BAM	Urban	Micro	Commercial
	Santo Amaro	BAM	Urban	Medium	Commercial/residential
	São Miguel Paulista	BAM	Urban	Micro	Commercial/residential
	Penha	BAM	Urban	Micro	Commercial/residential
	Pinheiros	BAM	Urban	Micro	Residential
Rio de Janeiro	Jacarepaguá	BAM	Suburban	Medium	Commercial/residential
	Centro	BAM	Urban	Micro	Commercial/residential
	São Cristovão	TEOM	Urban	Micro	Commercial/residential
	Saens Pena	TEOM	Urban	Micro	Commercial/residential
	Largo da Carioca	TEOM	Urban	Micro	Commercial/residential
	Arco Verde	TEOM	Urban	Micro	Commercial/residential
Porto Alegre	Esef	BAM	Urban	Micro	Commercial/residential
	Rodoviária	BAM	Urban	Micro	Commercial
	Santa Cecília	BAM	Urban	Micro	Commercial/residential

[a] Site: urban, suburban, or rural.

[b] Scale: micro, medium, local, urban, regional, or national.

[c] Classification: residential, commercial, industrial, or mixed use.

Appendix Table D.2. Chile: Characteristics of PM_{10} Monitoring Stations

City	Monitoring Station	Type of Equipment	Site[a]	Scale[b]	Classification[c]
Santiago	Cerrillos	TEOM	Local	Medium	Industrial
	Cerro Navia	TEOM	Local	Medium	Commercial/residential/ industrial
	El Bosque	TEOM	Urban	Medium	Commercial/residential
	La Florida	TEOM	Urban	Medium	Commercial/residential
	La Paz	Gravimetric/TEOM	Urban	Medium	Commercial/residential
	Las Condes	Gravimetric/TEOM	Urban	Medium	Residential
	Parque O'Higgins	Gravimetric/TEOM	Urban	Medium	Residential
	Providencia	Gravimetric/TEOM	Urban	Medium	Residential
	Pudahuel	TEOM	Urban	Medium	Residential/industrial
Concepción	Kingston College	BAM	Urban	Medium	Commercial/residential/ industrial
Temuco	Las Encinas	TEOM	Urban	Medium	Commercial/residential

[a] Site: urban, suburban, or rural.

[b] Scale: micro, medium, local, urban, regional, or national.

[c] Classification: residential, commercial, industrial, or mixed use.

Appendix Table D.3. México: Characteristics of PM_{10} Monitoring Stations

City / Monitoring Station	Type of Equipment	Site[a]	Scale[b]	Classification[c]
Mexico City				
Cerro de la Estrella	TEOM	Urban	Medium	Commercial/residential
ENEP Acatlán	TEOM	Urban	Medium	Residential
Hangares	TEOM	Urban (traffic)	Micro	Commercial/residential
La Villa	TEOM	Urban	Medium	Commercial/residential/industrial
Merced	TEOM	Urban	Medium	Commercial/residential
Pedregal	TEOM	Urban	Medium	Residential
Plateros	TEOM	Urban	Medium	Residential
San Agustin	TEOM	Urban	Medium	Residential
Santa Ursula	TEOM	Urban	Medium	Commercial/residential
Tlahuac	TEOM	Rural	Local	Residential
Taxqueña	TEOM	Urban (traffic)	Micro	Commercial/residential
Tlanepantla	TEOM	Urban (industrial)	Medium	Commercial/residential/industrial
Tultitlán	TEOM	Suburban	Local	Commercial/residential/industrial
Villa de la Flores	TEOM	Suburban	Local	Residential
Xalostoc	TEOM	Urban	Micro/medium	Commercial/industrial
Monterrey				
La pastora	BAM	Urban	Medium	Residential
San Nicolás	BAM	Urban	Medium	Residential
Obispado	BAM	Urban (traffic)	Medium	Residential/industrial
San Bernabé	BAM	Urban	Medium	Residential/industrial
Santa Catarina	BAM	Urban	Medium	Commercial/residential
Toluca				
San Lorenzo Tepaltitlán	BAM	Urban	Medium	Residential
Aeropuerto	BAM	Urban	Micro	Industrial
San Cristobal Huichochitlán	BAM	Suburban	Local	Residential
Oxtotitlán	BAM	Urban	Medium	Residential
Toluca-Centro	BAM	Urban	Medium	Commercial
Metepec	BAM	Urban	Medium	Commercial/residential
San Mateo Atenco	BAM	Urban	Medium	Residential/industrial

[a] Site: urban, suburban, or rural.

[b] Scale: micro, medium, local, urban, regional, or national.

[c] Classification: residential, commercial, industrial, or mixed use.

APPENDIX E. Time-Series Analysis Protocol

The analysis stage will take advantage of the experience and recommendations of groups that have already used different daily time-series studies approaches for mortality and morbidity.

GAMs, which allow nonparametric smooth functions to control for seasonality and long-term trends, have become a standard approach.

A two-stage analysis will be conducted. In the first stage, data for each city will be analyzed separately using a standard protocol and, depending on the issue, city-specific model adjustments may be necessary. In the second stage, pooled results will be obtained using meta-regression in which between-city heterogeneity will be explored.

STAGE 1: CITY-SPECIFIC ANALYSES

Proposed Core Model Protocol for Single-City Analysis

The single-city analysis will consider the following:

1. GAM with penalized splines;
2. Poisson model assumption for daily mortality from cardiovascular causes, respiratory causes, or all-natural-cause mortality for selected age groups;
3. spline of the time indicator, initially using 3, 6, 9, and 12 *df* per year, and the number of degrees of freedom that will optimize both the PACF and the periodogram (spectral density);
4. day-of-week indicators;
5. indicators for public holidays, allowing for different indicators according to the sign and magnitude of holiday effects;
6. controlling for influenza epidemics according to Braga and colleagues (2000);
7. splines of the mean daily temperature and mean daily humidity indicators, initially using 3 or 6 *df*, each at lags 0, 1, and 2, and moving averages of previous days. Rely on model diagnostics to adequately choose the indicator and the number of degrees of freedom (see item 8). Check standardized deviance residuals for each meteorologic indicator before and after its inclusion in the model;
8. residual diagnostics, including a deviance and dispersion parameter estimates for overdispersion, ACF and PACF for residual autocorrelation and overfitting, periodogram for residual seasonality, Q-Q plot and simulated envelope for normality of standardized deviance residuals, the Cook distance to assess influence, sequence of plots of standardized deviance residuals for extreme values, AIC for model parsimony;
9. review model specification according to residual diagnostics (e.g., switch from Poisson to quasi-likelihood families in case of overdispersion, refit model, and carry out new model diagnostics). When all model diagnostics are satisfactory, proceed to item 10;
10. estimates of the effect of the exposure with the chosen DLM (DLM specification is defined in the Methods section of the Investigators' Report).

Calculate estimates of the effect of exposure to other pollutants. Two-pollutant models will be considered, as well as three-pollutant models for selected pollutants.

Items 3 to 7 should be revised after introducing a new term into the model, to adapt to collinear adjustments.

At the end of step 8, several critical issues need to be considered to ensure the comparability of data and analyses among cities:

- adequate control for seasonal and long-term patterns;
- adequate adjustment for effects of weather, seasonal features, and influenza and other viral epidemics;
- adequate methods for handling autocorrelation;
- adequate methods for handling the presence of outliers and overdispersion.

After the core model specification is complete, a thorough model diagnostics will be carried out and documented for further reference (item 8).

City-Specific Analysis

Initial analyses will aim to identify data anomalies and inconsistencies for each city-specific data set. We will then describe, for each city, patterns of mortality and pollution variables by year, season, and geographic area using graphical methods and tabulation.

The critical issues to be considered for ensuring comparability of data between cities are:

- health outcome categories and air pollutant measurements are comparable;
- the approaches for imputing missing data are uniform;
- the same criteria are used to select and to aggregate air pollution data across monitoring sites.

Spatial Aggregation

It is recommended that multiple monitoring sites be used to reflect population exposure to pollutant concentrations. These monitoring sites should comply with the selection criteria described in Appendix D. The correlations between monitoring sites will be examined.

Depending on the size of the city, the analysis will be performed at different levels of aggregation. For smaller

cities that have one monitor, the city will be considered a single unit. A city with two monitors will be considered a single unit if the monitors have consistently similar measurements. In that case we will use the average of the monitors' measurements.

Larger cities will be divided into geographically homogenous regions for the purposes of computing population exposure to outdoor air pollution. The population exposure will be characterized using the closest monitors in each region. Health effects analyses will then be performed at the region level or at the city level, using a population-weighted average of pollutant concentrations. The level of spatial aggregation may vary according to the outcome studied, to ensure sufficient power of analysis. For example, for infant mortality, it may be necessary to use a larger level of aggregation to have enough cases in each region. A preliminary analysis of this type will be performed in Mexico City.

Base Models

Use of the standard protocol to conduct city-specific analyses will ensure that methods are uniform across the cities. However, when there appear to be good reasons for using a specific modeling technique to attain a better model fit in a specific time-series and location, the three statistical teams will discuss whether to use that technique, and will consider the consequences of that use on the analysis of the pooled results.

Total daily mortality for all ages and for several age groups, and daily mortality from specific causes will be analyzed. Daily pollutant measurements will include PM_{10} and O_3 concentrations. If possible, a restricted analysis will be conducted with available series of $PM_{2.5}$ air pollution data from Santiago and Mexico City. A GAM Poisson regression will be applied to model the nonlinear effects of potential confounders such as seasonality, long-term trends, weather, and influenza epidemics.

The time-series models for a given pollutant are of the form:

$$\ln\left(E\left(Y_t^c\right)\right) = \beta^c X_{1t}^c + \sum_{i=2}^{p} S_i^c\left(X_{it}^c\right) \qquad (1)$$

where: Y_t^c and X_{1t}^c are the number of deaths and the air pollutant concentrations, respectively, on day t in city c; X_{it}^c are the other predictor variables in city c on day t, and S_i^c are the smooth functions of those variables applied in city c.

Pattern of Pollution Effects

To explore the pattern of the lagged effect of air pollutants on health, we will adopt constrained lag structures, that is, polynomial DLMs (Schwartz 2000b). Different lengths of cumulative effects will be used, as well as different degrees of polynomials to assess the best approach for the analyses. The best polynomial degree will provide the models with enough flexibility to estimate a biologically plausible lag structure while controlling for multicollinearity.

Age-Specific or Cause-Specific Group Analysis

Model building techniques to be applied to distinct outcomes (age groups or causes) are basically the same, however, for a given outcome, models may require specific adjustments with respect to one or more covariates to attain a better fit. Thus, a slightly different base model may be used for the analysis of each specific age group.

In a first approach, the same base model will be used for all age groups; nevertheless, if seasonal patterns are not effectively controlled under the common base model, different seasonal controls may be used for each age group.

Adjustment for the Mortality Displacement Effect

To obtain estimates that are adjusted for the mortality displacement effect (harvesting), we will follow methods applied by Zanobetti and colleagues (2000) that fit DLMs to the association between air pollution and daily mortality in Milan, Italy. Nonparametric smoothed DLMs and parametric models will be examined. Because this method provides more temporal detail, we propose using it as our primary approach in the adjustment for harvesting effects.

STAGE 2: BETWEEN-CITY ANALYSES

Graphical display (forest plots) will be used to compare associations of mortality and air pollution between cities and to explore modification by city-level variables. The effect parameter estimates for specific pollutant–mortality associations from different cities will be checked for heterogeneity.

