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Ozone Exposure and Daily Mortality in Mexico City: A Time-Series Analysis

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Includes the Commentary of the Institute's Health Review Committee

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HEI HEALTH EFFECTS INSTITUTE

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HEI Statement

Synopsis of Research Report Number 75

Is Increased Mortality Associated with Ozone Exposure in Mexico City?

BACKGROUND

Fossil fuel combustion from motor vehicle and industrial sources produces a number of air pollutants, including ozone, volatile organic compounds, oxides of sulfur and nitrogen, particles, and acid aerosols, all of which have the potential to cause health effects. The Clean Air Act authorizes the U.S. Environmental Protection Agency to set National Ambient Air Quality Standards for a variety of pollutants; the Agency is currently considering revised standards for ozone and particulate matter.

It is well-established that large, short-term increases in air pollution, such as those that occurred earlier in this century, are associated with an increased number of deaths. Recent epidemiologic studies suggest that smaller increases in some air pollutants are also associated with increases in daily mortality. In light of these observations, the Health Effects Institute funded epidemiologic studies on the association between increased mortality and exposure to ambient ozone or particulate matter. As part of the ozone program, the HEI funded a project by Dr. Dana Loomis and his colleagues to evaluate the hypothesis that ozone exposure is associated with increased mortality during episodes of high ambient ozone levels in Mexico City. This location offers the investigators advantages over many locations in the United States and Europe because (1) ambient ozone levels are high, (2) these levels are a more reliable measure of personal exposure than in the United States because indoor heating and air conditioning are rare, and (3) weather-related variables are less likely to confound the results.

APPROACH

Dr. Loomis and colleagues at the University of North Carolina and Dr. Víctor Borja-Aburto of the Instituto Nacional de Salud Pública in Cuernavaca, Mexico, collected mortality, air quality, and weather data from records and monitoring stations in Mexico City from 1990 through 1992. Using statistical techniques, the investigators evaluated the association between increased mortality and ambient levels of ozone, sulfur dioxide, and total suspended particles, both individually and in a model that included all three pollutants.

RESULTS AND IMPLICATIONS

In this study, elevated levels of ambient ozone, total suspended particles (TSP), and sulfur dioxide were associated to some degree with increased mortality in Mexico City. When ozone was the only air pollutant considered in the statistical model, the investigators found that daily deaths increased 2.9% for each 100-parts-per-billion (ppb) increase in ozone concentration. This excess mortality was greater for individuals over 65 years of age. For TSP, daily deaths increased 5.4 percent for each 100-$\mu g/m^3$ increase in TSP concentration. When sulfur dioxide was considered alone, daily deaths increased 7.5 percent for each 100-ppb increase in sulfur dioxide concentration. When all three pollutants were included in the model, however, only the association of TSP with the observed increase in daily mortality was statistically significant.

In summary, although the investigators found an increase in mortality associated with periods during which ambient levels of ozone were elevated, this increase cannot necessarily be attributed to ozone because it was not statistically significant when other air pollutants were included in the analysis. Overall, the results of this study conducted in Mexico City appear largely consistent with what has been reported in other locations worldwide, namely that short-term increases in indices of particulate air pollution are associated with increased daily mortality. However, further research is needed to disentangle the effects of the various pollutants and to gain insights into the association of individual pollutants with morbidity and mortality.

This Statement, prepared by the Health Effects Institute and approved by its Board of Directors, is a summary of a research project sponsored by HEI from 1993 through 1995. This study was conducted by Dr. Dana P. Loomis and colleagues of the University of North Carolina, Chapel Hill, and Dr. Víctor Borja and associates at the Instituto Nacional de Salud Pública, Cuernavaca, Morelos, México. The following Research Report contains both the detailed Investigators' Report and a Commentary on the study prepared by the Institute's Health Review Committee.

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INVESTIGATORS' REPORT

Ozone Exposure and Daily Mortality in Mexico City: A Time-Series Analysis

Dana P. Loomis, Víctor H. Borja-Aburto, Shrikant I. Bangdiwala, and Carl M. Shy

ABSTRACT

Daily death counts in Mexico City were examined in relation to ambient ozone levels during 1990–1992 for the purpose of investigating the acute, irreversible effects of air pollution, with emphasis on ozone exposure. Air pollution data were obtained from nine monitoring stations operated by the Departamento del Distrito Federal. Mortality data were provided by the Instituto Nacional de Estadística, Geografía, e Informática. Increases in numbers of deaths were positively associated with elevated air pollution levels on the same day and on the previous day. The magnitude of the increases was small but statistically significant, after Poisson regression models were used to adjust for temperature and long-term trends. In models using data for a single pollutant, the "crude" rate ratio for total mortality associated with an increase of 100 parts per billion (ppb)* in one-hour maximum ozone concentration was 1.029 (95% CI 1.015, 1.044). A moving average of ozone showed a stronger association (rate ratio [RR] = 1.048, 95% CI 1.025, 1.070), and excess mortality (an increase in the number of deaths, relative to the average on days with low pollution levels) was more evident for persons over 65 years of age. Separate analyses of the effect of elevated ozone for different areas of the city showed similar results, but they were not statistically significant. Other pollutants also were related to mortality. The RR was 1.075 (95% CI 0.984, 1.062) per 100-ppb increase for sulfur dioxide and 1.049 (95% CI 1.030, 1.067) per 100 $\mu g/m^3$ increase in total suspended particulates (TSP) when these pollutants were considered in separate models. However, when all three pollutants were considered simultaneously, only TSP remained associated with mortality, indicating excess mortality of 5% per 100 $\mu g/m^3$ increase (RR = 1.052, 95% CI 1.034, 1.072). The excess mortality associated with TSP is consistent with that observed in other cities in America and Europe. This study provides some evidence that ozone is associated with all-cause mortality and with mortality among the elderly after controlling for long-term cycles. However, ozone levels exhibited little or no effect on mortality rates when other air pollutants were considered simultaneously. Particulate matter appeared to be an important pollutant; it independently predicted changes in mortality. Nevertheless, because of the complexity and variability of the mixtures to which people are exposed, it is difficult to attribute the observed effects to a single pollutant. The technical feasibility and scientific validity of isolating the effect of single pollutants in such complex mixtures requires further research and careful consideration. Given the large population living in and exposed to ambient air pollution in Mexico City and other metropolises throughout the world, these small but significant associations of mortality with air pollution indices are of public health concern.

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

This Investigators' Report is one part of Health Effects Institute Research Report Number 75, 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. Dana P. Loomis, Department of Epidemiology, School of Public Health, University of North Carolina, Chapel Hill, NC 27599.

Although this document was produced with partial funding by the United States Environmental Protection Agency under Assistance Agreement 816285 to the Health Effects Institute, it has not been subjected to the Agency's peer and administrative review and therefore may not necessarily reflect the views of the Agency, and no official endorsement should be inferred. The contents of this document also 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 those parties, and no endorsement by them should be inferred.

INTRODUCTION

SOURCES OF OZONE EXPOSURE

In contrast to stratospheric ozone with its protective effect, tropospheric ambient ozone is a widespread pollutant that has been hard to control. Tropospheric ozone comes from a complex series of chemical reactions involving sunlight and various compounds largely produced by the incomplete combustion of vehicular fuels. Exhaust gases contain varying amounts of carbon dioxide, carbon monoxide, and gaseous organic compounds (collectively known as volatile organic compounds). The initial reaction, photolysis of nitrogen dioxide, produces nitric oxide and atomic oxygen. Concurrent photodissociation of some organic compounds produces various free radicals. Depending on meteorologic conditions, and on the mixture and raw materials available in the air, sequences of chemical and photochemical reactions increase the levels of ozone and

oxidized hydrocarbons. Despite introduction of the catalytic converter, which reduced vehicular hydrocarbon emissions per mile traveled, ozone levels have remained fairly stable since the mid-1970s. High levels of ozone are most common in areas having sunny, dry, warm climates and large numbers of automobiles, such as Los Angeles and Mexico City.

ACUTE HEALTH EFFECTS

Acute adverse respiratory effects of ozone exposure are well documented in animal and human populations. Exposure chamber assessments of lung function have demonstrated transient, apparently reversible effects after short-term exposure lasting from five minutes to a few hours (Folinsbee et al. 1988; Fouke et al. 1988; McDonnell et al. 1991). Ozone inhalation causes concentration-dependent decreases in average lung volume and flow resistance (Hazucha 1987; Higgins et al. 1990), epithelial permeability, and reactivity to bronchoactive challenges (Becket et al. 1988). Changes in several parameters of pulmonary function have been reported in normal subjects during exercise. Such effects can be observed within the first hours after the start of the exposure and may persist for many hours or days after the exposure ceases (Lippmann 1989). Some authors suggest that adaptation to chronic exposure occurs. Any long-term health implications of an adaptation response are unknown.

Functional responsiveness to ozone appears to be greater in children with asthma than among persons who smoke (Shepard et al. 1983; Kagawa 1984), older adults (Drechsler-Parks et al. 1987; Reisenauer et al. 1988) adults with asthma (Linn et al. 1983; Koenig et al. 1987), or patients with chronic obstructive pulmonary disease (Solic et al. 1982; Linn et al. 1983). In addition, increases in hospitalization rates for respiratory diseases have been observed (Bates and Sizto 1989) with increases in ozone exposure.

Field and epidemiological studies have provided evidence of adverse human responses to ozone and other photochemical oxidants at concentrations as low as 0.10 parts per million (ppm) per hour. Symptoms include eye, nose, and throat irritation; cough; increased mucus production; chest tightness; substernal pain; and lassitude, malaise, and nausea (Hammer et al. 1974). The threshold for symptoms is lowered by exercise and heat (McDonnell et al. 1983; Folinsbee et al. 1984). For ethical reasons, challenges to persons with asthma and other susceptible individuals with acute or chronic lung diseases have not been as rigorous as challenges to normal subjects. Challenges to susceptible individuals can occur only outdoors during the course of actual pollution episodes.

Both in vitro and in vivo studies with animals have demonstrated that ozone can affect the ability of the immune system to defend against infection (Goldstein and Tyler 1971; Miller et al. 1978; Ehrlich 1980). However, interspecies extrapolation, uncertain at best, is required to use these data to estimate the possible effects of ozone on infectivity in humans.

Although we know much about some of the transient effects following single exposures to ozone, there has been controversy regarding their health significance. In addition, our knowledge about chronic health effects, which may include alterations in lung function or structure (Schwartz 1989), is much less complete. Such effects may result from cumulative damage caused by chronic or repetitive intermittent exposure.

MORTALITY

There is abundant evidence in the early literature that air pollution episodes acutely increase the mortality of exposed populations, as found in London, New York, the Meuse Valley, Belgium, and Donora, PA. These effects have been related especially to particulate matter and sulfur dioxide (Mazumdar et al. 1982; Ostro 1984; Hatzakis et al. 1986; Derriennic et al. 1989; Thurston et al. 1989). More recent reports have shown statistically significant associations between various measures of particulate matter and mortality counts in the United States (Fairlay 1990; Schwartz and Marcus 1990; Schwartz and Dockery 1992a,b; Dockery and Pope 1994; Schwartz 1994a,b,c) and other locations in Europe, China, and Brazil (Katsouyanni et al. 1990, 1993; Spix et al. 1993; Saldiva et al. 1994; Xu et al. 1994). Results from these epidemiologic studies are coherent. However, the biological mechanism leading to such an association is still uncertain (Utell and Samet 1993).

On the basis of what is known about the acute and intermittent pulmonary effects of ozone and the association of other pollutants with mortality, an association of ozone exposure with mortality can be expected. However, the specific biological mechanism of the linkage between air pollution exposure and mortality is unknown. Certainly air pollutants do not cause death in the sense that acutely toxic materials might, but in some cases they may cause additional environmental stress that can lead to the death of seriously ill persons. In this regard Bates (1992) suggested that acute bronchitis and bronchiolitis may be diagnosed as pulmonary edema; that air pollutants may increase lung permeability and precipitate pulmonary edema in people with myocardial damage and increased left atrial pressure; and that bronchiolitis or pneumonia induced by air pollution, in persons with preexisting heart disease, might precipitate congestive heart failure. In addition, Dockery and

Pope (1994) suggest that respiratory causes of death, either primary or contributing, can be erroneously reported as cardiovascular.