To provide a quantitative summary of city-specific results and to investigate potential effect modifiers, we will use univariate (for one-pollutant models) or multivariate (for multiple-pollutant models) meta-regression models. In such models, fixed-effects pooled regression coefficients are estimated by a weighted regression of city-specific estimates on potential effect modifiers (at the city level), with weights inversely proportional to the city-specific variances. If the heterogeneity of effects among cities is significantly greater than the variation associated with fixed effects, random-effects meta-regression models will be used. The meta-regression approach can be conceptualized as a two-level hierarchical model, with cities constituting

the highest hierarchy levels and successive days constituting the lowest levels. Using this approach, we can examine whether the effect of potential modifiers is similar across cities. Similar analyses will be conducted for each country to obtain country-specific summary estimates for Brazil, México, and Chile.

Models for multivariate meta-regression analyses will be of the form:

$$\beta^c = X^c\alpha + \delta^c + \varepsilon, \quad (2)$$

Here, β^c is the air pollutant coefficient estimated from the time-series model (equation 1) corresponding to one unit of increase in air pollution in city c for a given pollutant; X^c represents the observed values of the city-level covariates for city c; α is the vector of unknown meta-regression coefficients; δ^c is a random effect representing, for each pollutant, the city's deviation from the average of all cities having the same values of covariates; and ε represents the random errors.

The $p \times p$ matrix $\text{cov}(\delta^c) = D$ represents the between-city covariance that is unexplained by the fixed effects (i.e., the regression). It is assumed that:

$\delta^c \sim \text{MVN}(0, D)$

$\varepsilon^c \sim \text{MVN}(0, S^c)$

$\beta^c \sim \text{MVN}(X^c\alpha, D+S^c)$

where S^c is the estimated variance–covariance matrix in city c for the pollutants p. When $D \approx 0$ we have the corresponding fixed-effects estimates, while when $D \neq 0$ we have the random-effects estimates.

To estimate the model parameters, the method described by Berkey and colleagues (1998) will be applied. Unlike the usual meta-regression analysis in which results for each pollutant are analyzed separately, the multivariate meta-regression analysis provides more accurate estimates by incorporating the correlation among pollutants within each city.

Univariate meta-regression models represent a specific case of multivariate meta-regression models where $p = 1$ (one-pollutant city-specific models). In such cases, the between-city variance is estimated from the data using the maximum likelihood method described by Berkey and colleagues (1995) and is added to the city-specific variances.

This method has been used in the APHEA study (Katsouyanni 1996) and allows for exploring possible heterogeneity among city-specific results and for obtaining summary estimates. Specific S-plus functions have been written to fit univariate and multivariate meta-regression models.

SOFTWARE ISSUES

All statistical analyses will be carried out using the statistical environment R. However, some routines are not yet available and have to be implemented, which are mainly related to case–crossover design and some specific issues with respect to meta-analysis models. Missing data imputation routines are already implemented as an R-package. In addition, a multitool package for environmental time-series analyses is being finalized. This includes model building techniques, model diagnostics, specific graphical displays, and tailor-made model fit summaries.

APPENDIX F. SES Index Protocol

One objective of the ESCALA project is to evaluate the potential modifying effect of SES. The purpose is not only to test for these modifying effects within each city, but also to explore possible differences among cities and countries. Therefore, it is particularly important to generate comparable SES measures across cities and countries.

AVAILABLE DATA FOR COMPARABLE SES VARIABLE CONSTRUCTION

The number of comparable SES variables is limited by the reduced number of SES-related variables that city and country mortality data sets have in common. Four SES-related variables are available in the three countries: race, occupation, educational level, and place of residence. However, differences among the first two variables present problems that significantly reduce their utility for characterizing SES for the entire study population.

The variable *race* is present in the death certificates of the three countries. However, the meaning of *race* as an indicator of SES is different in Brazilian cities than in Mexican and Chilean cities. A significant percentage of the population in Brazilian cities is of African-origin, but this is not true in cities of México and Chile.* On the other hand, indigenous ethnicity, that is, whether a person belongs to an indigenous population group, might be a better indicator of SES in Mexican and Chilean cities. However, the indigenous percentage of the population is very small in large metropolitan areas such as Mexico City (between 1.5% and 2.0% in 2000). (Figures obtained from the Mexican 2000 Population Census are available online at *www.inegi.gob.mx/est/default.aspx?c=2397*.) The association between SES and race is not clear, thus reducing the utility of this variable as a common indicator of SES.

* Even in Brazil, for historical and institutional reasons, the association between race and SES is different and more complex than in countries such as the United States (Telles 2006).

The variable *occupation* is also available for the three countries. In contrast with *race*, *occupation* is the variable most often used to measure SES status in the specialized literature on social stratification, followed by the variables *education* and *income* (see Grusky 2000). However, using *occupation* to construct a standardized SES measurement has a major drawback: a large percentage of adult women in the nine cities is not in the labor force, and therefore cannot be classified by their occupation. Even in São Paulo, where women's participation in the labor force is among the highest in Latin America, the percentage of women in the labor force is around 50%†, implying that a measure of SES cannot be obtained from occupational status for half of the female population in São Paulo.

The remaining two variables in this study (*educational level* and *place of residence*) are also associated with SES, but in different ways. In the social stratification literature, educational attainment has been conceived of as both an outcome of the social position of the family of origin and as a predictor of an individual's social position (see: Blau and Duncan 1967; Kerbo 1996; Grusky and Kanbur 2006). In the specific context of Latin America, educational inequality is considered to be one of the core mechanisms through which social inequality reproduces over time, and also the single variable that most affects an individual's job and income opportunities (CEPAL 1998; Behrman et al. 2001). Therefore, the educational level attained by individuals can be utilized as a proxy for their SES, both in relation to their social origins and their current SES.

On the other hand, the variable *place of residence* relates to SES through patterns of residential segregation. People with high SES tend to reside in the most affluent areas of the city, whereas residents with low SES are segregated in the low-income areas. Individuals who reside in low-income neighborhoods may be characterized as disadvantaged, not only because they are more likely to possess a low SES, but also because they tend to have a higher exposure to the negative ecological consequences of socioeconomic segregation, such as a high concentration of poverty, deficiencies in public services (including schooling, healthcare, and sanitation), and higher rates of delinquency. In this sense, by characterizing individuals according to the socioeconomic characteristics of their place of residence, it is possible to obtain an area-based measure of SES.

The information about educational level and place of residence will be used to develop two separate variables to measure SES. The first variable, based on educational level, will classify the study population at an individual level. The second variable, based on place of residence, will classify the study population at an area-based level. These two separate measures may be used individually or may be combined in multilevel models to explore the possible modifying role of SES in the association between exposure to air pollution and mortality, as well as in differences of these effects among cities and countries.

PROPOSED PROCEDURE FOR THE CONSTRUCTION OF AN INDIVIDUAL-LEVEL SES VARIABLE

In Brazil and México the variable *educational level* is precoded in death certificate data sets as grouped categories of the years of education (five categories in Brazil and six in México). In Chile, the variable is not precoded into categories, and therefore it can be used both as single years of education or as a grouped variable.

Differences in the coding scheme used by each country represent a first obstacle that must be overcome before a comparable SES variable can be generated. A second obstacle is that the average educational level of the population differs across cities and birth cohorts, and therefore a similar number of years of education may represent a different position in the relative distribution of educational assets, depending on the city of residence and the age group.

To illustrate how these problems might affect the construction of a comparable SES variable based on years of education, consider the cumulative distribution of deaths by years of education and age group for adult males in São Paulo, Rio de Janeiro, Mexico City, and Santiago. The data for Santiago have been coded according to the categories used in Mexico City, and therefore it is possible to make a direct contrast between these two cities. However, the different coding used in São Paulo makes it difficult to make any contrast with Mexico City and Santiago.

In addition to these coding discrepancies, the distribution of deaths by years of education significantly changes according to the age of the deceased. The educational level gradually decreases as age increases in the three cities. In Mexico City, for instance, 76.2% of people 70 years or older have ≤ 6 years of education versus 28.7% for the 18–29 age group. Similar changes are observed in the other two cities. These changes are not likely to be associated with a change in relative risk of death among different educational groups, but rather, to the average increase in educational levels of younger cohorts. In this sense, it is evident that an individual who is 70 with 6 years of education has a relatively high level of education for the standard of his or her birth cohort, whereas an individual with

† 48.9% in April of 1996, according to the Pesquisa Mensal de Emprego. See the report prepared by IBGE available online at: *www.ibge.gov.br/home/estatistica/populacao/condicaodevida/indicadoresminimos/suppme/default_educacao.shtm.*

6 years of education who is between 18 and 29 has a relatively low level of education in relation to other members of his or her birth cohort. Therefore, if *years of education* is used as an indicator of SES and SES is a relative measure, the same number of years of education may indicate a different SES depending on the age group to which the individual belongs.

The proposed solution to these two problems (different coding and changes by age in the relative value of education) is to create a standardized measure that reflects the position of the individual in the relative distribution of years of education (and not the absolute number of years). This procedure will produce a classification of individuals based on a similar relative scale, which subsequently can be used to generate a stratification of the study population by SES.

There are several possible solutions to create this relative scale. The most common procedure is to standardize according to the city-specific and age-group–specific means and standard deviations of *years of education*. However, this solution may be a problem for Brazil and México, where *years of education* is grouped, making it difficult to obtain precise estimations of the respective means and standard deviations. In addition, this standardization procedure may generate problems when the variable to be standardized significantly departs from the normal distribution, a situation that is common with the distribution of that variable.

An alternative proposed in this protocol is to use the city-specific and age-group–specific cumulative distribution of *years of education* to mark the position of each case in the relative distribution of educational assets. This relative position is given by the cumulative percentage that corresponds to the educational group in which the individual is located. The cumulative distributions required for this procedure will be calculated from the same mortality data sets. For example, using the distributions for Mexico City, this procedure would assign to a case with 6 years of education and age ≥ 70 a value of 76.2 in the relative scale (thus marking a relatively high SES), whereas a case with the same number of years of education but in the age group 18–29 would be assigned a value of 28.7 (reflecting a relatively low SES).

Once individuals are classified according to this relative scale, they can be individually ranked by SES using this variable, or grouped in different categories to construct SES strata.

Two additional problems arise with the use of *years of education* as a proxy for SES. The first problem is that this variable can adequately reflect the social position of adults or children in late adolescence (ages 16–19). Children under 6 have not yet entered into primary school, and therefore they cannot be classified according to their years of education. Children between ages 6 and 15 have already entered school, but for the majority who are currently attending school, their final educational attainment has not been achieved. The proposed solution for this problem is: (1) classify children under 6 according to the years of education of the mother; (2) exclude individuals between 6 and 15 years of age from this part of the analysis (i.e., restrict the mortality data to individuals over 15 years of age).

Finally, the second problem is the relatively high percentage of missing values for the variable *years of education* in Brazilian mortality data sets (around 25% of adults in São Paulo). To explore possible biases in SES effects associated with the incompleteness of the information; deaths with no data will be classified separately and will be included in the analysis as an additional SES group.

PROPOSED PROCEDURE FOR THE CONSTRUCTION OF AN AREA-BASED SOCIOECONOMIC VARIABLE

The area-based socioeconomic variable will be constructed at the municipality level. There are two reasons for not considering smaller area units. First, residence information in the current mortality data sets of México and Chile only include the municipality of residence. Therefore, even when mortality data sets for some Brazilian cities include information on smaller area units (such as districts or neighborhoods), the requirement of comparability leads to the use of municipalities as the smallest area units available in the three cities (Mexico City, Santiago and São Paulo). Second, even if all mortality data sets included information for smaller area units, it would be difficult to obtain socioeconomic data for such units.

An index of socioeconomic characteristics of the municipalities will be constructed using data obtained from external sources. The index will be calculated separately for each city to adequately reflect relative differences in socioeconomic conditions within each city, although the same methodology will be used in all cases.

An important restriction for the construction of the socioeconomic index is that cities must comprise a relatively large number of municipalities to adequately reflect socioeconomic differences. To illustrate this restriction, consider the extreme but likely case of a city comprising only one municipality. In such a case, it would not be possible to identify any variability among municipalities in socioeconomic conditions. Conversely, metropolitan areas comprising a large number of municipalities are more likely to reflect socioeconomic differences among these municipalities. Therefore, it is only appropriate to calculate the socioeconomic index for cities comprising a relatively large number of municipalities. For this reason, the

socioeconomic index will be calculated only for metropolitan areas that comprise six or more municipalities. The largest cities in each country (Mexico City, Rio de Janeiro, São Paulo, and Santiago) accomplish this criterion. The pertinence of including additional cities will be evaluated on a case-by-case basis.

The data used to develop the index will come primarily from the year 2000 population census of each country. Other possible data sources will be explored, such as sample surveys large enough to obtain precise estimations at the municipality level. These data are available at the Web sites of the respective statistical offices of each country (Brazil: *www.ibge.gov.br/home/*; México: *www.inegi.gob.mx;* Chile: *www.ine.cl/*), or in specialized data sets developed by the same offices. However, a revision and further adjustment of the available socioeconomic indicators will be necessary to maximize the ability to compare SES data across countries.

The area-based socioeconomic index will include variables for three categories: *education*, *income*, and *housing conditions*. Since statistical offices in each country determine their own definitions for constructing aggregate-level measures, the specific variables available in each country may not be identical. In this sense, the ability to compare variables across countries will not be based on the use of identical variables, but rather on the selection of variables that reflect the same underlying categories and indicators within each category.

The index will be obtained through the application of PCA. As mentioned before, a separate analysis will be performed for each city included in the analysis, thus ensuring that the index reflects differences in socioeconomic characteristics among municipalities within the cities, not differences in absolute levels between cities that may obscure the potential effects of within-city heterogeneities. Because all variables included in the analysis are highly correlated, it is expected that a PCA solution with a single factor will adequately summarize a large percentage of the common variance among them.

The resulting factor will be used as a comparable area-based index of SES among cities. This index will be applied in multilevel analyses as an indicator of SES for the municipality of residence.

APPENDICES AVAILABLE ON THE WEB

Appendices G–J contain supplemental material not included in the printed report. They are available on the HEI Web site *http://pubs.healtheffects.org.*

Appendix G. Data Description Time-Series Figures and Tables

Appendix H. Methods Tables

Appendix I. Time-Series Analysis and Meta-Analysis Tables

Appendix J. Data Correlation Tables

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Currently, she works at the Instituto Nacional de Ecología in Mexico City where she contributed to ESCALA. Her research agenda includes benefits assessment for the implementation of emissions control measures for atmospheric pollutants, the assessment of personal exposure and air quality inside houses due to firewood combustion for cooking in rural areas in México, and personal exposure associated with vehicular transportation.

Isabelle Romieu is a graduate from the Medical School of Montpellier, France, where she did an internship and residency in internal medicine and intensive care. She obtained postgraduate training in statistics from the National Center of Statistics in Villejuif, and in nutrition from the University of Nancy in France. She later obtained a master's degree in public health and a doctorate of science in epidemiology from the Harvard School of Public Health in the United States. Dr. Romieu worked as a medical officer for the Division of Environmental Health of the Pan American Health Organization and as professor of environmental epidemiology at the Instituto Nacional de Salud Pública in Cuernavaca, Morelos, México. Her work focused on the adverse effects of air pollution on health, in particular among children with asthma, as well as the adverse effects of heavy metals and pesticides. She has a strong interest in the interaction between diet and environmental exposures as well as between genes and the environment. She is a member of various scientific societies, has taken part in different expert scientific committees, and has published more than 250 research papers and book chapters. She is a member of the National Mexican Academy of Medicine and has won several awards for her research. In 2010, she joined the International Agency for Research on Cancer as head of the section of nutrition and metabolism.

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OTHER PUBLICATIONS RESULTING FROM THIS RESEARCH

Carbajal-Arroyo L, Miranda-Soberanis V, Medina-Ramón M, Rojas-Bracho L, Tzintzun G, Solís-Gutiérrez P, Méndez-Ramírez I, Hurtado-Díaz M, Schwartz J, Romieu I. 2011. Effect of PM_{10} and O_3 on infant mortality among residents in the Mexico City Metropolitan Area: A case-crossover analysis, 1997–2005. J Epidemiol Community Health 65:715–721.

ABBREVIATIONS AND OTHER TERMS

AIC	Akaike information criteria
APHEA	Air Pollution and Health: A European Approach
APHEA2	Air Pollution and Health: A European Approach Part II
APHENA	Air Pollution and Health: A European and North American Approach
ARES	Ar e Saúde (Air and Health in Portuguese and Spanish)
BAM	beta attenuation monitor
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CPM	cardiopulmonary causes
CVD	cardiovascular disease
CVE	cerebrovascular–stroke causes
df	degrees of freedom
DLM	distributed lag model
ESCALA	Estudio de Salud y Contaminación del Aire en Latinoamérica
GAM	generalized additive model
GLM	generalized linear model
IBGE	Brazilian Institute of Geography and Statistics
ICD	International Classification of Diseases
INE	National Institute of Statistics, Chile
INEGI	National Institute of Statistics, Geography and Informatics
INSP	Instituto Nacional de Salud Pública
LRI	lower respiratory infection
NMMAPS	National Morbidity, Mortality, and Air Pollution Study
NO_2	nitrogen dioxide
O_3	ozone
PACF	partial autocorrelation function
PAHO	Pan American Health Organization
PAPA	Public Health and Air Pollution in Asia
PCA	principal components analysis
$PM_{2.5}$	particulate matter $\leq$ 2.5 μm in aerodynamic diameter

PM_{10}	particulate matter ≤ 10 μm in aerodynamic diameter
QA	quality assurance
QC	quality control
Ref_R	reference risk
REML	restricted maximum likelihood
RPC	risk percent change
RRR	relative risk ratio
SEMARNAT	Secretaria del Medio Ambiente y Recursos Naturales (Secretary of Environment and Natural Resources)
SES	socioeconomic status
SLM	single lag model
TEOM	tapered element oscillating microbalance
U.S. EPA	U.S. Environmental Protection Agency

COMMENTARY
Health Review Committee

HEI

Research Report 171, *Multicity Study of Air Pollution and Mortality in Latin America (the ESCALA Study)*, I. Romieu et al.

INTRODUCTION

For nearly two decades, scientists seeking to understand the role that air pollution might play in population health effects have relied heavily on epidemiologic studies known as time-series studies. Time-series studies use information on daily changes in air pollutant concentrations and daily counts of mortality and morbidity. Although initially conducted at the individual city level, coordinated analyses across many cities have more recently emerged as the tool of choice for developing more reliable and comparable estimates of the short-term health effects of air pollution. HEI has a long-standing interest in these coordinated analyses, funding studies such as the National Morbidity, Mortality, and Air Pollution Study (NMMAPS*); Air Pollution and Health: A European and North American Approach (APHENA); Public Health and Air Pollution in Asia (PAPA); and the current study, *Multicity Study of Air Pollution and Mortality in Latin America*, referred to hereafter by its Spanish acronym — ESCALA (Estudio de Salud y Contaminación del Aire en Latinoamérica). Focused, relevant studies like these contribute not only to the epidemiologic evidence in specific geographic regions, but also to the growing body of evidence on the short-term effects of air pollution worldwide.

The ESCALA study was initiated to address underlying data and methodologic limitations in the epidemiologic literature on the health effects of air pollution in Latin America that had been identified in a review by the Pan American Health Organization (PAHO 2005). The William and Flora Hewlett Foundation, with a strong interest in understanding air pollution and health in Latin America, provided HEI with supplemental support to address gaps in the evidence necessary to inform regulatory decisions, and in the process to build a network of health experts capable of carrying out research on air pollution in the future.

In response to Request for Preliminary Applications (RFPA 04-6), Isabelle Romieu, then of the Instituto Nacional de Salud Publica, México, and coinvestigators submitted a preliminary application in the fall of 2004 titled "Multicity Study of Air Pollution and Health Effects in Latin America." Her coinvestigators were Nelson Gouveia, of the Universidade de São Paulo, Brazil and Luis Cifuentes, of the Pontificia Universidad Católica de Chile. The application proposed using a common protocol to conduct coordinated analyses in several Latin American cities. In addition to studying morbidity and mortality in whole populations and in adults, the investigators proposed a special focus on children's health and on the influence of socioeconomic status (SES) and other potential modifying factors on health outcomes related to air pollution. The project would include a meta-analysis of the results from all cities analyzed, and study results would be integrated with the wider international literature on the subject. The HEI Research Committee was generally supportive of the proposal, noting that the study design would contribute to international efforts to develop definitive estimates of the effects of short-term exposure to air pollution. They asked that the investigators submit a full application that would address any unique aspects of the effects of short-term exposures in the region.

The investigators responded to the Research Committee's concerns and proposed a two-phase study: (1) individual city and combined analyses according to a common analytic framework for time-series studies in 14 cities in Brazil, Chile, and México; and (2) expansion of results to additional Latin American cities that met the inclusion criteria. The revised study was recommended for funding in June 2005, with funding contingent upon the successful completion of one year of preparatory work to ensure the adequacy of the air pollution and health outcomes data. After reviewing an addendum to the approved proposal in October 2005, the Research Committee recommended that the investigators focus primarily on three major cities in each country, and that they include additional cities only if the data were remarkable. The final approved study began in January 2006.

Dr. Romieu's 3-year study, "Multicity Study of Air Pollution and Health Effects in Latin America," began in April 2006. Total expenditures were $330,894. The draft Investigators' Report from Romieu and colleagues was received for review in January 2010. A revised report, received in October 2010, was accepted for publication in February 2011. During the review process, the HEI Health Review Committee and the investigators had the opportunity to exchange comments and to clarify issues in both the Investigators' Report and the Review Committee's Commentary.

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

This Commentary is intended to aid the sponsors of HEI and the public by highlighting both the strengths and limitations of the study and by placing the Investigators' Report into scientific and regulatory perspective.

SCIENTIFIC BACKGROUND

In air pollution epidemiology, a commonly exploited dimension of exposure variability is short-term temporal variability. Application of time-series statistical techniques to the analysis of daily variations in mortality and air pollution concentrations has become particularly common. Relatively simple and inexpensive to conduct when the relevant data are available, time-series studies have been conducted in cities all around the world (Anderson 2009).

The results of several daily time-series studies were first reported in the early 1990s for individual cities or countries (Hatzakis et al. 1986; Derrienic et al. 1989; Fairley 1990; Katsouyanni et al. 1990; Schwartz and Marcus 1990; Schwartz 1991; Dockery et al. 1992; Pope et al. 1992; Schwartz and Dockery 1992; Schwartz 1993; Sunyer et al.1993; Touloumi et al. 1994). These studies used time-series data and Poisson regression models to estimate the association between daily changes in pollution and daily changes in mortality while controlling for other time-dependent covariates that were potential confounders. They found small, but statistically significant effects of air pollution on daily mortality even at relatively low pollutant concentrations. The original research was largely replicated (Samet et al. 1995), and similar associations were observed in other cities with different climates, alternative modeling approaches for weather conditions, different pollution mixes, and different demographics (Pope and Kalkstein 1996; Samet et al. 1998; Pope 1999; Bell et al. 2004b).