Existing epidemiologic studies have focused on short-term relations between mortality and ozone exposures. Some of the early studies reported a positive relation between ozone and mortality, but the results were confounded by the occurrence of high temperatures, a factor strongly connected with mortality. A study in the Netherlands, in contrast, did not show a relation between ozone and mortality, possibly because ozone levels were very low (Brersteker and Erendijk 1976). Some of these studies also could have misclassified exposure because ambient pollution data from only one monitoring site were used to represent uniform exposure of all individuals living in the study area.

Two reports surveying a number of locations have indicated positive associations between daily changes in mortality and ozone levels. In a 10-year study of records from Los Angeles County, California, daily total noninjury mortality and cardiovascular mortality were positively associated with elevated ozone levels the previous day (results were controlled for temperature and nitrogen dioxide); annual regressions demonstrated the consistency of the results over time (Kinney and Ozkaynak 1991). The analysis was later extended to New York City, where the association of ozone with mortality was stronger than in Los Angeles, perhaps reflecting an influence of other unmeasured pollutants (Kinney and Ozkaynak 1992). However, another study by Dockery and others (1992) did not find an effect of low ozone levels on mortality in St. Louis, Missouri, or Tennessee. In São Paolo, Brazil, daily respiratory mortality among infants was not associated with ozone levels, but was associated with levels of nitrogen oxides when all pollutants were simultaneously included in a model (Saldiva et al. 1994). The suggestive but inconsistent results of these mortality studies indicate that exposures to ozone and other pollutants may overlap, and their health effects may be interdependent.

A study in Mexico City offered potential opportunities to fill gaps in present knowledge and improve on earlier investigations. First, a gradient in exposure and response could be compared in time and space, using data from several fixed monitors. The city has 2.5 million motor vehicles, the principal source of ambient ozone in the Mexico City region, most of which would be without emission controls during the study period. Daytime ozone concentrations are typically near the United States National Ambient Air Quality Standard (0.120 ppm, not to be exceeded for more than one hour once per year) and frequently exceed it by a factor of 2 or 3, with variations throughout the city. Second, outdoor ozone monitoring might provide better estimates of actual human exposure than previous studies conducted in the U.S. and Europe, where large differences between indoor and outdoor ozone levels have complicated exposure assessment. Indoor heating and air conditioning are rare in Mexico City, and windows are usually open throughout the year. Third, confounding of results by high ambient temperatures would be reduced because Mexico City's climate is mild all year and maximal air pollution levels and temperatures generally do not occur on the same day. Episodes causing temperature inversions, and consequently pollutant stagnation, are more frequent in the winter when temperatures are lower. Nevertheless, control for temperature could be achieved in the analysis. Fourth, a study in Mexico City would have impressive statistical power to detect small effects of exposure; its large population results in at least 50,000 nonviolent deaths per year, or about 140 per day.

SPECIFIC AIMS

This epidemiologic study was undertaken to evaluate the hypothesis that increased ozone exposure is associated with greater daily mortality. The following specific questions were addressed:

- Is ozone exposure related to total daily mortality in Mexico City?
- Is ozone exposure associated with respiratory and cardiovascular causes of death?
- If there is a relation between ozone and mortality, does it vary by age group?
- Are there combined effects of ozone exposure and other pollutants or weather variables that relate to daily mortality?

METHODS

STUDY DESIGN

This study examined variations in mortality in relation to ozone concentrations over time in Mexico City. It can be classified as an ecological study with days as the units of analysis. In a daily time-series analysis of this type, factors such as occupational exposure and socioeconomic structure are not likely to confound the results, because they are not expected to vary concurrently with ozone over time. However, direct estimation of effects is complicated by the potential existence of factors, correlated in time with ozone pollution, that influence mortality independently of air

pollution. For this reason it is necessary to consider weather (temperature and humidity) and other time-related variables in the analysis. Other pollutants that have been associated with mortality, sulfur dioxide and total suspended particulates (TSP), may be correlated to ozone concentrations. In previous analyses, the effects of each of these pollutants have not been isolated because of this multicollinearity. As in any comparison of the health in different geographical areas, population characteristics such as age also are potential confounders.

This study encompassed the Distrito Federal (DF; Federal District), which includes approximately half of the total population of Mexico City's metropolitan area (Table A.1 in Appendix A). Originally we planned to study all the metropolitan areas of Mexico City, including the adjacent State of Mexico. However, because of the geopolitical assignment of deaths, this was not possible. For example, Tlalnepantla, one municipio from the State of Mexico, is spread between the Northeast and Northwest regions, so it would not have been possible to assign it to one region. Other areas such as Netzahualcoyotl and Chalco belong to municipios that are half rural and half urban, with the likelihood of different ozone exposures, and difficulties of determining exact place of residence.

Air pollution differences within the Mexico City area can be large, and similar air pollution changes might not occur on the same day in all parts of the city. This is due to meteorological factors, particularly to the direction of winds. To better estimate daily exposure to ozone, separate analyses by area within the city were performed. Five subareas within the DF were defined, taking into account previous reports of isopleths of ozone distribution (see Figure A.1) and the geopolitical division of the city: Northeast, Northwest, Central, Southeast, and Southwest. The highest ozone levels are registered by monitors in the Southwest; the lowest, in the Northeast. The Central (downtown) area has intermediate ozone levels. The final delimitation of the areas depended on a given delegación's limits and distance to the most reliable monitors. A delegación is the smallest administrative area (equivalent to a county) in Mexico City. This is also the smallest area of residence coded on death certificates. Temperature and relative humidity measurements have been reported similarly in all areas. Delimited areas included monitors that produced highly correlated data in preliminary analyses of ozone concentrations. Each area includes at least one delegación. Table 1 and Figure 1 show the distribution of delegaciónes in the five defined areas. Milpa Alta is a mainly rural delegación that does not have an air monitoring station, thus it was excluded from these groups. Classification of exposure should be more accurate with this sacrifice of statistical precision.

AIR POLLUTION MEASUREMENTS

Data Acquisition and Management

The Departamento del Distrito Federal (DDF) supplied air quality and weather data, supplemented by particulate matter data collected by the Centro de Ciéncias de la Atmósfera from the Universidad Nacional Autónoma de México. The DDF operates an automatic atmospheric monitoring network of 33 stations that measure gases; however, the information from these monitors was incomplete for the period of interest. Therefore, the exposure measurements were taken from the nine monitoring stations with the most complete information for the areas of interest; these stations measure sulfur dioxide, carbon monoxide, ozone, nitrogen oxides, and an array of meteorological parameters. Particulate matter is measured manually in a network that includes 19 stations; we selected monitors to represent each of the five areas, taking into account the available information for the period under consideration. Exposures in each area of the city were monitored by at least one station (Table 1). Because three of the five regions had two monitoring sta-

Table 1. Grouping of Monitors and Delegaciones[a]

Area	Monitor Stations	Delegaciones (Counties)
Southwest	Plateros Pedregal[b]	Alvaro Obregon Coyoacan Tlalpan M. Contreras Cuajimalpa
Southeast	Cerro de la Estrella[b]	Iztapalapa Xochimilco Tlahuac
Central	Merced[b,c] Hangares Museo[b,d]	Benito Juarez Venustiano Carranza Cuauhtemoc Iztacalco
Northeast	Xalostoc La Villa[b,d]	Gustavo A. Madero
Northwest	Azcapotzalco Tlalnepantla[b]	Azcapotzalco Miguel Hidalgo

[a] Refer to Figures 1 and A.1 for geographic locations.

[b] Stations where TSP measurements were available.

[c] PM_{10} monitoring station.

[d] Stations for TSP only.

tions and the remainder had only one, spatial variability within regions could not be examined effectively. The analytical methods used are the standard ones recommended by the U.S. Environmental Protection Agency (EPA). Selected characteristics of the monitoring system are shown in Table A.2. Data for ozone, sulfur dioxide, carbon monoxide, temperature, and relative humidity were provided on an hourly basis for each monitoring station. Gas measurements were available in parts per million, which we converted to parts per billion, temperature in degrees Celsius (°C), and relative humidity in percentages.

The validity of the air quality measurements was assessed by comparing our data with measurements from EPA audits since 1990. In general, these audits report good data quality for the last two to three years. Correlations of known concentrations with monitor readings exceeded 0.99. Data also were analyzed graphically to screen for potential problems. Inspection of the ozone time series showed some data problems not detected by EPA audits, starting in the second trimester of 1991 and possibly related to changes in analyzer configuration. A shift in daily minimum and maximum ozone concentrations, especially for the Xalostoc monitoring station (Northeast), indicates a change in monitoring or data processing methodologies (Figure 2). To control for the potential effect of changes in the ozone monitoring system, a dummy variable for the two periods was included in the regression models.

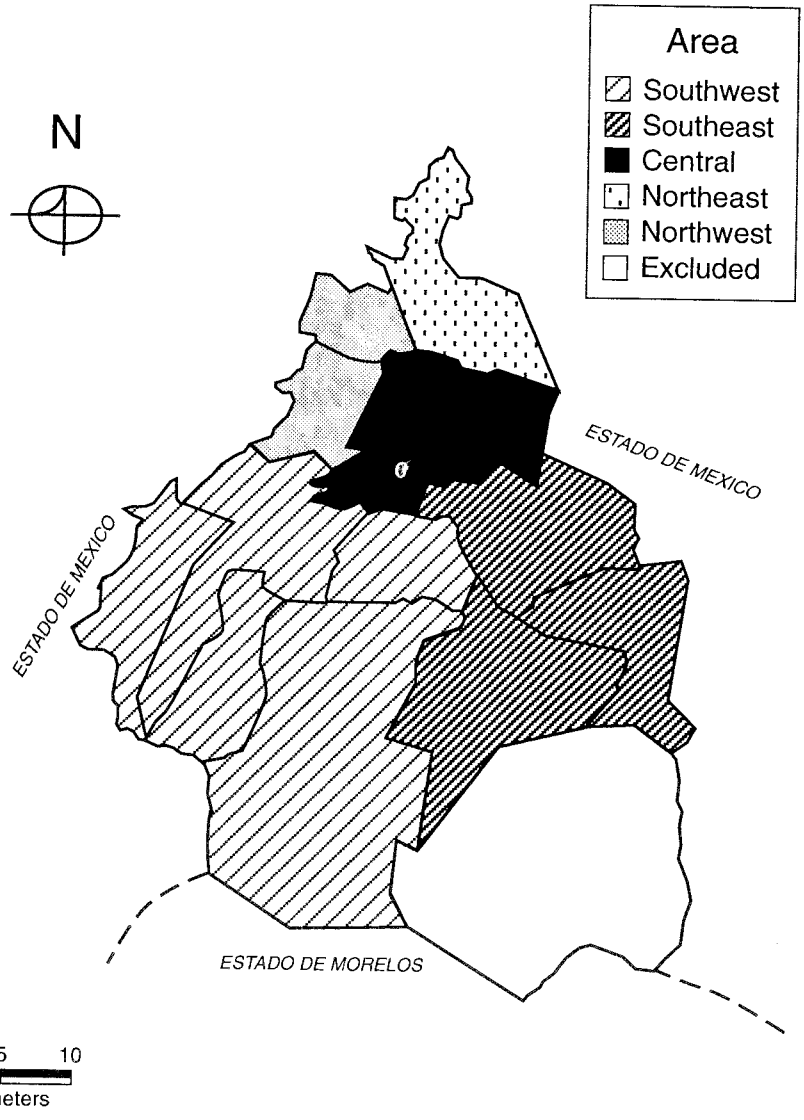

Figure 1. Delimited subareas of the Distrito Federal (Mexico City).

The basic metric of exposure was the daily one-hour maximum concentration of ozone, because U.S. and international standards are based on this metric. However, in an exploratory analysis, we examined the association of mortality with four other indices of ozone exposure. These were: the mean ozone concentration for 24 hours, the average ozone concentration between 8 a.m. and 6 p.m. each day, an 8-hour moving average around the daily maximum concentration of ozone, and the cumulative 8 a.m. to 6 p.m. ozone concentration for three days.

Inclusion of the 8 a.m. to 6 p.m. average ozone concentration is consistent with the hypothesis of Rombout and colleagues (1986) that day-long exposure is of greater concern than a 1-hour maximum exposure. Cumulative ele-

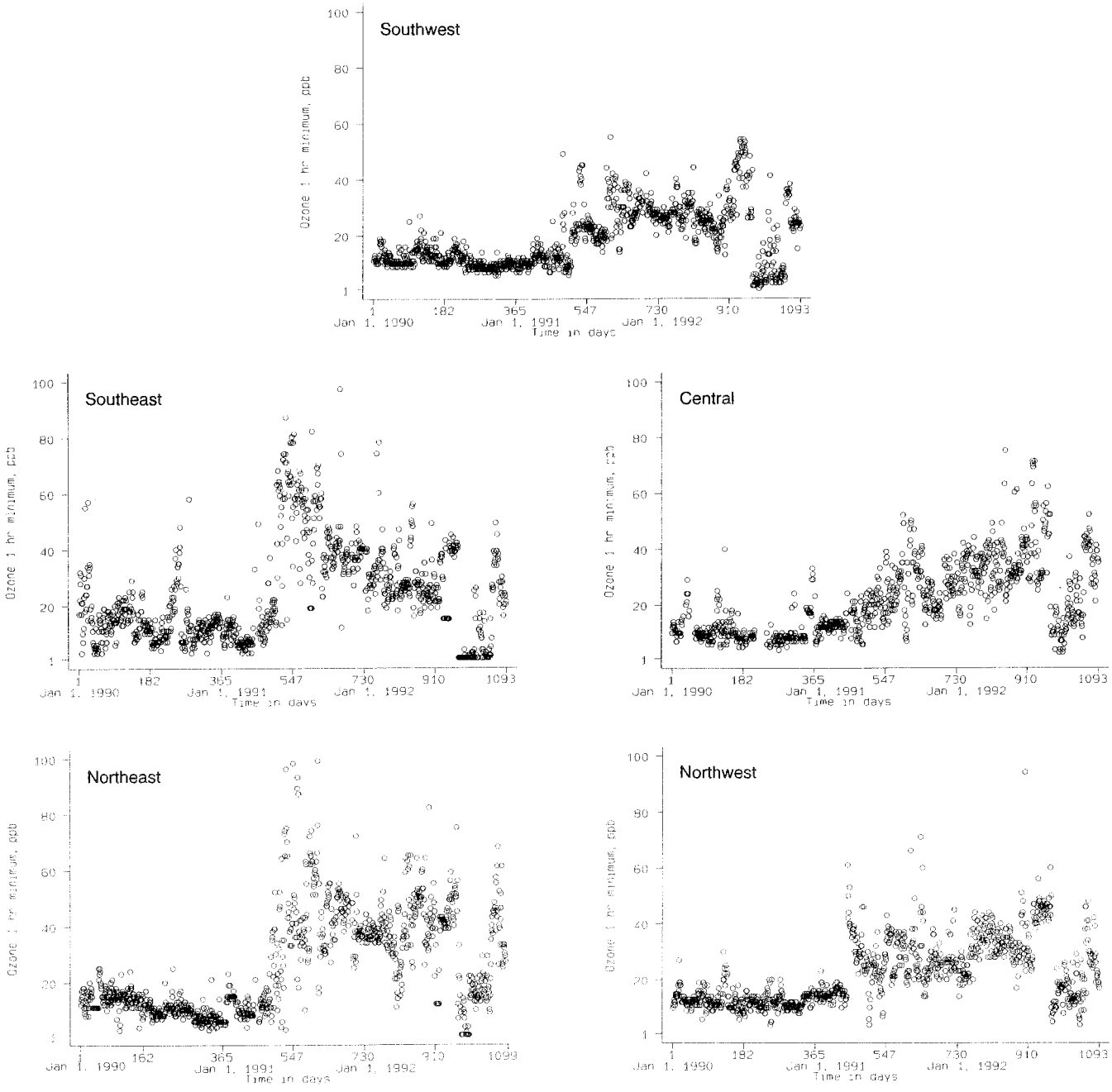

Figure 2. Time series of daily ozone minimum values for Mexico City, 1990–1992. Each O represents a daily value. (Xalostoc is in the northeast section of the city).

vated exposure for several days may have an effect on mortality, a phenomenon that has not been studied in previous reports. The effects of repetitive high or medium exposure for several days may be more severe than those of a single peak exposure. Adaptation to ozone exposure has been reported in some clinical and field studies (Lippmann 1993). Intermittent exposures to low and high concentrations may prevent this apparent "physiological" adaptation. In addition, such adaptation may be lost after several days of low exposure. A measure of relative change of ozone concentration can reflect the temporal stability of exposure; thus, an index of relative change in ozone concentration was explored. Also, because the effects of ozone on health might be observed only after several days, we measured exposure both with same-day ozone and covariates, and using previous (one to four days) levels of ozone and covariates to predict current mortality.

The five indices of estimated ozone exposure for each calendar day were derived from the hourly measurements as follows: (1) The 1-hour daily maximum concentration was obtained by selecting the maximum value from among the valid hourly measurements for each day. (2) The 8 a.m. to 6 p.m. mean concentration was calculated as the sum of the valid hourly measurements during the time interval, divided by the number of such measurements. (3) The 24-hour mean was calculated as the sum of the valid hourly measurements for each calender day divided by the number of measurements. (4) The 8-hour moving average was computed by selecting the maximum value of the day, and then determining the average of the previous four hours, the maximum value, and the three hours after the maximum value. (5) The cumulative 8 a.m. to 6 p.m. exposure for three days was estimated by summing the values of the 8 a.m. to 6 p.m. mean concentration for three consecutive days. To estimate any of these indicators, at least six valid observations per day were required. If fewer than six observations were available, that day's data were treated as missing.

The mean levels of sulfur dioxide and carbon monoxide were estimated by summing the observed values for each day, and then dividing by the number of observations. Total suspended particulates, measured every sixth day, were provided as a 24-hour integrated measure. No transformation of this metric was required. However, the ability to control for the potential effect of particulate matter was limited by the six-day sampling regime used until 1992 for direct gravimetric measurement of TSP.

Gravimetric measurements of particulate matter of less than 10 μm in diameter (PM_{10}) were available only for one monitor, operated from Monday to Friday, 1991–1992, by the Centro de Ciencias de la Atmósfera, at La Merced (Central); these measurements were provided by Dr. Irma Rosas. The appropriateness of using TSP as a measurement of particulate exposure was evaluated for the Central area by comparing the estimates obtained for those days when both TSP and PM_{10} data were available.

Missing Values

Data for all pollutant concentrations were not available for every station each day. Prior to estimating average levels for each of the five areas, missing values for the daily average and maximum were assigned using the mean of all available stations with a station-specific correction factor, following the method of Kinney and Ozkaynak (1991).

To fill in missing pollution data ($Xijk$) for station i, on day j, in year k,

$$\hat{X}ijk = \overline{X} \cdot jk \frac{\overline{Xi} \cdot k}{\overline{X} \cdot k} \quad (1)$$

in which $\overline{X} \cdot jk$ = daily mean of other stations on day j; $\overline{Xi} \cdot k$ = annual mean for station i and year k; and $\overline{X} \cdot \cdot k$ = annual mean across stations for all stations reporting on day j.

Days for which six or more stations were without data were excluded from the analysis. At least six observations were required to compute a daily average. Missing values were not assigned if more than either 30 consecutive or 90 separated observations were missing in a year. Daily averages for regions with more than one monitoring station were estimated as the arithmetic mean, if at least two observations were available for each station. Weighted means were estimated if one of the values was assigned, with assigned values arbitrarily given half the weight of observed values. The numbers of missing and assigned values, by monitor, are shown in Table A.3.

MORTALITY DATA

Data Acquisition and Management

The Instituto Nacional de Estadística, Geografía, e Informática of Mexico supplied detailed mortality data in the form of individual records on computer diskettes. Each record includes the person's age, gender, delegación of residence (county), date of death, date of death registration, delegación of death, and cause of death. The data were reduced to total deaths and number of cause-specific deaths per day, by age group, in each of the five geographic areas defined previously. Only deaths of DF residents that occurred within the DF were considered. Eligible deaths were assigned to the region of residence, regardless of where the deaths occurred within the city. Deaths of DF residents that occurred outside the DF were excluded, as were deaths within the DF of people who resided elsewhere.

The number of daily deaths, rather than the death rate, is used as the outcome measure, as population size did not change substantially during the years under consideration. Deaths were grouped by age and cause. The data were divided into the following three groups of causes of death according to the ninth revision of the International Classification of Diseases (ICD-9):

- Respiratory diseases, including acute respiratory infection (ICD-9 460–466); pneumonia and influenza (ICD-9 480–487); chronic obstructive pulmonary disease and allied conditions (ICD-9 490–496); pneumoconiosis and other lung diseases caused by external agents (ICD-9 500–508); and symptoms involving the respiratory system and other chest symptoms (ICD-9 768, 786).
- Cardiovascular diseases, defined as hypertensive disease (ICD-9 401–405); ischemic heart disease and diseases of pulmonary circulation (ICD-9 410–417); stroke (ICD-9 430–438); and symptoms involving the cardiovascular system (ICD-9 785).
- Other causes. Violent and "accidental" causes of death were excluded to avoid the possibility that a correlation between ozone and mortality might be introduced by a higher rate of traffic-related mortality during the days with heavier traffic (and therefore higher pollution levels).

Quality of Mortality Data

The quality of mortality data for the metropolitan area of Mexico City has been evaluated and found satisfactory (Bustamante-Montes et al. 1990). In that study, 100 percent of deaths were found to be registered and certified by a physician; fewer than 1 percent of the deaths did not have the exact day of death recorded; and more than 70 percent of deaths occurred in hospitals. There was no appreciable delay in notification, and coding was carried out by trained specialists.

We studied a subsample of deaths to assess the quality of additional aspects of the mortality data; details of the results are presented in Appendix B. Briefly, comparisons of the place of residence and the place of death suggested moderate mobility within the city, with 30 percent of deaths occurring outside the geographic region of residence. Examination of the medical portion of the death certificate indicated that most deaths (97.7 percent) were certified by a physician, although more than half of these physicians (57 percent) had not previously treated the person who died. The coherence of the cause-of-death information was good, with 80 percent of certificates codable using the ICD general rules. However, 20% of certificates had to be coded using other rules, indicating some problems in the order of the causes of death on the certificate. In addition, recoding of a sample of death certificates by an expert nosologist suggested that 12 percent of deaths would have been classified to a different one of the three disease categories if information concerning all causes of death were recoded.

DATA ANALYSIS

We used Poisson regression to model the daily death counts as a function of air pollution parameters, simultaneously controlling for potentially confounding covariates. The general form of the model is: $RR = \exp(\beta_1 X_1 + \beta_2 X_2 + \ldots \beta_k X_k)$, in which X_1–X_k is a vector of predictor variables with regression coefficients β_1–β_k, and RR is an estimate of the adjusted mortality rate ratio associated with a unit change in any predictor. This model assumes that mortality can be modelled as a Poisson process that generates random occurrences across time and space.

The variability of mortality is associated with temperature and with periodic phenomena related to the year, the month, the day of the week, and holidays. These periodic cycles could comprise a substantial fraction of the variance of mortality. We therefore conducted a sensitivity analysis to test different smoothed functions of time as explanatory variables in the regression model. Knotted cubic spline functions were fit to the data to directly remove the longer wavelength fluctuations (Durrlelman and Simon 1989). These are smooth functions with a variable number of inflection points (knots) that can be selected by the investigator. A sine-cosine function also was considered as an alternative function to remove long-cycle variations. To control for possible residual cyclic variation, indicator variables for month and day-of-week were tested for inclusion in the model as well. Results from regressions using these functions were compared to those using only temperature to control for long-term cycles in order to select the simplest model that explained variations in mortality. The model that best fit the mortality data by visual examination of residuals and goodness-of-fit statistics was developed before testing any contribution to mortality resulting from air pollutants.