Studies of short-term exposure have found associations between concentrations of airborne particulate matter (PM) and a large range of outcomes; these findings have been reviewed more extensively elsewhere (Pope 1999; Bell et al. 2004b; Pope and Dockery 2006; Anderson 2009). PM pollution has been associated with increases in daily mortality (from all natural causes, respiratory causes, or cardiovascular causes), in hospital admissions for a range of respiratory and cardiovascular diseases. At the same time, numerous concerns have been voiced regarding sources of uncertainty in the findings of individual studies that might undermine the hypothesis of a cause-and-effect relationship between PM and mortality (PM–mortality). One was that the magnitude of the relative-risk estimates from time-series studies of daily mortality depends on the approach used to model both the temporal pattern of exposure (Braga et al. 2001) and potential confounders that vary with time (such as season and weather) (HEI 2003). Other concerns included the role of uncontrolled confounding or effect modification by the pollutants not classified as PM (Moolgavkar et al. 1995; Gamble and Lewis 1996), variations in statistical approaches to modeling of time-series data in individual cities (Thurston and Kinney 1995), and exposure measurement error (Lipfert and Wyzga 1997).

Investigators have attempted to address these concerns in a variety of ways. One of the most common approaches has been to conduct larger studies that rely on uniform methods for assembling and analyzing data from multiple cities. Several multicity studies have now been conducted, but three in particular became the foundation for the ESCALA study, representing different regions of the world as well as different methodologic approaches to the multicity analyses.

One of the largest of these multicity daily time-series studies was NMMAPS. It began with efforts to replicate several early single-city time-series studies (Samet et al. 1995) and ultimately developed multistage hierarchical methods to assess the relationship between air pollution and mortality and morbidity in the 90 largest U.S. cities. NMMAPS Part I (Samet et al. 2000a) was designed to address methodologic issues including uncertainties about exposure measurement error, about whether increases in mortality simply represented short-term shifts in the time of death among people likely to die (mortality displacement), and the analysis of data from multiple, differing locations. NMMAPS Part II (Samet et al. 2000b) addressed questions about potential bias resulting from the selection of locations to study, differences in the statistical techniques applied, and the adequacy of control for the effects of weather and of other pollutants on the associations between PM_{10} ($PM \leq 10$ µm in aerodynamic diameter) and morbidity and mortality. Results of various analyses of these data have been reported (Dominici et al. 2000, 2002, 2003; Samet et al. 2000b; Peng et al. 2005). The PM–mortality effect estimates were somewhat sensitive to modeling and city-selection choices. However, relatively small but statistically significant PM–mortality associations were consistently observed, and little evidence was found to attribute the PM–mortality effect to any of the copollutants studied (nitrogen dioxide, carbon monoxide, sulfur dioxide, or ozone [O_3]). Subsequent analysis of the NMMAPS data did find associations of O_3 with mortality (Bell et al. 2004a).

The APHENA study (Katsouyanni et al. 2009) was designed to take advantage of three large databases that

had been compiled by investigators conducting earlier multicity time-series studies in Europe (APHEA2 – Air Pollution and Health: A European Approach [Katsouyanni et al. 2001]), the United States (NMMAPS), and Canada. While the use of existing databases was successful at reducing costs and shortened the project's time frame, the inherent differences between methods of air pollution data collection among governments remained a source of uncertainty. The APHENA methods consisted of a two-stage process typical of multicity studies. In the first stage, the data for individual cities were analyzed. In the second stage, a systematic comparison of statistical approaches was conducted that pooled the estimates across cities and explored variations in the effect estimates. An important goal of the second-stage analyses was to explore city-level characteristics that might modify the observed effects of air pollution, although these analyses were limited by the number of variables that were common to the different data sets.

HEI's PAPA studies were the first set of coordinated time-series studies ever undertaken in Asian cities and represent a major step toward addressing uncertainties in estimating the adverse health impact of air pollution in Asia (HEI PAPA 2010, 2011; HEI Collaborative Working Group 2012). These studies were designed and conducted by local investigators in concert with local air pollution and public health officials and with international experts. The investigators followed a common protocol that 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.

Latin America was a logical region to consider next for a coordinated multicity time-series analysis. As in other regions of the world, numerous single-city studies had been conducted. PAHO identified 47 time-series studies that had been published from 1994 to 2004, with the vast majority in Mexico City, México; São Paulo, Brazil; and Santiago, Chile (PAHO 2005). As part of its report, PAHO conducted a careful meta-analysis of the PM_{10} time-series studies. Several more individual time-series studies in Latin America have been published since then (Bakonyi et al. 2004; Freitas et al. 2004; Gouveia et al. 2006; Nascimento et al. 2006; Sanhueza et al. 2006; Braga et al. 2007; Hernández-Cadena et al. 2007; Arbex et al. 2009; Dales et al. 2009; Moura et al. 2009; Román et al. 2009).

The ESCALA study of nine cities in Brazil, Chile, and México provided an opportunity to address challenges involved in conducting and interpreting meta-analyses of studies that differ in design, underlying data, and statistical approach. ESCALA is the first coordinated multicity time-series study to be conducted in Latin America. It has created a firm foundation for future work in the region and provides important results for comparison with those of similar studies around the world.

STUDY SUMMARY

OBJECTIVES

The overall objective of the ESCALA project was to produce estimates of the effect of air pollution on mortality from several causes in different age groups in nine Latin American cities, using a common analytic framework. The study had the following specific objectives:

1. Develop a common protocol for the design and analysis of time-series data from multiple Latin American cities that would be followed by all investigators involved in the project;
2. Conduct a coordinated analysis to examine the effect of exposure to outdoor air pollution on mortality from multiple causes and in subgroups defined by age and cause of death in different Latin American cities;
3. Assess the effect of air pollution in sensitive populations such as infants, young children, and people 65 years or older;
4. Conduct meta-analyses and meta-regression analyses with results from all of the cities in the study to develop region-wide estimates of the effects of air pollution on health and to explore whether individual city-level characteristics might explain or modify the observed effects of air pollution on health;
5. Contribute to the international scientific discussion about the conduct and interpretation of time-series studies that report the effects of short-term exposure to air pollution;
6. Report the results of these coordinated analyses in the broader peer-reviewed literature; and
7. Provide relevant information to decision makers in Latin America to support prevention and control strategies for air pollution.

An important, albeit secondary, objective was to explore the feasibility of evaluating the role of SES as a potential modifier of the effect of air pollution on mortality, using the same SES indicators in México, Brazil, and Chile.

METHODS

Structure of the Collaboration

The ESCALA study involved a multicenter effort involving teams of investigators from Brazil, Chile, and México. Dr. Isabelle Romieu, then at the Instituto Nacional de Salud Pública (INSP) in México, served as principle investigator with Luis Cifuentes taking the lead in Chile and Nelson Gouveia in Brazil. In addition, two consultants were added to provide specialized expertise in biostatistics for the time-series analyses (Dr. Joel Schwartz of Harvard University in Cambridge, Massachusetts) and in social sciences for the collection of SES data (Dr. Patricio Solis Gutierrez of Colegio de México in Mexico City). The full team held a series of four workshops over the course of the project to discuss and develop standardized protocols for the data collection and analysis and to discuss results.

Data

Each country team identified the three largest cities that had sufficient mortality and air pollution data with which to conduct the time-series analyses. These were São Paulo, Rio de Janeiro, and Puerto Alegre for Brazil; Concepción, Santiago, and Temuco for Chile; and Mexico City, Toluca, and Monterrey for México.

Mortality and air pollution data were collected and underwent quality assurance and quality control checks according to the protocols established by the study team. These protocols may be found in Appendices B and C of the Investigators' Report. Data were stored in a relational database at INSP and made available to all teams.

Mortality Data The ESCALA investigators obtained mortality data for several causes of death: all-natural-cause (i.e., excluding accidental deaths), cardiopulmonary (a broad category including respiratory and cardiovascular causes), respiratory, cardiovascular, cerebrovascular–stroke, lower respiratory infection (a subcategory of respiratory mortality), and chronic obstructive pulmonary disease (COPD). In most cities, data were collected from the appropriate agencies in each country for an 8-year period (1997–2005). Two cities had shorter data collection periods: Rio de Janeiro (2001–2005) and Porto Alegre (2002–2005). Deaths were coded according to the *International Classification of Diseases Revision 9* (ICD-9) or ICD-10 (see Investigators' Report Table 2 for individual codes); data coded in ICD-9, typically from earlier years in the study, were translated into ICD-10 codes according to a common protocol.

The primary age categories for which mortality data were studied were all ages (all-age) and people 65 years or older ($\geq$ 65 years). Respiratory mortality was also analyzed for infants under the age of one (< 1 year) and for children under the age of five (1–4 years). Mortality from lower respiratory infection was evaluated in infants < 1 year and in children at least one year old and under the age of 15 (1–14 years).

Air Pollution and Climatologic Data The ESCALA team developed estimates of the daily 24-hour mean average PM_{10} and the daily 8-hour maximum moving average O_3 concentrations for each city. These measures of PM_{10} and O_3 exposure were developed using a standard protocol (see Investigators' Report Appendix C) from hourly air monitoring data for PM_{10} and for O_3 obtained from the environmental agencies responsible for monitoring ambient air pollution in each country. Although $PM_{2.5}$ (PM $\leq$ 2.5 μm in aerodynamic diameter) has come to replace PM_{10} as the preferred measure of exposure to PM for health effects studies, the investigators chose PM_{10} because of the limited availability of $PM_{2.5}$ measurements. O_3 data were available for only six of the nine cities in the project.

For most cities, the daily PM_{10} and O_3 exposure estimates were derived by averaging data from multiple monitors, with the number of monitors varying by city. Monitors selected to represent exposures for the populations in each city were chosen according to a standard protocol (Appendix D of the Investigator's Report). Depending on the city, PM_{10} was measured by either a tapered element oscillating microbalance (TEOM), a beta attenuation monitor (BAM), or in some cases both methods, depending on the city (see Appendix Tables D.1–D.3 for details). O_3 concentrations were measured with ultraviolet photometry in Brazil and Chile and with ultraviolet fluorescence in México.

Daily mean temperature and humidity were estimated from data collected from one or more meteorologic stations, depending on the city. Warm and cold seasons were defined for each city according to variation in temperature (i.e., not by calendar month).

Socioeconomic Data An important goal of the ESCALA team was to evaluate the extent to which SES could modify the observed relationship between air pollution and mortality. They sought to develop a standardized index of SES across locations assigned to geographic units of comparable size and population within each country (e.g., *districts* in São Paulo and Rio de Janeiro; *comunas* in Santiago, and *delegaciones* in Mexico City). The index was constructed from data on educational level, income, and housing conditions; because specific variables available to define these characteristics differed among countries,

strategies were developed to identify those that would be comparable across countries. Sufficient data were available to develop an SES index for only the largest cities: São Paulo and Rio de Janeiro in Brazil; Santiago in Chile; and Mexico City in México.

Data on City-Level Characteristics for the Meta-Regression Analyses For the meta-regression analyses, the investigators considered a wide range of city-level characteristics, or covariates, that might explain or modify the effects of air pollution observed across the nine cities but ultimately settled on a limited number for which sufficient data were available across all cities. These included altitude, average temperature (by season), annual average rainfall, PM_{10} concentration averaged over the period of the study, geographic density of PM_{10} monitors, population density, age structure, prevalence of smoking, and lung cancer mortality rates in men and women (Investigators' Report Table 6).

Statistical Analyses

The investigators conducted their analysis of the mortality and air pollution data according to common protocols and using a standard library of R software routines developed for the project (*Ar e Saúde*; i.e., *Air and Health* in Portuguese (available within R or at *http://cran.at.r-project.org/web/packages/ares/index.html*). The analysis was conducted in two stages, first at the city level and then at the regional level (i.e., across all nine cities).

City-Specific Analyses In the first stage, the investigative teams in each country fit Poisson regression models to the air pollution and mortality time-series data in each city to develop city-specific estimates of the effect of PM_{10} or O_3 on mortality. The teams followed a common methodologic protocol for modeling the daily time-series data on mortality and pollution and for estimating health effects while controlling for other factors that might also explain the temporal patterns of mortality (e.g., temperature, humidity, season, day-of-the-week) in individual cities. The protocol was developed in the series of workshops described earlier and provided a framework for exploration of model fit and analysis of the sensitivity of results to various model specifications.

The final models used in the individual cities were chosen to fit specific patterns of mortality in those cities and thus differed from city to city. In this way, the investigators followed the methodology used in the Air Pollution and Health: A European Approach (APHEA) multicity time-series study (see, for example, Katsouyanni et al. 1995), rather than that used in the NMMAPS, APHENA, and PAPA multicity studies, in which a common model was fit to data in all cities.

The models were used to estimate effects of PM_{10} or O_3 on mortality by cause and SES for each age group; effects were presented as the percentage change in risk of mortality per 10-μg/m^3 increase in PM_{10} or O_3, referred to in the report as the risk percent change. Investigators explored the effects of single-day exposures on mortality, from the same day (lag 0) up to 3 days earlier (lag 3). They used distributed lag models (DLMs) to explore the ability of an exposure to affect mortality over several days (3, 5, and 10 days). Two-pollutant models were also explored, in which PM_{10} results were controlled for the presence of O_3 and O_3 results were controlled for the presence of PM_{10}. In addition, the association of O_3 with mortality was analyzed separately by season in the cities for which O_3 data were available.

SES Analyses Evaluation of the influence of SES on health was carried out by stratifying the mortality databases in São Paulo, Rio de Janeiro, Santiago, and Mexico City by low, medium, and high SES. Time-series analyses were conducted for each cause-of-death and age group in which the observed numbers of deaths were sufficient to permit stable estimates.

Meta-Analyses In the second stage, the investigators combined the individual effect estimates using meta-analytic techniques (DerSimonian and Laird 1986) to provide overall mean estimates of the effects of air pollution on mortality across cities. Both random- and fixed-effects models were used to combine the individual city results by cause of death for the all-age and the $\geq$ 65 years age groups. Because the numbers of daily deaths among infants and children were low in most cities, meta-analyses of the results for these age groups were not conducted.

The Cochran Q test was used to test for the presence of heterogeneity in effect estimates among the cities. (The null hypothesis is that the true effect in each city is the same.) The I^2 index was calculated to estimate the percentage of observed heterogeneity that is due to true differences between cities as opposed to random noise in the results.

Meta-Regression Analyses The investigators conducted meta-regression analyses using restricted maximum likelihood for the estimation procedure. They ran univariate regressions in which they evaluated the extent to which each of the individual city-level covariates described earlier could explain variation in each set of nine city-specific PM_{10} mortality DLM effect estimates. The analyses were

run only for PM_{10} results, because PM_{10} data were available for all nine cities, and only for the all-age and the ≥ 65 years age groups, because those groups had the most observations.

SUMMARY OF MAJOR RESULTS

CITY-LEVEL ANALYSES

The primary mortality results presented in the Investigators' Report are those estimated using the final DLM 0–3 models selected for each city. The HEI Research Committee supported presentation of the DLM 0–3 results given broad similarities with results using other lags. The specifications for the final DLM 0–3 models can be found in Appendix Tables H.6–H.20 of the Investigators' Report (available on the HEI Web site; *www.healtheffects.org*). The results for other individual lags and DLMs may be found in Appendix I of the Investigators' Report (available on the HEI Web site).

PM_{10} and Mortality

The ESCALA analysis found daily increases in PM_{10} to be associated with small increases in daily mortality for most causes of death in most of the cities studied. For the all-age group, PM_{10} was positively and significantly associated with an increased risk of mortality from all natural causes (seven cities), cardiopulmonary disease (eight cities), respiratory disease (eight cities), cardiovascular disease (seven cities), cerebrovascular–stroke (five cities), and COPD (eight cities) (for details, see Investigators' Report Table 10). The strength of the associations varied between cities, however, for all causes of death other than cardiopulmonary and cardiovascular diseases, which were the largest causes of death. The mean incremental risk of mortality from most causes was generally slightly higher in the ≥ 65 group than in the all-age group in most of the cities; however, the differences did not appear to be statistically significant in most cases.

In two-pollutant models, in which O_3 was included as the second pollutant, the mean PM_{10} effects on mortality were not significantly different from those observed with PM_{10} alone, although in some cities the effects appeared slightly strengthened (for example, in Santiago), while in others they were slightly weaker (for example, in Mexico City) (see Investigators' Report Table 11).

O_3 and Mortality

Among the six cities for which sufficient O_3 data were available, the investigators observed a pattern of small, but positive associations between daily increases in O_3 and increases in mortality in most cities, except in Toluca where associations tended to be negative and nonsignificant (Investigators' Report Table 12). The strength of the associations was generally weaker and more variable by the cause of death and across cities than those for PM_{10}. Among causes of death, positive and significant associations were most consistently observed for cardiopulmonary disease (for all except Toluca) and cardiovascular disease (for all except Toluca) and was least often observed for respiratory disease (only for São Paulo and Mexico City), cerebrovascular–stroke (only for São Paolo), and COPD (only for Mexico City). In general, positive and significant associations of O_3 with increased mortality from various causes were most often observed in the three largest cities — São Paulo, Rio de Janeiro, and Mexico City. As with the PM_{10} results, the percentage changes in mortality associated with an increase in O_3 were slightly higher in the ≥ 65 age group for most causes of death. When adjusted for PM_{10} in two-pollutant models, the effects of O_3 on mortality were weaker and no longer significant in most cities, and for most causes of death, than in models with ozone alone. An exception is Santiago, where the effects appeared substantially stronger for all causes of death except respiratory disease (Investigators' Report Table 13). When the data were stratified and analyzed by warm and cold season, the seasonal effects on mortality associated with O_3 differed by city but were generally stronger in the warm season than in the cold season or yearly analyses, although there were notable exceptions (Investigator's Report Tables 14–15). In Mexico City, stronger associations were generally observed in the cold season for most causes of death except respiratory disease, which appeared stronger in the warm season. Similarly, in Toluca, significant increases in mortality were observed only in the cold season and only for all-natural-cause and cerebrovascular–stroke mortality.

Respiratory Mortality in Children

The investigators reported varying impacts of PM_{10} on total respiratory mortality and on lower respiratory infection mortality in children across the three largest cities for which sufficient data were available — São Paulo, Santiago, and Mexico City (see Investigators' Report Table 16). Significantly increased respiratory mortality was observed in infants (< 1 year) and children 1–4 years, only in Santiago. The risk of mortality from lower respiratory infection was significantly increased for infants in Mexico City and for children 1–14 years in all three cities, but significantly so only in Santiago.

The results of the analyses with O_3 were similarly variable. In the analyses with yearly data, O_3 was associated

with significant increases in the risk of respiratory mortality in children 1–4 years and in the risk of mortality from lower respiratory infection in both infants and children 1–14 years in Mexico City, but not in the other two cities (Investigators' Report Table 17). When stratified by season, the observed mortality effects in Mexico City were stronger in the cold season, with the exception of respiratory mortality in children 1–4 years, which was higher in the warm season (see Investigators' Report Tables 18 and 19). In São Paulo, as was observed in the analyses of adult data, the risks of respiratory mortality were stronger in the warm season, particularly for infants.

Stratification by SES

The results of the SES analyses in Mexico City, São Paolo, Rio de Janeiro, and Santiago show that the effects of PM_{10} and O_3 on mortality were consistent — in terms of their relative magnitude — with the city-specific results discussed earlier, but that the effects of SES on those mortality effects varied from city to city (Investigators' Report Figures 5–10). The investigators concluded that the results provided some indication that people with low SES had a higher risk of death from air pollution, particularly from respiratory causes. They noted, however that the risk of air pollution related to cardiovascular mortality was larger in the medium- and high-SES populations.

META-ANALYSES AND META-REGRESSION ANALYSES

Meta-Analyses

PM_{10} The mean estimates of the effects of PM_{10} on all-natural-cause and cause-specific mortality from the meta-analyses were all positive and statistically significant (Commentary Figure 1). The magnitude of the effects from the random- and fixed-effect models was similar, although confidence intervals were generally wider for the random-effects estimates. The authors emphasized the results from the random-effects models, indicating that they are more consistent with the observations of heterogeneity in the effect estimates. Using the random-effects model, the mean effect for all-natural-cause, all-age mortality was 0.77% (95% CI = 0.60 to 1.00) per 10-$\mu g/m^3$ increase in PM_{10}; for all-age, cause-specific mortality categories, mean effect estimates were 0.94% (0.84 to 1.05) for cardiopulmonary, 1.39% (0.98 to 1.81) for respiratory, 0.72% (0.54 to 0.89) for cardiovascular, 1.10% (0.48 to 1.71) for cerebrovascular-stroke, and 2.44% (0.36 to 3.59) for COPD. As has been reported for other populations, mean effect estimates were similar or slightly stronger for the older age group from cardiopulmonary, cardiovascular, and cerebrovascular–stroke mortality. The opposite pattern was observed for respiratory and COPD mortality.

O_3 As in the case of the individual city results for O_3, the mean estimates across cities indicated small, though not always statistically significant, effects of O_3 on mortality (Commentary Figure 2). Using the random-effects model, the estimated increase in all-natural-cause, all-age mortality was marginally significant (0.16% [95% CI = -0.02 to 0.33]). The strongest associations observed in the all-age group were a 0.23% (0.11 to 0.36) increase in cardiopulmonary mortality, a 0.21% (0.10 to 0.31) increase in respiratory morality, and a 0.23% (0.09 to 0.37) increase in cardiovascular mortality. The associations were slightly stronger in the ≥ 65 years age group than in the all-age group for cardiopulmonary and cardiovascular mortality, but were the same or weaker for other causes of death.