Four different indices of temperature were tested to control for its effects: the daily minimum, maximum, and the daily average, as well as the difference between the maximum and the minimum. In addition, temperature indices with lags of one to nine days were tested. Minimum temperature with 0-day lag was the best predictor of daily mortality in Mexico City; therefore, this index was used in the analysis.

Because the validity of the results depended on the ability to control for potential confounders such as particu-

late matter, and because PM_{10} data were available only for the Central area, the statistical analysis was undertaken in the following sequence: The first step was a single time-series analysis of the Central area using measurements for the period 1991–1992. Air pollutant concentrations, in addition to temperature and the spline function of time, were used to predict total mortality, and the analysis was repeated using TSP in place of PM_{10} for days when both were available. Whether TSP is an adequate surrogate for PM_{10} was assessed by comparing the estimates of effects obtained from both analyses. Additional areas for which only TSP data were available then were studied.

The second step was to perform separate regression analyses for each of the five regions using the daily data for the period 1990–1992, but without including the particulate matter data.

In the third step, the data were analyzed for every sixth day for the period 1990–1992 for all five regions using TSP rather than PM_{10}. Separate regression coefficients were obtained for each area and the appropriateness of pooling data across sites was assessed. Then a single model incorporating the data from all areas was fitted, with area included as a fixed effect.

Total deaths were added in the fourth step, and citywide average exposures were estimated by calculating the daily mean across areas. Average values were calculated by summing values and dividing by the number of areas with valid measures. This final step allowed us to compare our results with previous studies in which deaths and air quality measurements were pooled for large regions.

Because the health effects of several days of high ozone concentrations may be cumulative, regressions were performed both with same-day ozone and covariates, and with 1- to 4-day lags of this variable; that is, using previous days' concentrations and the average of the last three days' ozone and covariates to predict today's mortality.

To identify differential effects by age, regressions were stratified by age group (all ages, under 5 years of age, and age 65 and over). However, cause-specific mortality for the three age groups was reported separately only for pooled analyses because of the small numbers produced when deaths were subdivided simultaneously by region, cause, and age.

To evaluate the evidence of a dose-response relation between daily mortality and ozone and to allow for nonlinearity, ozone concentrations were divided into quintiles, and nominal variables for those quintiles were used in the final model.

To account for serial correlation common in longitudinal data (Liang and Zeger 1993) the final models were estimated again using the iteratively weighted and filtered least-squares (IWFLS) method developed by Samet and associates (1995). This is an extension of Poisson regression designed to account for possible overdispersion and autocorrelation.

RESULTS

CENTRAL AREA, 1991–1992

Descriptive Analysis of Air Pollution and Mortality

Selected aspects of the mortality and air quality data for the Central region in 1991–1992 are shown in Table 2. The 1-hour daily maximum value of ozone was above the U.S. standard of 120 ppb (0.12 ppm) approximately 75 percent of the days. The 8-hour moving average around the maximum 1-hour value was correlated highly with peak ozone and with the 8 a.m. to 6 p.m. average (Table A.4), as the maximum value usually occurred at 2 p.m.

The median number of deaths per day from all causes was 31, of which 2 were among children under age 5, and 18 were among persons over age 65. Table 3 shows the mean and SD of the daily number of deaths by cause. The average daily number of deaths was 3 for respiratory causes, and 7 for cardiovascular causes. The mean and variance are similar, as expected under the Poisson distribution.

Total mortality peaked during the winter months as illustrated in Figure 3. The number of registered deaths for the last day of the year drops unexpectedly, probably because of problems related to registration. This phenomenon also was observed for the other regions of the city, so we eliminated the interval December 29 to January 1 from all analyses.

Illustrative time series for pollutants and temperature are shown in Figures 4 through 8. Ozone does not present any apparent seasonal trend (Figure 4). Temperature, particulate matter, and sulfur dioxide show strong seasonal variation. Minimum temperature varies from 0°C in December and January to 17°C in May. Higher levels of particulates, as measured by both PM_{10} and TSP, are present during January and February when thermal inversions typically occur in Mexico City (Figure 5). Sulfur dioxide levels peaked during December 1991. The implementation of policies dictating changes in the use of fuel oils coincided with the decrease in sulfur dioxide observed at the beginning of 1992.

Measurements of TSP for the Downtown area of Mexico City are correlated highly with PM_{10} measurements from the independent monitor (Figure 6). The PM_{10}-to-TSP ratio is approximately 0.50.

Table 2. Distribution of Daily Data on Mortality, Temperature, and Air Quality[a] in Central Mexico City, 1991–1992

Parameter[a]	Days with Valid Observations	Min.	5%	25%	50%	75%	95%	Max.
Air Quality								
Ozone, 1-hour daily maximum	715	26	63	117	154	190	250	319
Ozone, daily mean	715	12	33	49	62	73	92	130
Ozone, moving average	696	8	47	79	102	125	155	212
Ozone, 8 a.m.-6 p.m. average	712	13	47	78	100	122	152	206
Ozone, 3-day cumulative	699	96	171	251	303	352	492	564
Sulfur dioxide, daily mean	704	9	23	43	54	70	95	135
Carbon monoxide, daily mean	633	100	3289	4718	5842	7015	8856	11338
TSP	129	86	94	129	168	223	328	460
PM_{10}	384	17	42	61	78	105	166	330
Temperature								
Daily minimum	706	2.8	7.4	10.4	13.3	14.6	16.5	19.5
Mortality								
All ages	723	17	22	27	31	36	42	54
< 5 yr	723	0	0	1	2	4	6	9
> 65 yr	723	5	12	15	19	22	27	34

[a] Ozone, sulfur dioxide, and carbon monoxide in ppb; TSP and PM_{10} in $\mu g/m^3$; temperature in °C; and mortality as daily number of deaths.

Table 3. Distribution of Daily Mortality, Central Mexico City, 1991–1992

Cause of Death and Age Group	Mean[a]	Standard Deviation	Mean/Variance
Total mortality	31.61	6.31	1.25
All causes (< 5 yr)	2.50	1.61	1.04
All causes (> 65 yr)	18.08	4.65	1.20
Respiratory (all)	3.02	1.93	1.24
Respiratory (< 5 yr)	0.34	0.60	1.06
Respiratory (> 65 yr)	2.12	1.60	1.22
Cardiovascular (all)	7.83	2.92	1.08
Cardiovascular (> 65 yr)	5.85	2.55	1.11
Accidents (all)	2.61	1.73	1.14
Accidents (< 5 yr)	0.15	0.40	1.07
Accidents (> 65 yr)	0.59	0.75	0.95
Other causes (all)	20.76	4.86	1.14
Other causes (< 5 yr)	2.15	1.48	1.02
Other causes (> 65 yr)	10.11	3.32	1.09

[a] Daily number of deaths.

Basic Model for Mortality

A basic Poisson regression model was developed to account for the effects of any other periodicity in mortality data before air pollution was considered. Daily death counts were modeled as a function of temperature and several time-related variables. A spline function with six knots fit the time series well, as indicated by the lack of trend in the residuals (Figures 3 and 7). A sine-cosine function also removed the seasonal trend (Figures 8 and 9). Formal testing was not used to compare the fit of the two alternative functions, but we judged from the residuals that some nonrandom pattern still remained in mortality data when the sine-cosine function was used.

Minimum temperature fit the data as well as the knotted spline function but with fewer independent variables, yielding a more parsimonious model. A graph of residuals from a regression model with minimum temperature as the only predictor shows the removal of the seasonal pattern (Figure 10 and 11). To control for possible residual cyclic variation, indicator variables for season, month, and day-of-week effects also were tested for inclusion in the model, but they did not significantly reduce the variance. Given these results, all analyses were performed using both the minimum temperature and the spline function models to control for long-term trends in mortality. The model incorporating temperature removed the long-cycle variation using the minimum number of variables. The overdispersion parameter (McCullagh and Nelder 1989) for the basic model, adjusted for temperature, indicated 12 percent excess dispersion of mortality relative to that predicted by the Poisson model.

Correlations Among Air Quality Parameters

The crude pair-wise correlations observed between pollutants were weak. Consequently, collinearity was not ex-

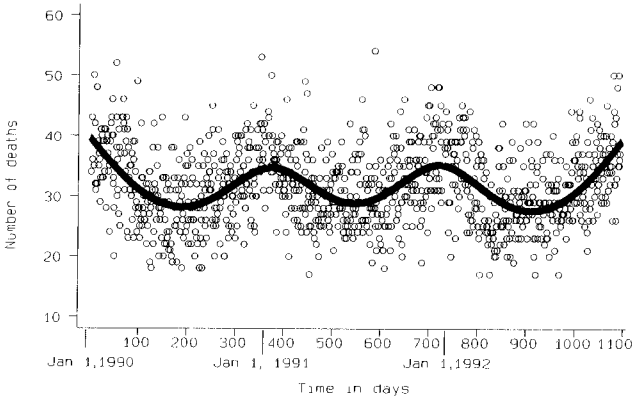

Figure 3. Time series of total mortality. Central Mexico City, 1990–1992. Each O represents one day of observation. The curved line is the result of plotting the predicted number of deaths on a given day. The data points (Δ) fall so closely together they appear to be a solid, continuous curve.

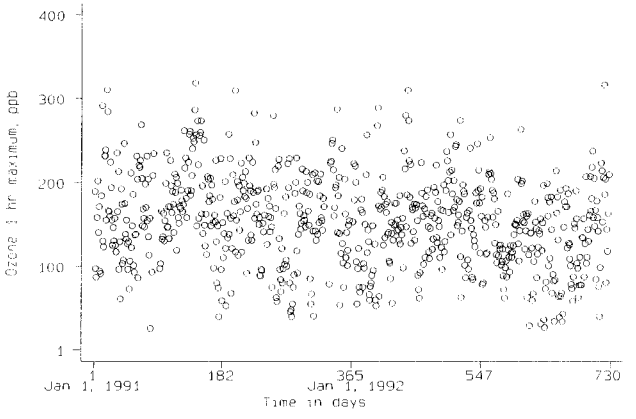

Figure 4. Time series of daily 1-hour maximum ozone levels. Central Mexico City, 1991–1992. Each O represents one day of observation.

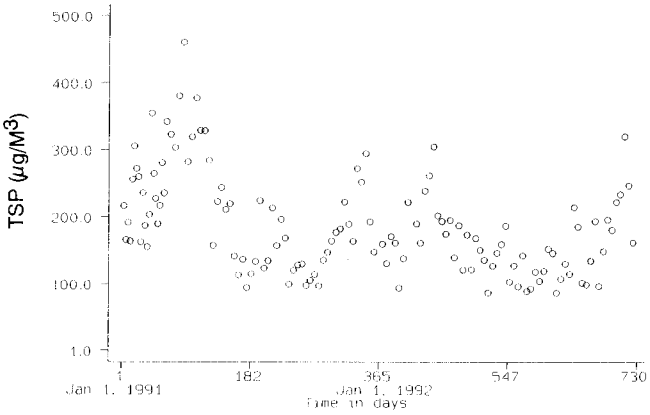

Figure 5. Time series of TSP levels. Central Mexico City, 1991–1992. Each O represents one day of observation.

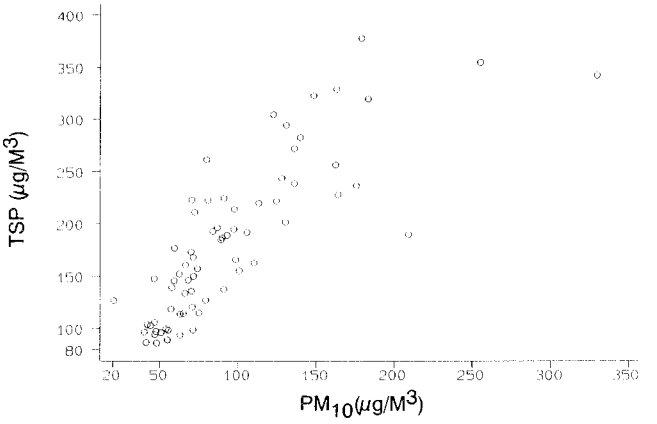

Figure 6. TSP values plotted against PM_{10} values. Central Mexico City, 1991–1992. Each O represents one day of observation.

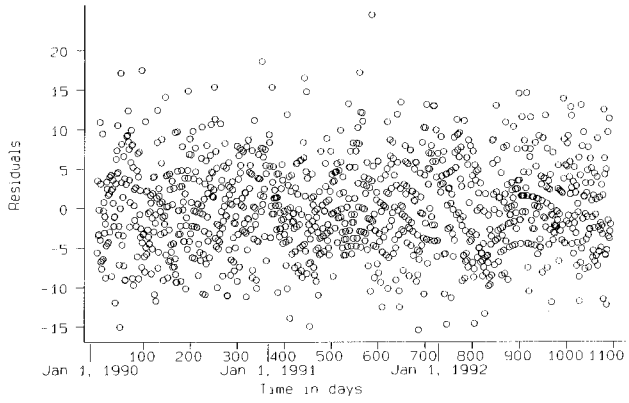

Figure 7. Residuals from regression model with a spline function of time (6 knots) as a predictor of daily mortality. Central Mexico City, 1990–1992. Each O represents one day of observation.

pected in regression models that simultaneously included total mortality and air pollutants. Table 4 shows the matrix of partial correlation coefficients among air quality indicators estimated by fitting a Poisson model that includes all pollutants. In general, the partial correlations are very small, suggesting no important problems of collinearity. Only the correlation of relative humidity with TSP was noteworthy.

Epidemiological Results

We used naive Poisson regression to estimate rate ratios for daily mortality from all causes in all ages, relative to ozone exposure for the Central area of the city in 1991–1992, restricted to days when TSP and PM_{10} data were both available in order to have comparable models (Table 5). Adjusting only for the smoothed spline function of time, a

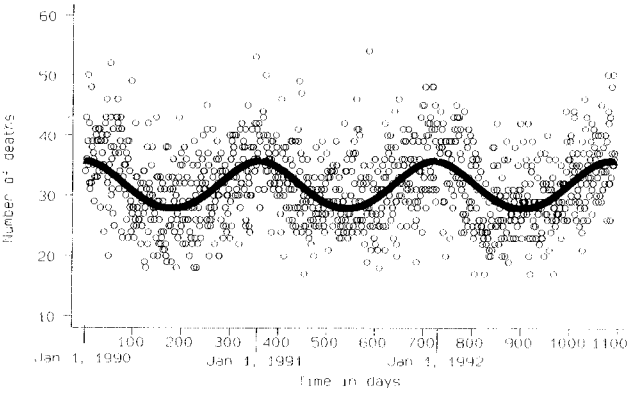

Figure 8. Crude and predicted mortality from Poisson regression model with a sine-cosine function as a predictor of daily mortality. Central Mexico City, 1990–1992. Each O represents one day of observation. The curved line is the result of plotting the predicted number of deaths on a given day. The data points (Δ) fall so closely together they appear to be a solid, continuous curve.

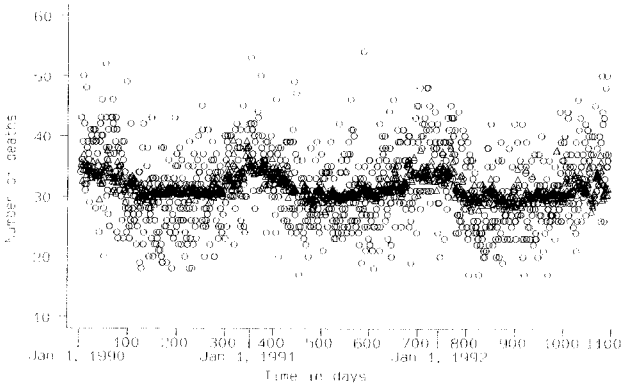

Figure 10. Observed and predicted mortality from a Poisson regression model using minimum temperature as a predictor of daily mortality. Central Mexico City, 1990–1992. O indicates observed number of deaths; Δ indicates predicted number of deaths.

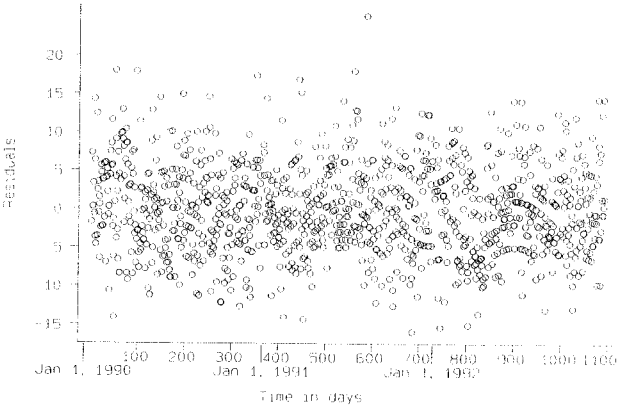

Figure 9. Residuals from a regression model with a sine-cosine function as a predictor of daily mortality. Central Mexico City, 1990–1992.

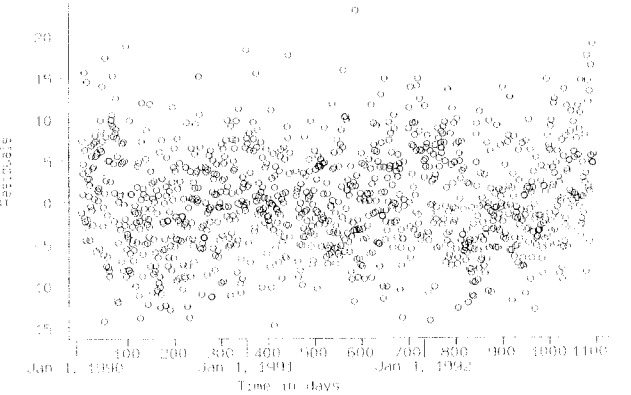

Figure 11. Residuals from a regression model using minimum temperature as a predictor of daily mortality. Central Mexico City, 1990–1992. Each O represents one day of observation.

100-ppb increase in 1-hour daily maximum ozone concentration was associated with a 3.9 percent increase in total mortality. Lower estimates of the association of ozone with total daily mortality were obtained when temperature was used instead of the spline function to control for seasonal trends. With adjustment for temperature only, a 100-ppb increase in 1-hour maximum ozone concentration was associated with an increase of 1.9 percent in mortality.

Models fitted to assess the appropriateness of using TSP instead of PM_{10} measurements (Table 5) to control for confounding by particulate exposures showed that the estimated relative risks for ozone exposure obtained when TSP was included in the model were similar. Therefore, TSP was used for other geographic areas without the risk of residual confounding by particulate matter. For the Central area of the city, adjustment for particulate exposure using daily PM_{10} values or TSP measurements on every sixth day strengthened the association of ozone with mortality; all confidence intervals included the null value, however.

Adjustment for sulfur dioxide with TSP already in the model made little difference in the association of ozone and mortality. Inclusion of relative humidity, season, and other time-related variables, such as month and day of the week, did not change point estimates of the relative risk for ozone when TSP was already in the model, but confidence intervals were wider. Inclusion of interaction terms for ozone and other pollutants did not significantly improve the fit of the model.

ALL AREAS OF MEXICO CITY, 1990–1992

Descriptive Analysis of Air Pollution and Mortality

The five areas of the city vary in population size and death rate (Table 6). The Southwest region has the largest population, followed by the Central area. Air quality also varies from area to area. The highest ozone levels were observed in the Southwest and the lowest in the Northeast. The Central area, where hospitals, government, and commerce are concentrated, has intermediate ozone levels. Concentrations of TSP were highest in the Southeast area, which is the least urbanized, with large unpaved zones providing natural sources of particulates. Note that the Xalostoc TSP monitor in the Northeast, which historically has had the highest levels of particulate matter, has been excluded because it is outside the study area defined by the DF, although it is in the industrial metropolitan area of Mexico City. Sulfur dioxide levels were higher in the Northeast area, but temperature and relative humidity were similar among all areas. Differences in spatial variations among these five areas can be appreciated from pairwise correlations (Table 7). Ozone varies from area to area. Carbon monoxide and sulfur dioxide levels are weakly correlated among areas. In contrast, particulate matter is highly correlated over time among the five areas.

Table 5. Rate Ratios for Total Mortality in Relation to 100-ppb Increase in 1-Hour Ozone Maximum, Using Alternative Model Specifications, Central Mexico City, 1991–1992[a]

Control Variables in Model	Rate Ratio[b]	95% CI
Temperature	1.019	0.945, 1.099
Spline function	1.039	0.962, 1.012
Temperature + PM_{10}	1.039	0.956, 1.233
Temperature + TSP[c]	1.041	0.918, 1.097
Spline function + PM_{10}	1.065	0.976, 1.164
Spline function + TSP	1.041	0.946, 1.148
Temperature + TSP + sulfur dioxide	1.041	0.915, 1.094

[a] n = 70 days when TSP and PM_{10} data were both available.

[b] Mortality rate ratio estimated by Poisson regression; model contains the adjustment variables indicated in addition to ozone.

[c] For illustration purposes, an example of this mathematical model is shown in Table A.5.

Table 4. Correlation Matrix of Estimated Coefficients in a Poisson Model with Temperature, Ozone, Sulfur Dioxide, Total Suspended Particulates, Carbon Monoxide, and Humidity as Predictors of Total Mortality

	Temperature	Ozone	Sulfur Dioxide	TSP	Carbon Monoxide	Humidity
Temperature	1					
Ozone	0.0303	1				
Sulfur dioxide	0.2174	−0.0939	1			
TSP	0.1070	−0.3922	−0.1892	1		
Carbon monoxide	0.2154	−0.1733	−0.0653	−0.0337	1	
Humidity	0.0623	0.0239	−0.2382	0.5261	−0.1637	1

Epidemiological Results

Epidemiological results of the analysis of the effect of ozone levels on mortality from all causes, adjusted for temperature, are presented in Table 8 for models with and without TSP to show the confounding effect of particulate matter. The inclusion of indicator variables (for season, month, day-of-week), and sulfur dioxide and carbon monoxide, did not change the estimates of the effect of ozone on mortality; estimates were similar for all areas of the city. We estimated the effect of ozone for the entire study area by including area as a fixed effect in the model, to control for differences in population size and other sociodemographic factors. The apparent ozone effect of 1% to 2% excess mortality per 100-ppb increase disappears after adjusting for TSP. Most confidence intervals include the null value, except for the rate ratios for the Northwest area, in which the confidence interval did not include a null value before adjustment for particulate matter. Similar models adjusted for cubic-spline-smoothed function of time, instead of temperature, yielded similar estimates of the effect of ozone (Table A.6).

Table 9 illustrates the effect of 1-hour maximum ozone concentration on mortality from respiratory and cardiovascular causes. There was no effect on respiratory mortality when adjustments were made for temperature and TSP. If the model is adjusted for the spline function of time and TSP, a 100-ppb increase in maximum ozone level is associated with a 4 percent excess in respiratory mortality; however, the 95 percent confidence interval includes 1.0. Rate ratios for cardiovascular deaths show a small effect of ozone exposure; a 100-ppb change in ozone exposure is accompanied by a 1 percent change in cardiovascular mortality. However, all 95% confidence intervals include 1.0.

Stratification by age group suggested some effect of ozone exposure on mortality among persons over 65 years of age but none on children under age 5 (Table 10). The association between persons over age 65 and mortality related to ozone exposure was weakened and its precision was decreased when TSP was included in the model.

The effect of ozone on total mortality increased slightly when exposure was lagged one or two days, but it decreased after the third day (Tables 11 through 13 and Tables A.7 through A.13). Similar lag effects were observed for respiratory and cardiovascular mortality. Although lagged ozone exposures appeared to have no effect on children under the age of 5, ozone exposure seemed to affect people older than age 65 more strongly. This effect achieved statistical significance when ozone was lagged one day after adjusting for TSP, regardless of the method used to control for seasonal trends.