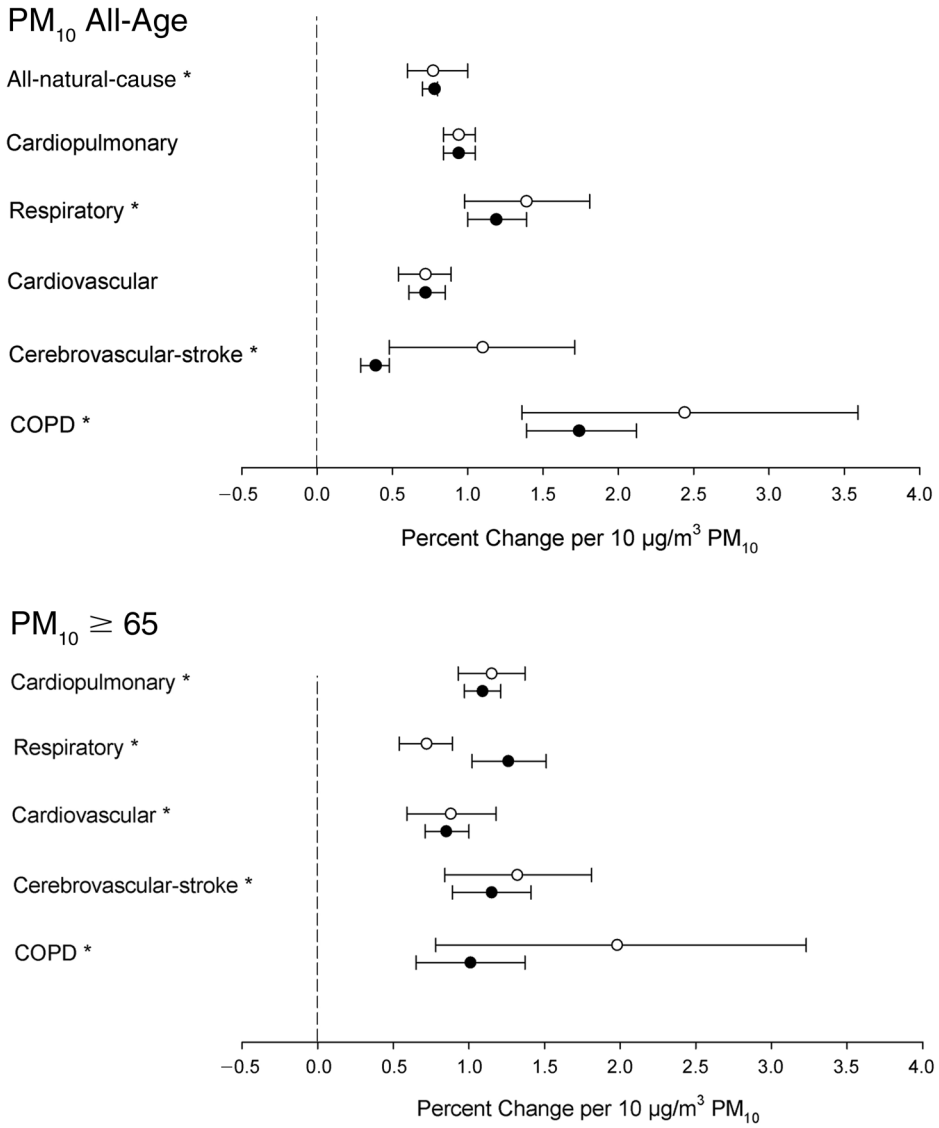
Meta-Regression Analyses

In the meta-regression analyses, the statistic of interest for evaluating whether city characteristics or covariates (e.g., altitude) might modify the risk of PM_{10} exposure, and thus explain some of the variability in effect estimates between cities, is the "relative risk ratio" (Investigators' Report Tables 24–34). A relative risk ratio greater than 1.0 is interpreted as an increase in the relative risk associated with an increase of 25% of the range of each covariate.

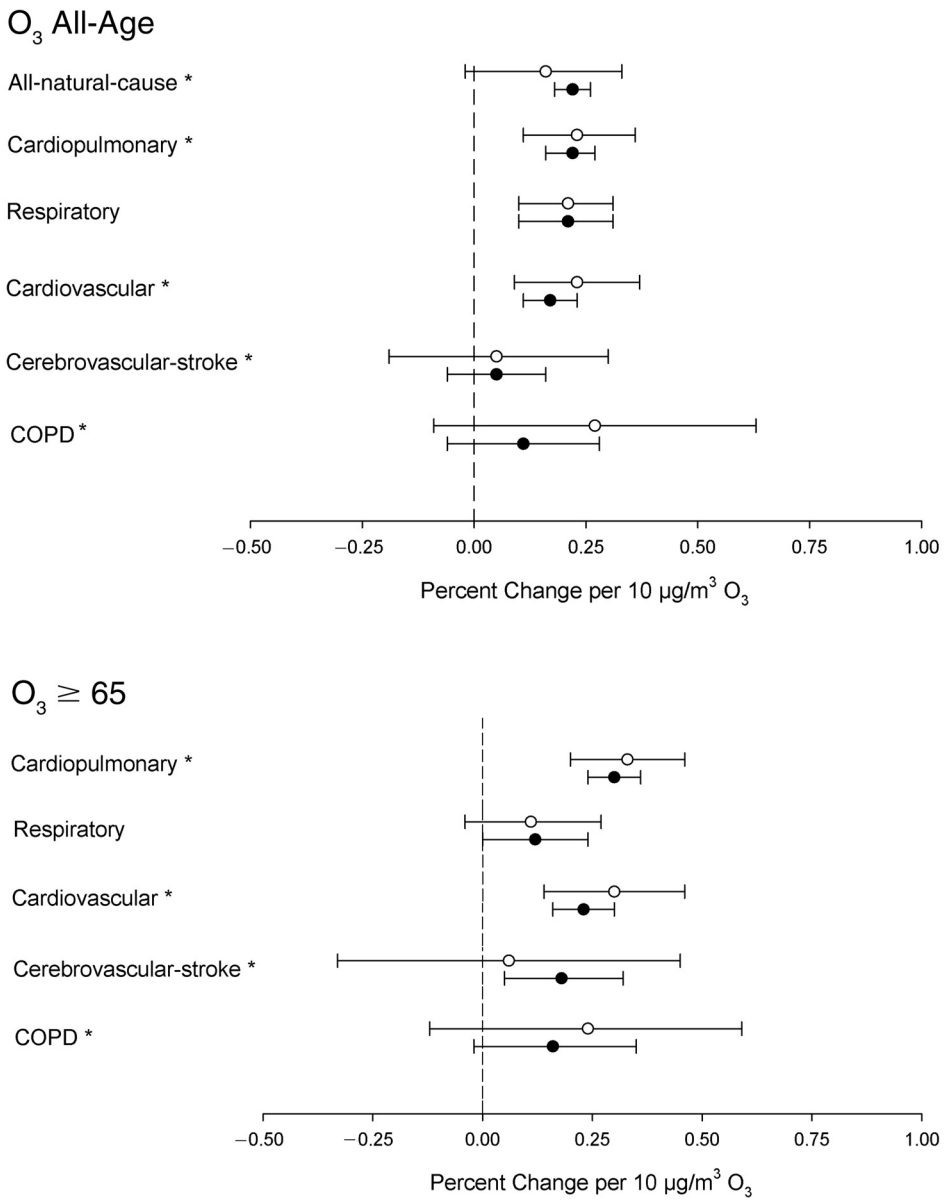
The investigators found few covariates in their analyses that appeared to significantly modify the relative risk of mortality in a consistent way. The rate of lung cancer among males, which is often interpreted as a proxy for the rate of smoking in a population (cases/100,000 men/year) was the covariate most commonly associated with changes in relative risk; it was associated with increases in the relative risks of all-natural-cause, cardiopulmonary, cardiovascular, and cerebrovascular–stroke mortality but with decreases in the relative risks of COPD and respiratory mortality. The percentage of infants and children in a population also seemed to be associated with increases in the relative risks of some kinds of mortality (all-natural-cause, cardiovascular), but again with decreases in the relative risks of COPD and respiratory mortality.

HEI EVALUATION OF THE STUDY

In its independent evaluation of the study, the HEI Health Review Committee considered carefully the methodologic approaches taken to meeting the goals of the study, and the completeness and transparency with which



Commentary Figure 1. PM_{10} meta-analysis results for all-natural-cause and cause-specific mortality for the all-age and ≥ 65 years age groups. Estimates with ○ are from the random-effects model, and estimates with ● are from the fixed-effects model (Source: Investigators' Report Table 20). *Indicates significant heterogeneity in the city-specific effect estimates as determined by the Cochran Q test of heterogeneity (Source: Investigators' Report Table 22).



Commentary Figure 2. O_3 meta-analysis effect estimates for all-natural-cause and cause-specific mortality for the all-age and ≥ 65 years age groups. Estimates with ○ are from the random-effects model, and estimates with ● are from the fixed-effects model (Source: Investigators' Report Table 21). *Indicates significant heterogeneity in the effect estimate as determined by the Cochran Q test of heterogeneity (Source: Investigators' Report Table 22).

the results, related sensitivity analyses, and limitations were presented and discussed.

The ESCALA study represents an important advance in the analysis of daily associations between air pollution and mortality and morbidity in Latin America. Led by an experienced principal investigator, it represents the first coordinated, systematic multicity analysis whose results are comparable with those reported from similar multicity studies conducted in Europe, Canada, the United States, and Asia.

In addition to studying mortality in all ages grouped together and in older adults (≥ 65 years), as in those studies, the ESCALA investigators focused specifically on the potential effects of air pollution on mortality from respiratory diseases in susceptible subgroups in the population — infants and children. Also building on the experience of those earlier studies, the investigators developed a careful approach to studying the role of socioeconomic and other factors in explaining or modifying the effects of air pollution on human health.

The Committee found that the ESCALA team's findings on the adverse effects of daily PM_{10} and O_3 concentrations in Latin America echoed those in other major regions of the world. However, the Committee noted that the investigators also encountered a number of the common limitations facing studies of this nature.

MORTALITY AND AIR POLLUTION DATA

The investigators' choice of cities to study appeared to be appropriate and well-reasoned. The health data collected were classified according to standard ICD codes and appeared to be of good quality. They had reasonably large populations of infants and children with which to explore the effects of air pollution, particularly in the three largest cities in the study. The investigators had access to relatively long periods of reliable monitoring data from instruments using standard methods (for example, TEOM and BAM for PM_{10}).

Most of the cities had multiple monitors, with the most monitors in Mexico City (16 PM_{10} and 20 O_3) and São Paulo (14 PM_{10}, 8 O_3) and the fewest in Concepción (2 PM_{10}, 0 O_3). Pearson correlations among PM_{10} monitors were reasonably high (median correlations ranged from 0.66 to 0.88) in most cities; the correlations were poor (−0.17) in Porto Alegre and moderate (0.48) in Concepción. Correlations in O_3 concentrations among monitoring stations were also generally high except in Rio de Janeiro (0.083) and Porto Alegre (−0.004) (Investigators' Report Table 5). The generally high correlations support the investigators' decision to average concentrations across monitors in all cities. However, the poor correlations observed in some cities create concern about how well those monitoring data represent population exposures and in turn about the accuracy and precision of the health effect estimates in those cities. For this and other reasons, the investigators chose to drop the O_3 analyses in Porto Alegre.

A potential weakness in the monitoring data is that the different PM_{10} monitoring methods have different biases that could potentially impact results. For example, the TEOMs appear to have a low bias at high levels, meaning that they may tend to underestimate high PM_{10} concentrations. It is not entirely clear whether the investigators accounted for potential biases in particular monitors before averaging across results from different monitors.

STATISTICAL ANALYSES

The major strength of the ESCALA study is that the investigators applied a coordinated and consistent approach to the statistical analysis of air pollution and mortality time-series data from three countries in Latin America. They established a library of standard R statistical routines and analysis protocols that were used by all investigators. These routines and protocols can also facilitate the conduct of and comparisons with follow-up studies in the original cities, as well in new cities.

City-Specific Analyses

The investigators chose the most widely used models for time-series analysis, which assume that the daily numbers of deaths in a given city can be modeled using the Poisson distribution. The mean of the Poisson distribution is modeled as a function both of pollution and of potential confounding variables that may affect pollutant concentrations and may also be associated with mortality. Possible confounding variables evaluated by the investigators included those related to weather (e.g., humidity or temperature) or time (e.g., season, day-of-week, holidays).

Once these model assumptions have been made, many details still need to be specified to separate the effects of pollution on mortality from those of potential confounding variables. The effects of time, temperature, and humidity are modeled with smooth functions, but there are several classes of smooth functions that have been evaluated over the years. The ESCALA investigators conducted analyses with both natural and penalized splines. Each type has a tuning parameter, usually referred to as degrees of freedom (*df*), that is used to describe how many parameters are estimated by the smooth function, or equivalently, how smooth the fitted function is.