POOLED ANALYSIS FOR ALL AREAS OF MEXICO CITY

Most previous studies have treated cities as single, homogeneous entities. For a more parsimonious analysis analogous to this approach, data from the five regions were

Table 6. Descriptive Statistics for Air Quality and Mortality Data for Five Areas in Mexico City, 1990–1992

Parameter	Southwest	Southeast	Central	Northeast	Northwest
Population size (× 1000)	2082	1968	1971	1268	881
Mean number of daily deaths	25	22	34	18	15
Mean number of daily deaths excluding accidents	22	19	32	17	14
Mean ozone 1-hour daily maximum (ppb)	177	137	148	109	140
Mean TSP ($\mu g/m^3$)	116	335	191	213	220
Mean PM_{10} ($\mu g/m^3$)	–	–	88	–	–
Mean sulfur dioxide (ppb)	49	39	56	69	51
Mean carbon monoxide (ppb)	5479	6101	6011	6002	5232
Mean relative humidity (%)	54	54	49	44	47
Mean minimum temperature (°C)	10	11	12	11	11

Table 7. Spatial Correlations of Air Pollutants Between Areas of Mexico City, 1990–1992

Pollutant	Area	Southwest	Southeast	Central	Northeast	Northwest
Ozone maximum	Southwest	1.0000				
	Southeast	0.5698	1.0000			
	Central	0.6796	0.6352	1.0000		
	Northeast	0.4602	0.4605	0.6548	1.0000	
	Northwest	0.4601	0.2913	0.5923	0.5627	1.0000
Ozone average	Southwest	1.0000				
	Southeast	0.5699	1.0000			
	Central	0.5557	0.5393	1.0000		
	Northeast	0.5369	0.6300	0.6350	1.0000	
	Northwest	0.5752	0.4301	0.4301	0.5721	1.0000
TSP	Southwest	1.0000				
	Southeast	0.7959	1.0000			
	Central	0.8685	0.8734	1.0000		
	Northeast	0.8555	0.8959	0.8959	1.0000	
	Northwest	0.8183	0.6430	0.7895	0.7438	1.0000
Minimum temperature	Southwest	1.0000				
	Southeast	0.5383	1.0000			
	Central	0.7610	0.5527	1.0000		
	Northeast	0.5578	0.4705	0.6503	1.0000	
	Northwest	0.7797	0.6286	0.8607	0.6830	1.0000
Sulfur dioxide	Southwest	1.0000				
	Southeast	0.3983	1.0000			
	Central	0.2558	0.5883	1.0000		
	Northeast	0.3541	0.4810	0.4825	1.0000	
	Northwest	−0.0694	0.0844	0.0421	0.2841	1.0000
Relative humidity	Southwest	1.0000				
	Southeast	0.4341	1.0000			
	Central	0.7864	0.4933	1.0000		
	Northeast	0.7941	0.3942	0.6689	1.0000	
	Northwest	0.3491	0.4233	0.3345	0.4348	1.0000
Carbon monoxide	Southwest	1.0000				
	Southeast	0.2587	1.0000			
	Central	0.3593	0.4733	1.0000		
	Northeast	0.2760	0.0971	0.0625	1.0000	
	Northwest	0.3948	0.1144	0.2524	0.2562	1.0000

pooled, with deaths summed to obtain a single count for each day; and air pollutants and temperature were averaged across all areas.

After adjustments were made for temperature, total mortality, cardiovascular mortality, and mortality for persons over age 65 were associated with maximum ozone concentration (Table 14). A 100-ppb increase in daily maximum ozone level was associated with an increase of 1.7 percent in total mortality, 2.7 percent in cardiovascular deaths, and almost 3 percent in mortality from all causes for persons over age 65. However, these rate ratios decreased and were no longer significant after adjusting for TSP. No changes in the estimates were observed if sulfur dioxide was added with TSP already in the model.

Similar estimates were obtained with the smoothed function of time to control for seasonal changes. A 100-ppb

Table 8. Rate Ratios for Total Mortality in Relation to 100-ppb Increase in 1-Hour Ozone Maximum, by Area, Adjusted for Temperature and TSP, Mexico City, 1990–1992[a]

Adjusted for	Region	n[b]	Rate Ratio[c]	95% CI
Temperature	Southwest	208	0.961	0.923, 1.000
	Southeast	191	0.970	0.905, 1.030
	Central	189	1.010	0.961, 1.062
	Northeast	209	1.030	0.951, 1.116
	Northwest	203	1.083	1.010, 1.150
	All	1000	1.000	0.980, 1.020
Temperature and TSP	Southwest	208	0.942	0.896, 0.980
	Southeast	191	0.970	0.990, 1.041
	Central	189	0.980	0.932, 1.041
	Northeast	209	0.970	0.887, 1.051
	Northwest	203	1.030	0.951, 1.116
	All	1000	0.980	0.961, 1.010

[a] Restricted to days when TSP data were available.

[b] Number of days of observation.

[c] Mortality rate ratio estimated by Poisson regression; model contains temperature or temperature and TSP, in addition to ozone. Model for all regions combined also includes an indicator variable for region.

Table 9. Rate Ratios for Respiratory and Cardiovascular Mortality in Relation to 100-ppb Increase in 1-Hour Ozone Maximum[a]

Adjustment Variables	n[b]	Rate Ratio[c]	95% CI
Respiratory Causes			
Temperature and TSP	1000	0.980	0.905, 1.051
Spline smoothing and TSP	1025	1.041	0.970, 1.127
Cardiovascular Causes			
Temperature and TSP	1000	1.000	0.951, 1.062
Spline smoothing and TSP	1025	1.010	0.961, 1.072

[a] Mexico City, 1990–1992, including area as a fixed effect.

[b] Number of days of observation.

[c] Mortality rate ratio estimated by Poisson regression; model contains the adjustment variables indicated, in addition to ozone and an indicator variable for region.

Table 10. Rate Ratios for All Causes of Mortality by Age Group in Relation to 100-ppb Increase in 1-Hour Ozone Maximum[a]

Control Variables	n[b]	Rate Ratio[c]	95% CI
< 5 Years of Age			
Temperature and TSP	1000	0.961	0.905, 1.030
Spline smoothing and TSP	1025	0.970	0.905, 1.041
> 65 Years of Age			
Temperature and TSP	1000	1.000	0.970, 1.041
Spline smoothing and TSP	1025	1.030	0.990, 1.072
Spline smoothing	1025	1.030	1.000, 1.072

[a] Overall estimates for Mexico City, 1990–1992, including area as a fixed effect.

[b] Number of days of observation.

[c] Mortality rate ratio estimated by Poisson regression; model contains the adjustment variables indicated, in addition to ozone and an indicator variable for region.

increase in the 1-hour maximum ozone concentration was associated with increases of 2.1 percent in total mortality, 2.3 percent in cardiovascular deaths, and 2.7 percent for deaths in persons over age 65 (Table A.14). Adding TSP to the model did not diminish the rate ratios to the same extent as in the previous models using temperature to control long-term cycles, but all confidence intervals still included the null value.

To examine the trend of the association between the number of deaths and ozone exposure, days were ranked by 1-hour maximum ozone level and divided into quintiles. These quintiles then were used as nominal variables in Poisson regression models, with the lowest quintile as the reference category. Figure 12 shows the change in total mortality by quintile of ozone level. When ozone concentration increased from 62 ppb to 217 ppb, the mortality rate increased 3.5 percent. This association disappeared after

Table 11. Rate Ratios for Total Mortality in Relation to 100-ppb Increase in 1-Hour Ozone Maximum, Lagged 0 to 4 Days and Adjusted for TSP and Temperature[a]

Lag Time (days)	Rate Ratio[b]	95% CI
0	0.980	0.961, 1.010
1	1.020	0.990, 1.041
2	1.000	0.980, 1.030
3	0.980	0.961, 1.010
4	0.990	0.970, 1.020

[a] Overall estimates for Mexico City 1990–1992, including area as a fixed effect.

[b] Mortality rate ratio estimated by Poisson regression; model contains TSP, temperature, and an indicator variable for region in addition to ozone.

Table 12. Rate Ratios for Mortality of Persons Over Age 65 in Relation to 100-ppb Increase in 1-Hour Ozone Maximum, Lagged 0 to 4 Days and Adjusted for TSP and a Spline Function of Time[a]

Lag Time (days)	Rate Ratio[b]	95% CI
0	1.030	1.000, 1.072
1	1.041	1.010, 1.072
2	1.030	0.990, 1.062
3	1.010	0.980, 1.051
4	1.030	0.990, 1.062

[a] Overall estimates for Mexico City, 1990–1992.

[b] Mortality rate ratio estimated by Poisson regression; model contains TSP, 6-knot cubic spline function, and an indicator variable for region in addition to ozone.

Table 13. Rate Ratios for Mortality of Persons Over Age 65 in Relation to 100-ppb Increase in 1-Hour Ozone Maximum, Lagged 0 to 4 Days and Adjusted for TSP and Temperature[a]

Lag Time (days)	Rate Ratio[b]	95% CI
0	1.000	0.970, 1.041
1	1.041	1.010, 1.072
2	1.030	0.996, 1.062
3	1.020	0.980, 1.051
4	1.020	0.980, 1.062

[a] Overall estimates for Mexico City, 1990–1992.

[b] Mortality rate ratio estimated by Poisson regression; model contains TSP, temperature, and an indicator variable for region in addition to ozone.

Table 14. Rate Ratios for Mortality in Relation to 100-ppb Increase in 1-Hour Ozone Maximum by Control Variables[a]

Cause or Age Group	Rate Ratio[b]	95% CI
Temperature		
Total mortality	1.024	1.011, 1.039
Respiratory causes	1.023	0.981, 1.067
Cardiovascular causes	1.036	1.006, 1.066
< 5 years of age	0.967	0.931, 1.003
> 65 years of age	1.039	1.019, 1.059
Temperature and TSP		
Total mortality	0.982	0.951, 1.014
Respiratory causes	0.981	0.890, 1.082
Cardiovascular causes	1.024	0.956, 1.096
< 5 Years of age	0.962	0.882, 1.049
> 65 Years of age	0.990	0.946, 1.036
Temperature, TSP, and Sulfur Dioxide		
Total mortality	0.982	0.950, 1.015
Respiratory causes	0.991	0.897, 1.095
Cardiovascular causes	1.019	0.950, 1.094
< 5 years of age	0.972	0.890, 1.064
> 65 years of age	0.985	0.941, 1.033

[a] All Mexico City treated as a single region, 1990–1992.

[b] Mortality rate ratio estimated by Poisson regression; model contains the control variable(s) listed in addition to ozone.

adjusting for TSP (Figure 13). As a control, we examined the effect of ozone and TSP on accidental deaths and, as expected, no association was found.

OTHER INDICES OF OZONE EXPOSURE

Tables 15 and 16 show mortality rate ratio estimates for other indices of ozone exposure. Indices of average ozone exposure generally were associated more strongly with mortality than was the 1-hour peak index. With adjustment for temperature, an increase of 100 ppb in the 24-hour average ozone concentration was associated with a 5.6 percent increase in total deaths, and estimates of excess mortality associated with the 8-hour moving average index and the 8 a.m. to 6 p.m. average were double that associated with the ozone maximum (Table 15). However, adjustment for TSP, in addition to temperature, eliminated most of these associations (Table 16).

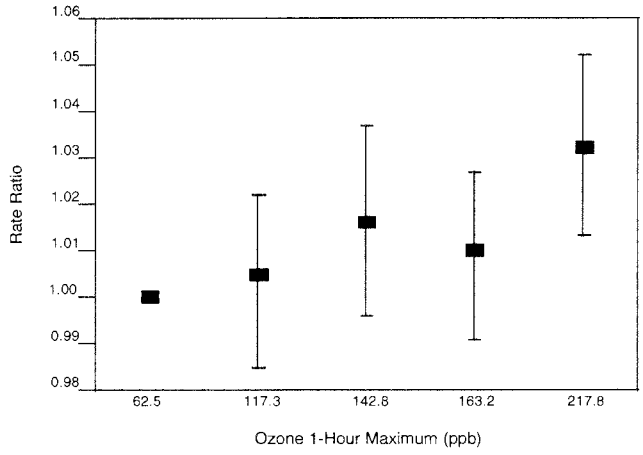

Figure 12. Rate ratios for total mortality by quintile of 1-hour maximum ozone level. Mexico City, 1990–1992.

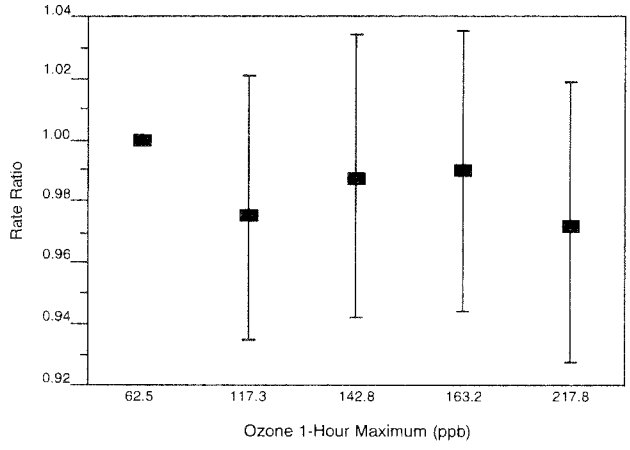

Figure 13. Rate ratios for total mortality by quintile of 1-hour maximum ozone level, adjusted for temperature, sulfur dioxide, and TSP. Mexico City, 1990–1992.

EFFECT OF OTHER AIR POLLUTANTS

Estimation of the effects of air pollutants other than ozone was not the main purpose of this study, so these pollutants were treated only as confounders in most analyses. We present data for these other pollutants to show how the association of mortality with air quality compares with results from previous studies in other cities (Table 17). The effect of other pollutants was important. The rate ratio was 1.024 (95% CI 0.984, 1.062) per 100-ppb increase in sulfur dioxide and 1.049 (95% CI 1.030, 1.067) per 100 $\mu g/m^3$

Table 15. Rate Ratios for Mortality in Relation to 100-ppb Increase in Ozone Exposure, Adjusted for Temperature[a]

Ozone Index	Rate Ratio[b]	95% CI
Total Mortality		
1-hour maximum	1.024	1.011, 1.039
24-hour average	1.058	1.022, 1.094
Moving average	1.043	1.021, 1.064
8 a.m.–6 p.m. average	1.040	1.018, 1.062
Respiratory Mortality		
1-hour maximum	1.023	0.981, 1.067
24-hour average	1.015	0.912, 1.131
Moving average	1.034	0.969, 1.101
8 a.m.–6 p.m. average	1.028	0.963, 1.093
Cardiovascular Mortality		
1-hour maximum	1.036	1.006, 1.066
24-hour average	1.121	1.042, 1.207
Moving average	1.077	1.031, 1.125
8 a.m.–6 p.m. average	1.072	1.025, 1.122
< 5 Years of Age		
1-hour maximum	0.967	0.931, 1.003
24-hour average	0.820	0.747, 0.902
Moving average	0.927	0.876, 0.980
8 a.m.–6 p.m. average	0.933	0.881, 0.988
> 65 Years of Age		
1-hour maximum	1.039	1.019, 1.060
24-hour average	1.122	1.069, 1.178
Moving average	1.074	1.043, 1.010
8 a.m.–6 p.m. average	1.069	1.038, 1.010

[a] Mexico City, 1990–1992.

[b] Mortality rate ratio estimated by Poisson regression; model contains one ozone index and minimum temperature.

increase in TSP, when these pollutants were considered in separate models. However, when all three pollutants (sulfur dioxide, ozone, TSP) were simultaneously included in the model, only the rate ratio for TSP remained greater than 1.0, indicating a statistically significant excess mortality of approximately 5 percent per 100 $\mu g/m^3$ increase in particulates (RR = 1.05, 95% CI 1.034, 1.072). No serious problems of collinearity were evident in a collinearity diagnosis, in which conditional numbers were used to assess singularity. Large values indicate near singularity, a condition in which a given term in a model provides little information, given the other terms present. All conditional numbers for the multipollutant model were below 16 (Table A.15). The trend of these associations is shown in Figure 14 by quintiles of TSP, after adjusting for minimum temperature, ozone, and sulfur dioxide.

Table 16. Rate Ratios for Mortality in Relation to 100-ppb Increase in Ozone Exposure, Adjusted for Temperature and TSP[a]

Ozone Index	Rate Ratio[b]	95% CI
Total Mortality		
1-hour maximum	0.982	0.990, 1.014
24-hour Average	0.975	0.901, 1.055
Moving average	0.999	0.953, 1.047
8 a.m.–6 p.m. average	0.992	0.946, 1.041
Respiratory Mortality		
1-hour maximum	0.981	0.890, 1.082
24-hour average	0.924	0.724, 1.179
Moving average	0.969	0.839, 1.116
8 a.m.–6 p.m. average	0.957	0.828, 1.107
Cardiovascular Mortality		
1-hour maximum	1.024	0.956, 1.096
24-hour average	1.080	0.913, 1.280
Moving average	1.066	0.964, 1.178
8 a.m.–6 p.m. average	1.072	0.969, 1.189
< 5 Years of Age		
1-hour maximum	0.962	0.882, 1.049
24-hour average	0.786	0.634, 0.973
Moving average	0.928	0.817, 1.053
8 a.m.–6 p.m. average	0.927	0.814, 1.054
> 65 Years of Age		
1-hour maximum	0.991	0.946, 1.036
24-hour average	1.025	0.918, 1.147
Moving average	1.022	0.957, 1.092
8 a.m.–6 p.m. average	1.015	0.948, 1.085

[a] Mexico City, 1990–1992.

[b] Mortality rate ratio estimated by Poisson regression; model contains one ozone index, minimum temperature, and TSP.

EXTENDED POISSON REGRESSION ANALYSIS

As a final test of the robustness of the regression results to serial correlations among the observations, the final

Table 17. Mortality Rate Ratios for a 100-Unit Increase in Ozone, Sulfur Dioxide, and TSP in Different Models, Mexico City, 1990–1992

Model and Predictors	Rate Ratio[a]	95% CI
Total Mortality		
One-pollutant model		
Ozone	1.024	1.011, 1.039
Sulfur dioxide	1.024	0.984, 1.062
TSP	1.049	1.030, 1.067
Three-pollutant model		
Ozone	0.982	0.950, 1.015
Sulfur Dioxide	1.013	0.919, 1.116
TSP	1.052	1.034, 1.072
All-Cause Mortality, Age > 65 yr		
One-pollutant model		
Ozone	1.039	1.019, 1.059
Sulfur dioxide	1.044	0.988, 1.103
TSP	1.058	1.033, 1.083
Three-pollutant model		
Ozone	0.985	0.941, 1.033
Sulfur dioxide	1.024	0.895, 1.173
TSP	1.061	1.035, 1.089

[a] Mortality rate ratio estimated by Poisson regression; model contains variables listed, in addition to minimum temperature.

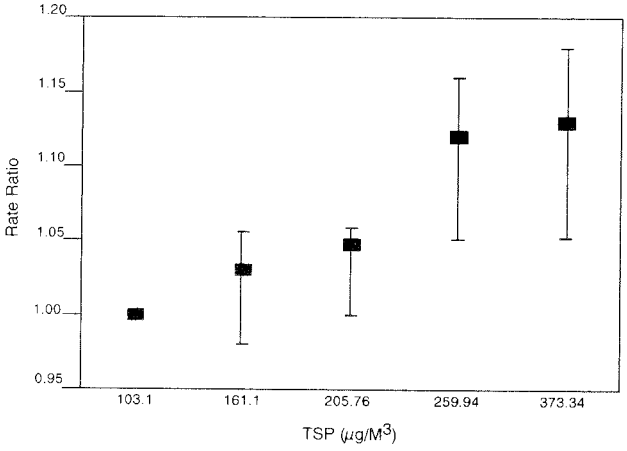

Figure 14. Rate ratios for total mortality by quintile of TSP level, adjusted for temperature, sulfur dioxide, and ozone. Mexico City, 1990–1992.

models were estimated again using the IWFLS method developed by Samet and colleagues (1995). This is an extension of Poisson regression designed to account for possible overdispersion and autocorrelation. The use of these extended models did not materially change either the point estimates of the association of mortality with air pollutants, or their precision. Table 18 shows that the effect of TSP is stronger for respiratory causes of death. The rate ratio for respiratory causes associated with an increase of 100 $\mu g/m^3$ in TSP was 1.095 (95% CI 1.013, 1.184). Exami-

Table 18. IWFLS[a] Log-Linear Regressions, Mexico City Total and Cause-Specific Mortality, 1990–1992, on 0-Day Lag

Variables in Model	Coefficient	Standard Error	Rate Ratio	95%CI
Total Mortality				
Minimum temperature	−0.01262	0.00338	0.881	0.825, 0.942
Sulfur dioxide	0.00022	0.00066	1.022	0.898, 1.163
TSP	0.00056	0.00012	1.058	1.033, 1.083
Ozone maximum	−0.00020	0.00012	0.999	0.942, 1.019
> 65 Years of Age				
Minimum temperature	−0.02221	0.00417	0.801	0.738, 0.975
Sulfur dioxide	0.00022	0.00082	1.022	0.871, 1.201
TSP	0.00056	0.00015	1.059	1.027, 1.090
Ozone maximum	−0.00010	0.00026	0.989	0.941, 1.041
Respiratory Mortality All Ages				
Minimum temperature	−0.04489	0.01065	0.638	0.518, 0.786
Sulfur dioxide	−0.00096	0.00211	0.907	0.600, 1.372
TSP	0.00091	0.00040	1.095	1.013, 1.184
Ozone maximum	0.00002	0.00064	1.002	0.885, 1.135
Cardiovascular Mortality				
Minimum temperature	−0.02198	0.00588	0.803	0.715, 0.901
Sulfur dioxide	0.00068	0.00115	1.071	0.855, 1.341
TSP	0.00051	0.00022	1.052	1.009, 1.099
Ozone maximum	0.00021	0.00038	1.021	0.948, 1.100

[a] Iteratively weighted and filtered least-squares (IWFLS) method for Poisson regression developed by Samet and associates (1995).

Table 19. IWFLS[a] Log-Linear Regressions of Mexico City Total Mortality, on 1-Day Lag, 1990–1992

Variables in Model	Coefficient	Standard Error	Rate Ratio	95% CI
Total Mortality				
Minimum temperature	−0.01222	0.00404	0.885	0.816, 0.958
Sulfur dioxide	0.00012	0.00078	1.126	0.967, 1.313
TSP	0.00025	0.00014	1.025	0.997, 1.055
Ozone Maximum	−0.00104	0.00021	0.990	0.990, 1.031
> 65 Years of age				
Minimum temperature	−0.01729	0.00453	0.840	0.770, 0.919
Sulfur dioxide	0.00088	0.00091	1.093	0.913, 1.308
TSP	0.00044	0.00017	1.045	1.045, 1.079
Ozone maximum	0.00006	0.00026	1.006	1.006, 1.059

[a] Iteratively weighted and filtered least-squares (IWFLS) method for Poisson regression developed by Samet and colleagues (1995).

nation of lags of various periods for TSP exposure indicated stronger associations for contemporary exposures and a 1-day lag (Table 19).

DISCUSSION

SUMMARY OF RESULTS

Analysis of 1990–1992 mortality statistics of the population of Mexico City shows increases in deaths when air pollution levels were elevated on the same day and on the previous day. The magnitude of the increases is small but statistically significant, especially for TSP, when Poisson regression models are used to adjust for temperature and long-term trends. For total mortality, the rate ratio associated with a 100-ppb increase in daily maximum ozone concentration was 1.029 (95% CI 1.015, 1.044). When days were ranked by quintile of maximum ozone level, the rate ratio increased with the categorical level of ozone, with a 3.5 percent excess of deaths in the highest quintile, relative to the lowest.

A moving average index of ozone was somewhat more strongly associated with total mortality (RR = 1.048, 95% CI 1.025, 1.070), and excess mortality was more evident for persons over age 65. Separate analyses of the association between ozone and mortality for different areas of the city showed similar results but they were not statistically significant. Smaller population sizes are a potential explanation for the lack of significance at this level of analysis, but lack of effect also must be considered. Stronger associations were observed in the northern areas, for which a different mixture of pollutants is a possible explanation. In these areas industrial and automotive sources of particles are predominant, so that the confounding effect of particulate matter may be stronger.