Experience with these time-series models has shown that the estimate of the pollution effect can be affected by details of choices for models of confounding variables, in particular on the degrees of freedom tuning parameters for the smooth functions for temperature and for time (Katsouyanni et al. 2009). The approach the ESCALA investigators used was to base the choices on the goodness-of-fit measures that yielded the best-fitting model in each city. Variants of this approach have been used and remain common in the field.

The Review Committee was concerned, however, that this approach might have left important bias in the pollution effect estimates. The assumption that model fit criteria can lead to optimal models is doubtful, for reasons that have been explored, for example, in the HEI Review Committee commentaries in the HEI Special Report, *The Revised Analyses of Time-Series Studies of Air Pollution and Health* (HEI 2003) and in the PAPA studies (HEI PAPA 2010, 2011, 2012). In an earlier published paper on the APHENA methodology, Peng and colleagues (2006) further concluded that "model selection methods which optimize prediction may not be suitable for obtaining an estimate with small bias." While the Committee acknowledged that no approach can guarantee against residual confounding, its members favor common models with sensitivity analyses, which facilitate comparing and combining estimates across cities.

Because of these methodological issues regarding control for confounders, it is necessary to examine the details of the city-specific models fit to the time-series data before focusing on the results themselves. The investigators have provided the most important information for the main models (i.e., the city-specific models; in particular the *df*/year used in the time smooth) in the Investigators' Report Appendix Tables H.6–H.20. The content of the model-description tables in the appendix broadly confirms how one would expect model selection led by a model fit criterion to work. For the more common causes of death, a larger number of *df*/year tended to be selected. For example, for all-natural-cause, all-age mortality, the smallest number of *df*/year selected in any city was 4 *df*/year (in Porto Alegre and Toluca) whereas the values ranged from 5–8 *df*/year in other cities. For the less common causes of death, however, the *df*/year selected for the main models were frequently lower than 5, and for the childhood deaths they were often 1 or 2.

Although one can never be sure how many *df*/year is enough to ensure adequate control for confounding, Peng and colleagues (2006) found in their simulations based on NMMAPS data that "the bias in the estimates is only serious for *df*/year between 1 and 4." The implication of their findings for the ESCALA results, is that serious bias due to too few *df*/year in the relative risks for all-age, all-natural-cause mortality and all-age, cardiopulmonary mortality is unlikely except in the two cities with 4 *df*/year (Porto Alegre and Toluca). For many of the cause- and age-specific groups, however, the potential for bias is greater, given the larger number of cities with 4 or fewer degrees of freedom. The absence in the ESCALA study of any exploration of the sensitivity of the results to higher *df*/year — as was done for NMMAPS, PAPA, and APHENA — is an important limitation.

Another factor limiting interpretation of the results is that not all model details that the Committee thought should have been provided appear in these tables (Appendix Tables H.6–H.20). Instead, the protocol for specifying these details is described generally in the text. For example, the Investigators' Report describes how the specific temperature and humidity model was fitted: "Meteorologic factors were adjusted by using natural splines of same day, 1-day lagged, 2-day lagged or cumulative mean temperature (with 4 *df*) and humidity (with 2 *df*). … The number of degrees of freedom for seasonal meteorologic factors in each city was chosen by examining the residuals diagnostics as well as by lowering the AIC (Appendix H)." Thus, these components of the model may also have differed across cities by lag and perhaps also by the number of degrees of freedom. Lack of information on the actual choice in each city is a limitation because it prevents complete independent evaluation of the final model specifications and their implications for the interpretation of the results. The experience in other studies (e.g., Welty and Zeger 2005), however, suggests that the resulting biases, if they were to exist, would probably be in the size, rather than the sign (negative or positive) of the coefficients — at least for PM. The implications for O_3 are less well studied and understood.

The investigators did provide results of some sensitivity analyses, but only for a selection of cause- and age-specific groups (see Investigators' Report Appendix Tables H.21–H.28). These analyses evaluated the sensitivity of the effect estimates for PM_{10} and O_3 exposures (DLM 0–3) in individual cities to (1) the effect of excluding days when pollutant concentrations were particularly high (that is > 75th percentile or > 95th percentile); (2) the addition of different lags for temperature control (lag 0–1 day or lag 3–7 days); and (3) the use of different smoothers for control of seasonality (penalized spline, natural spline, and the "common approach"). Although they covered a smaller range of models than did, for example, sensitivity analyses conducted for the HEI studies in Asia (HEI PAPA 2010, 2011; HEI Collaborative Working Group 2012), the ESCALA sensitivity analyses were nevertheless very

informative. The Committee suspected that the results for the other models would probably not be very different, but it is not possible to know, given the limited set of results provided and the absence of any discussion of the sensitivity analyses by the authors.

Substantively, the sensitivity analyses showed a varied picture, with some cities and some age–cause results very stable to model changes, but others very sensitive to them. For example, in the Brazilian cities, the all-natural-cause, all-age PM_{10} results showed broad robustness of the regression coefficients to model and other choices (see Investigators' Report Appendix Table H.21). The one exception was the sharp change resulting from dropping days with PM_{10} concentrations above the 75th percentile, which is understandable. The results in some Chilean cities, on the other hand, showed rather pronounced changes in estimates with model choice. For example, replacing a natural spline time smooth with a penalized spline using the same number of degrees of freedom resulted in substantial changes in the estimates for Santiago. Adding temperature lag 3–7 markedly changed estimates for Santiago and Concepción. The PM_{10} effect estimates in the Mexican cities were largely robust. Similar patterns in the sensitivity of results were also observed in the analyses conducted for the larger cause- and age-specific groups — that is, for cardiovascular mortality in the ≥ 65 age group and for cardiopulmonary mortality in the all-age group. For example, the estimate for cardiovascular mortality in the ≥ 65 age group in Monterrey effectively doubled when penalized splines, rather than natural splines, were used. Based on the extensive work done in APHENA (Katsouyanni et al. 2009), this kind of sensitivity to choice of smoother is unexpected and remains unexplained.

The sensitivity analyses for O_3 were presented only for the warm season. They showed similar variability in the sensitivity of effect estimates across cities and cause- and age-specific groups (Investigators' Report Appendix Tables H.25–H.28). In São Paulo and the Mexican cities, the effects of O_3 on all-natural-cause, all-age mortality, cardiovascular mortality in the ≥ 65 age group, and cardiopulmonary mortality in the all-age group were reasonably stable. Effects of O_3 on respiratory mortality in children 1–4 years were more variable in all cities except Mexico City. These variations in estimates were substantially larger than those shown in the APHENA, PAPA, or NMMAPS sensitivity analyses.

Sensitivity to model choice would be of less concern if one could rely on the criteria for choice of model to give an optimal model. In ESCALA, the model fit criteria may in some cities have led to inadequate control of confounding, and the variation in models between cities might explain some differences in pollution–mortality increments. Furthermore, the Committee would have liked the investigators to be clearer what the ultimate criteria were; the protocol outlines several criteria to consider but does not give a clear algorithm. This omission is an added reason not to rely heavily on the investigators' choice of the "main model".

Stratification by SES

An important question investigated by the ESCALA study was whether socioeconomic status affects susceptibility to the adverse effects of air pollution. The answer to this question is of considerable interest to public policy makers in countries around the world. It is not an easy question to answer in studies of this nature, even in larger multicity studies like APHENA (Katsouyanni 2009). The initial challenge is in identifying variables that are likely to be predictors of SES in any given city, but then, given inevitable differences in administrative data available from city to city, investigators must make reasonably sure that the chosen variables reliably represent the SES levels (e.g., low, medium, high) that they are trying to predict, and that these levels have the same meaning across locations.

The ESCALA investigators took notice of the difficulties previous investigators have encountered. They brought in sociological expertise to help design a systematic approach to identifying factors that would help characterize SES in each city at a comparable level of geographic aggregation.

Meta-Analyses and Meta-Regression Analyses

The investigators followed well-established methods in their meta-analyses of the city-specific effect estimates and in their meta-regressions. The presentation of the significance test results (via the Q statistic) for heterogeneity in pollution–mortality coefficients across cities and an index of its extent (I^2) was useful. In particular, when these measures show significant heterogeneity (as was the case in most analyses), the pooled means must be cautiously interpreted, as they depend critically on the selection of cities for inclusion in the study.

The Review Committee considered the "relative risk ratios" presented from the meta-regressions as the primary result from that analysis, because they summarized the extent to which each of the city characteristics explained variation in the pollution–mortality coefficients. However, the same caution applies to the interpretation of these values as to the pooled means, given the almost universal heterogeneity, most of which is unexplained by the city characteristics.

RESULTS AND INTERPRETATION

The ESCALA analysis found daily increases in PM_{10} to be positively associated with increases in daily mortality for most causes of death in most of the cities studied. Weaker, and sometimes inverse, associations were primarily reported in cities with smaller study populations, such as Concepción and Temuco in Chile, and Toluca in México. The associations between daily increases in O_3 and increased mortality were weaker and less consistent across cities than was the case for PM_{10}.

Residual confounding, as in many studies, requires careful consideration in ESCALA. Adding to this concern is the decision by the investigators to choose the *df*/year for individual cities on the basis of model fit criteria. As discussed, their approach led to model specifications for a number of cities, causes of death, and age groups that the Committee thought might inadequately control for temporal confounders. The limited sensitivity analyses provided by the investigators generated some additional concern about whether the control for the effects of meteorology using longer temperature lags had been aggressive enough. Consequently, the HEI Review Committee concluded that, as one would expect, the most robust estimates of the effect of air pollution on health were those for most of the larger cities and for age groups and the causes of mortality with the larger numbers of deaths.

For PM_{10}, this means greater confidence might be placed in the relative risks for all-natural-cause, all-age mortality and for cardiovascular and cardiopulmonary mortality in the all-age and the ≥ 65 age groups. The robustness of the all-natural-cause, all-age results for the Brazilian and Mexican cities is particularly noteworthy. The high sensitivity of the main results to model choice for many of the other causes of death and age groups, particularly among children, suggests that caution should be exercised in their interpretation. In particular, they should be evaluated carefully with regard to the degree of control for temporal confounding, as discussed in the previous section, and in the context of any sensitivity analyses (if provided). Similarly for O_3, the more robust associations were with all-natural-cause, all-age mortality and with cardiovascular and cardiopulmonary mortality in both the all-age and the ≥ 65 age groups. Sensitivity analysis of the effects of O_3 on mortality in children was limited, and results were provided only for respiratory mortality in children 1–4 years during the warm season. However, the analysis suggests that the effect estimates in this age group were reasonably robust in Mexico City and São Paulo.

Although they were not examined thoroughly by the ESCALA investigators, differences in how well population exposure is measured within and between cities can also contribute to differential levels of bias and uncertainty in the effect estimates. As in most time-series studies, population exposures were estimated based on existing monitoring networks. While the investigators followed a careful protocol to select monitor locations and to ensure that any data collected were complete, they could not change the number of PM_{10} and O_3 monitors in the individual cities, which varied widely. The high degree of correlation between pollutant concentrations in most, but not all, cities gives some assurance of a reasonable representation of population exposure for these pollutants; a clear presentation of the location of individual monitors relative to sources and populations might have been insightful and is advisable in future studies (see, for example, the HEI PAPA [2011] studies in India).

Stratification by SES

Despite the investigators' careful efforts to assign SES status to their study populations, the HEI Review Committee thought that the analyses did not provide convincing evidence that SES modifies the adverse effects of air pollution. The Committee advised caution in drawing any broad conclusions from these results. The investigators' reported patterns of stronger risks among low-SES groups for respiratory effects and stronger risks of cardiovascular disease among medium or high-SES groups were not consistently observed from city to city. For example, Mexico City did fit this pattern; for both PM_{10} and O_3, respiratory and COPD mortality were generally stronger in the low-SES group than in the medium- or high-SES groups, whereas both cardiovascular and cerebrovascular–stroke mortality were stronger in the medium- and high-SES groups than in the low-SES groups. In São Paulo, on the other hand, the magnitude of the effect of PM_{10} on respiratory mortality seemed to increase generally with increasing SES, but the effect of O_3 on respiratory mortality did appear to be stronger with decreasing SES. In Rio de Janeiro, the results showed that the risks of respiratory mortality associated with exposure to PM_{10} were larger for those with a higher SES, but that the risks of all-age, all-natural-cause and cardiovascular mortality were stronger for people with low SES. For Santiago, for both PM_{10} and O_3 exposures, the risk of respiratory mortality was slightly stronger in the high-SES group and the risk of cardiovascular disease was stronger in the low- and medium-SES groups than in the high-SES group.

Other studies have also have encountered challenges in understanding whether lower SES may increase susceptibility to the effects of air pollution and suggest that there may be more complex interactions between where people of different SES live, their exposures, diet, and other factors

that are not captured well in the analyses done to date (Brunekreef et al. 2009; Krewski et al. 2009). However, the reasons for the differences in SES effects among cities are unclear and might be clarified with more detailed analysis.

Meta-Analyses and Meta-Regression Analyses

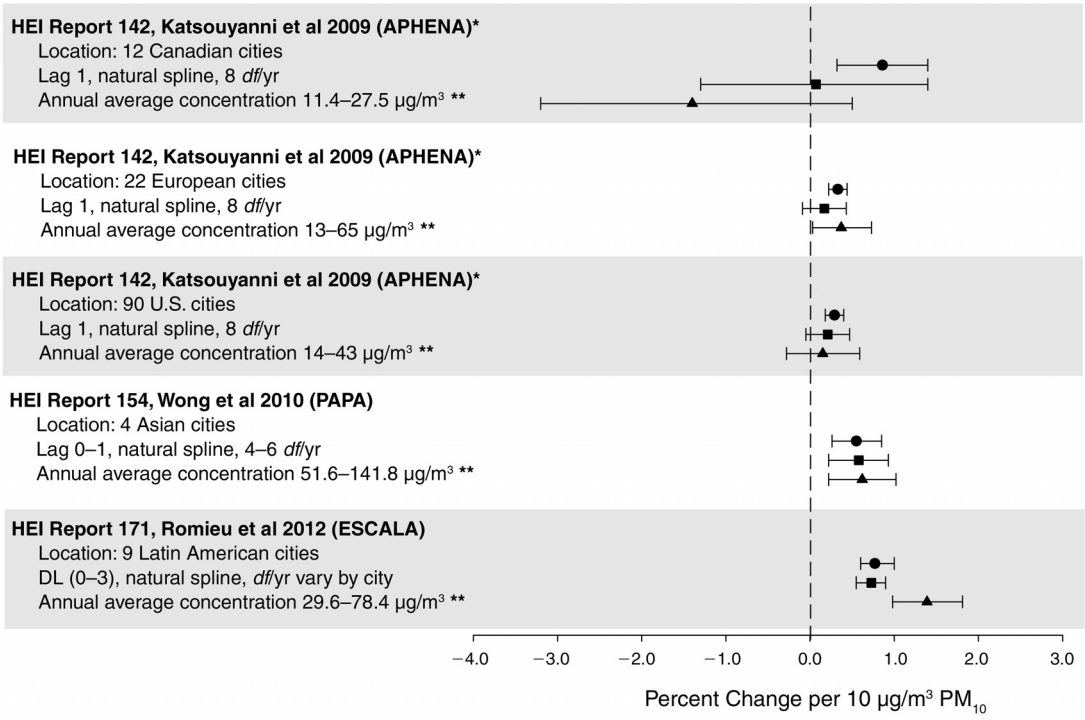
The weight that can be put on the pooled means from the meta-analyses is limited by the large amount of heterogeneity between city-specific results that remained largely unexplained by the later meta-regression analyses. A different sample of Latin American cities might have produced quantitatively very different results.

Aside from that, the robustness of the city-specific results also has direct bearing on the interpretation of the meta-analytic and meta-regression results. Again, greater confidence can generally be placed in the relative risks for all-natural-cause, all-age mortality, and for cardiovascular and cardiopulmonary mortality in the all-age or ≥ 65 age groups than in the risks for cerebrovascular–stroke mortality and mortality from most causes of death in infants and children. The investigators appropriately chose not to conduct separate meta-analyses or meta-regression analyses of data for the youngest age groups.

In the meta-regression analyses, the identification of some city characteristics as "significant" predictors of the size of a city's PM–mortality coefficients was interesting. However, the Committee cautions that conclusions about these predictors should be considered as suggestive, rather than definitive, because these few associations emerged from a large number of predictors considered, and because the patterns of results across cause-of-death groups did not fit an obvious causative pattern. Moreover, the residual biases discussed above might impact individual cities differently, thus leading to spurious evidence of effect modification.

ESCALA Results in the Context of Other Multicity Studies

One of ESCALA's goals was to contribute to the global literature on the adverse effects of PM_{10} and O_3 by providing results of the first coordinated multicity time-series analysis in Latin America. Commentary Figures 3 and 4



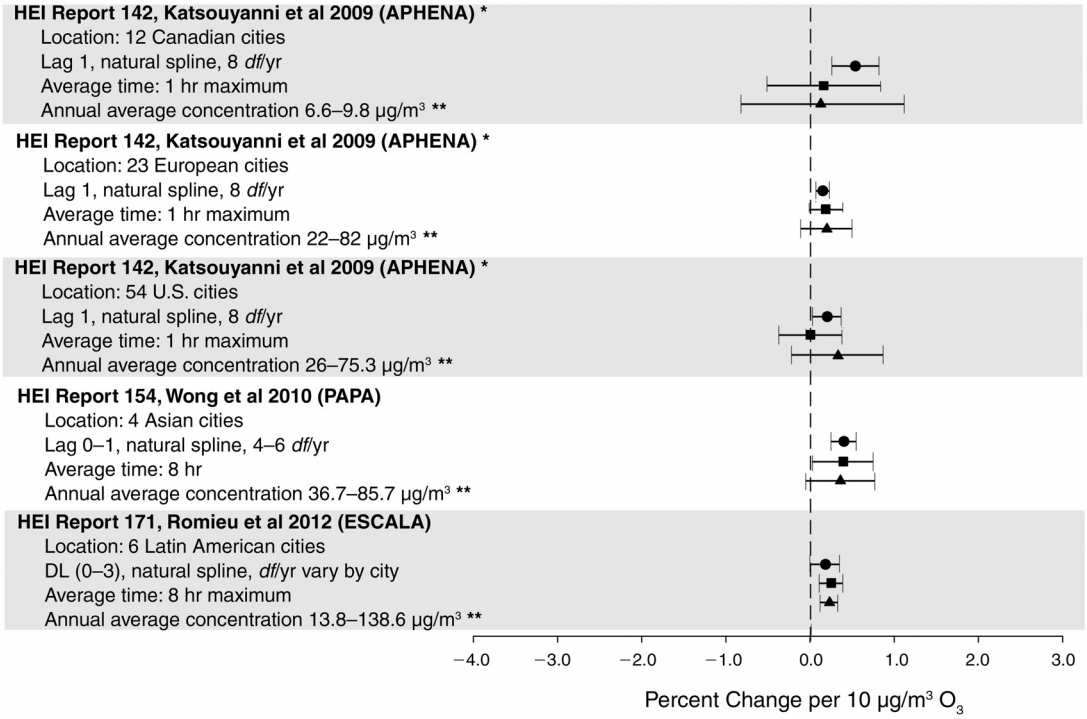
Commentary Figure 3. Estimates of the effect on all-natural-cause, cardiovascular, and respiratory mortality per 10-µg/m³ increase in PM_{10} as reported in several recent HEI-funded coordinated multicity studies for all ages. Estimates with ● indicate all-natural-cause mortality, estimates with ■ indicate cardiovascular mortality, and estimates with ▲ indicate respiratory mortality. ESCALA and PAPA results were estimated using random-effects models. APHENA model not specified. (ESCALA Source: Investigators' Report Table 20.) *Cardiovascular mortality values are for people < 75 years. All other values are for all ages. **Range of concentrations across cities. Values for APHENA studies are median annual concentrations; values for PAPA and ESCALA are averages.

compare the random-effects meta-analytic results of the ESCALA study for all-natural-cause, cardiovascular, and respiratory all-age mortality for a 10-μg/m^3 increase in PM_{10} and O_3, respectively, with those of other multicity studies published by HEI from Europe, Canada, the United States, and Asia. Despite some differences in the pollution measurements and lags used in the models, these figures suggest that the adverse effects of PM_{10} and O_3 on mortality in Latin America, though somewhat stronger, are similar to those found elsewhere. The all-age, all-natural-cause meta-analytic result for PM_{10} (0.77% [95% CI = 0.60 to 1.00]) is similar in magnitude to the result from a meta-analysis conducted by PAHO (2005) of 17 independently conducted single-city time-series studies in Latin America. Those investigators reported a summary estimate of a 0.61% increase in all-natural-cause, all-age mortality (95% CI = 0.16 to 1.07) per 10-μg/m^3 increase in PM_{10} with a random-effects model. Ultimately, interpretation and application of any meta-analytic result from the ESCALA study needs to take into consideration any specific limitations and uncertainties in the city-specific results discussed earlier.

SUMMARY AND CONCLUSIONS

The ESCALA study is an important extension of coordinated multicity time-series methods to the study of the effects of ambient PM_{10} and O_3 in a region of the world where they had not yet been applied — Latin America. The investigators sought to evaluate several issues of interest to air pollution science and public policy: they considered multiple causes of death that have been associated with air pollution in adults and older populations in other studies; they examined the susceptibility of infants and children to respiratory mortality; they undertook a careful analysis of the effects of SES on susceptibility to the effects air pollution exposures; and they made a strong effort to evaluate several city-level characteristics that might explain the differences between cities.

The ESCALA investigators found small but significant effects of daily exposure to PM_{10} and O_3 on daily mortality that were largely similar to those from other coordinated multi-city studies around the world. The relatively high degree of rigor used in carrying out ESCALA, with common protocols for data collection and analysis, and



Commentary Figure 4. Estimates of the effect on all-natural-cause mortality per 10-μg/m^3 increase in O_3 as reported in recent HEI-funded coordinated multicity studies for all ages. Estimates with ● indicate all-natural-cause mortality, estimates with ■ indicate cardiovascular mortality, and estimates with ▲ indicate respiratory mortality. ESCALA and PAPA results were estimated using random-effects models. APHENA model not specified. (ESCALA Source: Investigators' Report Table 21.) *Cardiovascular mortality values are for people < 75 years. All other values are for all ages. **Range of concentrations across cities. Values for APHENA studies are median annual concentrations; values for PAPA and ESCALA are averages.

sensitivity analyses to test alternative model assumptions, should provide policymakers with reasonable assurance that the main findings in the age groups for more common types of mortality have a solid foundation and are arguably the most reliable estimates for the region to date. However, given the potential uncertainties associated with interpretation of specific results, caution should be exercised in the interpretation of the more complex patterns observed in these studies such as the patterns of results between cities, between SES levels, and in the degree of effect modification by different covariates in the meta-regression analyses.

The ESCALA investigators have established an important methodologic foundation for future work in Latin America. The ESCALA study could be readily expanded to include other cities in Latin America, used to explore alternative analytical methods, and improved upon by taking into account both the recommendations of the Committee and the many insights gained by the investigators in the course of the study.

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