Other pollutants also were related to mortality. The rate ratio was 1.024 (95% CI 0.984, 1.062) per 100-ppb increase for sulfur dioxide and 1.054 (95% CI 1.035, 1.072) per 100- $\mu g/m^3$ increase for TSP, when these pollutants were considered in separate models. However, when all three (ozone, sulfur dioxide, and TSP) pollutants were simultaneously included in one model, only TSP remained significant, indicating excess mortality of 5 percent per 100-$\mu g/m^3$ increase in airborne particulates (RR = 1.05, 95% CI 1.033, 1.083). This is a small effect but it could be very important given the large exposed population. If we assume that the whole population is exposed, the total number of premature deaths associated with an increase of 100 $\mu g/m^3$ is approximately 2,430 for a population with 45,000 deaths per year. These findings are only for acute effects on mortality, because chronic or long-wave components were eliminated by the study design and statistical methods.

VALIDITY OF RESULTS

Although statistically significant associations were detected between mortality and air pollution, this does not by itself imply causation. Additional support is required from nonstatistical evidence, including the assessment of both internal and external validity. Measures of internal validity include the strength of the association, the evidence of a dose-response relation, a plausible temporal sequence, and freedom from bias caused by measurement error and the uncontrolled influence of extraneous factors. The assessment of external validity involves comparison of results with other studies and evaluation of scientific plausibility. The validity of epidemiological results also depends on the statistical methods used to analyze the data. The analysis of time-series data of the type used here can have two main problems: failure to control for seasonal or long-term variations in the series; and the possible existence of serial autocorrelation and overdispersion of residuals, which would invalidate the assumption that successive values are independent and have a Poisson distribution.

POTENTIAL ERRORS IN MEASUREMENT

Measurement of Exposure

All ecological studies in which measurements from fixed monitors are used to assess the human health effects of air pollution suffer from error in measuring the exposure of individuals. To conclude, using overall mortality statistics, that air pollution affects mortality, it is necessary to assess whether air pollution levels measured outdoors at fixed monitors could be affecting persons dying indoors. In Mexico City, with its mild climate, neither hospitals nor homes are tightly sealed to the outside. However, ozone is highly reactive; consequently, levels indoors are lower than levels outdoors. Reports from the southern area of Mexico City by Cortez-Lugo and associates (1993) and Perez-Neria and colleagues (1994) found ratios of ozone outdoors:indoors of 2:1 and 3.5:1, respectively. The first measurements were performed in a kindergarten, the latter in a classroom located in a hospital. This suggests that ozone concentrations measured by fixed monitors overestimate exposure, because people in Mexico City, as in other cities, spend most of their time indoors. However, people in Mexico City spend more time outdoors than people in cities elsewhere. Rojas-Bracho (1994) and Fernandez-Bremauntz and Quentin (1992) have reported that Mexico City inhabitants

spend on average 20 hours indoors, 2.76 hours outdoors, and 1.22 hours in transport each day. In contrast, Schwab and associates (1990) reported that people spend 1.16 hours outdoors in California; other authors have reported less than 1 hour spent outdoors in other locations in the U.S. (Freeman et al. 1991; Clayton et al. 1993).

It is possible that sensitive persons (the elderly and the chronically ill) stay at home on days with high air pollution and thus are less exposed than the measurements indicate. The altitude of Mexico City (2,240 m) also affects the actual dose. At sea level, 1 ppb is equivalent to 1.960 $\mu g/m^3$, whereas at Mexico City's altitude 1 ppb is equivalent to 1.489 $\mu g/m^3$. However, this difference in barometric pressure is not expected to affect the estimates of risk coefficients; it would affect only the regression constant. In addition, humans adapt to altitude by increasing ventilation, which may compensate for the decreased barometric pressure.

No information about individual activity or personal exposure was incorporated directly into this analysis. However, one of the advantages of time-series studies is that a defined population of individuals is examined over a short period of time, during which daily routines, and factors such as occupation, indoor residential exposures, diet, smoking, and exercise, are expected to be stable.

In consideration of the potential regulatory consequences of the findings from epidemiologic studies, it is important to recognize that standards are based on outdoor pollution levels measured by stationary monitors, and not on indoor levels or personal exposures. Because information on individual exposure generally is unavailable, the use of outdoor pollution levels in epidemiological studies is justified, despite the potential error in measuring the biologically-effective exposure.

Spatial misclassification of exposure is another potential source of error, because ozone levels vary across Mexico City. In order to take into account this heterogeneity of ozone concentrations, we performed separate analyses by geographic area. However, a comparison of places of residence and place of death suggested some mobility across areas. In light of this mobility, analyses of all regions of the city combined may provide a better estimate of exposure.

In general in epidemiologic studies, errors in exposure measurement can be regarded as nondifferential with respect to disease status unless there is evidence to the contrary. In this study, the units of analysis are days (or days within geographic area in some analyses), rather than individuals. Consequently, the assumption of nondifferential measurement error implies that the pattern of error in the exposure data would be the same for days with high and days with low numbers of deaths. There is no reason to suspect any other pattern, despite acknowledged imperfections in the air pollution data.

The effect on the results of errors in exposure measurement is more difficult to gauge. Attenuation of observed rate ratios toward the null is the most likely result; in studies with individuals as the units of analysis in which exposure is measured for each person, nondifferential error in measuring quantitative exposures such as air pollution attenuates rate ratios under most, but not all, circumstances (Armstrong 1990; Brenner and Loomis 1994). In an ecological study, the use of aggregate exposure data to represent the exposures of individuals may reduce this bias when the error in measuring individual exposures is large relative to the differences between persons who are grouped together. However, there also is evidence that nondifferential error in measuring some types of quantitative exposure variables in ecological studies can produce overstated associations between exposure and disease in some situations (Brenner et al. 1992). We do not have sufficient information about the nature of errors in measuring human exposure to air pollution in Mexico City to specify the direction or magnitude of any bias resulting from this source.

Measurement of Mortality

Total mortality is a well-defined outcome for which data are routinely collected and readily available for epidemiologic analysis. However, the causes of death of interest for studies evaluating the association of air pollution with mortality do not necessarily correspond to the underlying cause coded on death certificates. Further research on contributing causes of death is needed to evaluate the hypothesis that air pollutants contribute only as an additive stress to the severely ill. In this study the available data allowed assessment only of the effect of air pollution on the underlying cause of death because multiple-cause-of-death data tapes were not available. This study also did not include consideration of whether death occurred inside or outside hospitals; such an analysis could allow better estimates of exposure and control for possible effects of medical care.

Contributing causes of death and location of death were considered in a study of air pollution and mortality in Philadelphia (Schwartz 1994c), which supports the utility of such analyses. There was a substantial increase in the reports of respiratory factors as contributing causes for other underlying causes of death when air pollution levels were elevated. At those times dead-on-arrival deaths and deaths outside of hospitals and clinics also were increased

disproportionately. Indication of respiratory involvement in many of the excess cardiovascular deaths suggests that an air pollutant can be associated with such deaths. In addition, respiratory causes of death can be confused with cardiovascular causes.

EFFECTS OF OTHER FACTORS

The problem of controlling for the influence of annual, seasonal, and weekly cycles on mortality was examined using various methods to control for periodic variations. However, Poisson regression modeling with an array of smoothing techniques to control for periodic effects made little difference in the ozone parameter. Equally spaced knotted cubic splines and sine-cosine functions provided similar estimates of ozone coefficients. Nor did the results change with the addition of indicator variables for season, day of the week, and relative humidity to control for residual periodic cycles.

The use of minimum temperature only to control for these periodic trends gave comparable results. In other locations, excess mortality is associated with both high and low air temperatures (Katsouyanni et al. 1993; Kunst et al. 1993; Touloumi et al. 1994) in a J-shaped curve. Temperature in Mexico City is moderate, and extremes above 36°C or below 0°C almost never occur. Our analysis showed that mortality and temperature in Mexico City are in the descending limb of the association of temperature with mortality. Therefore, minimum temperature was used to develop the basic model of mortality. Minimum temperature had an effect only for the current day; no lag effect was observed. Secular trends in mortality also can be attributed to influenza epidemics. In this study, no information was available to control directly for possible epidemic effects.

OTHER POLLUTANTS

Other air pollutants were assessed primarily as confounders of the association of ozone with mortality. Particulate matter and sulfur dioxide were associated with both daily mortality and elevated ozone levels. However, the confounding effect of sulfur dioxide was minimal when a measure of particulate pollution was already in the model.

Error in measuring exposures to these other air pollutants can diminish the ability to control for their potential confounding effects, as well as affecting the observed association of these agents with mortality (Greenland 1980). In contrast to the large difference in the ratio of indoor-to-outdoor ozone levels, Rojas-Bracho (1994) reported a PM_{10} indoor-to-outdoor ratio of 1.054 in downtown Mexico City, suggesting that estimates of individual exposure based on fixed outdoor monitors may be more accurate for particulate matter than for ozone.

The composition of the complex mixture of air pollutants may vary from location to location and from time to time. The heterogeneity of the "crude" estimates for ozone exposure in the five areas could be attributable to differences in the composition of this mixture. The composition and size distribution of suspended particulates in Mexico City also may vary; whereas particulates in the North may come from industrial sources, in the Southeast an important component of particulate pollution may be natural sources in addition to automotive ones. The nature of particulates in Mexico City may differ from that of cities in the U.S. and Europe where previous studies have been reported. The latest such reports (for example, Schwartz 1993) have concentrated attention on the respirable fraction of particulate matter. Although we did not have data for this fraction for the entire study area, our data from the Central area, as in previous reports (Cicero-Fernandez et al. 1993), show a PM_{10}-to-TSP ratio of approximately 0.5. The composition and toxicity of the particulates remain open questions. Unfortunately, no measurements of organic compounds or nitrogen acids, which can have important roles, were available for the period studied.

The effort to examine the effect of ozone while controlling for other pollutants raises philosophical as well as technical challenges. Although statistical techniques can be used to examine one agent while artificially holding the level of others constant, this situation does not exist in nature. With epidemiological phenomena, there is indeed little theoretical justification for this approach, although making such adjustments with multivariable models is standard practice in epidemiological data analysis.

The complexity and variability of the mixtures in which pollutants coexist in urban environments also makes isolating the specific, biologically-active agents responsible for empirical associations between health endpoints and measured pollutant levels a challenging task. For example, the level of ozone is one possible index of exposure to photochemical oxidants, a mixture whose components share common sources. Ozone, as well as TSP, may be a surrogate marker for acid aerosols, which have been hypothesized to be the causal agents in the association found with increases in hospitalization rates and mortality (Thurston et al. 1994). It is possible that acid aerosols, of which sulfur dioxide is an important precursor, are a component of fine particulates. Acid aerosol measurements were not available in Mexico City during the study period.

Further challenges attend the interpretation of the relative importance of different pollutants based on empirical

relations between exposure and disease. A comparison of risk coefficients for different pollution indices is problematic, given their difference in scale and possibly different measurement errors (Ito et al. 1993). These errors include not only analytical errors, but also errors in the spatial representativeness of the samples in relation to the distribution of the exposed population.

We do not have sufficient information to characterize quantitatively these potential sources of error, but they would contribute to the total error when measuring air pollutant exposures. As noted previously, recent research on the effects of measurement error in epidemiological studies suggests that whether the total error in measuring exposure is entirely random or partially systematic, its most likely effect is to attenuate the apparent association between human exposure to air pollutants and mortality (Armstrong 1990; Brenner and Loomis 1994; Weinberg et al. 1994; Wacholder 1995). The apparent differences in magnitude and precision of pollutant coefficients may result from variable measurement quality for the respective pollutants. In particular, the more precise estimate for particulates may result in part from the stronger spatial correlations, which lead to better estimates of aggregate exposure for particles relative to gases, and yield less attenuated regression coefficients. The influence of errors in exposure measurement can not be ascertained directly without a thorough evaluation of analytical errors and a detailed assessment of individual air pollution exposures.

STATISTICAL CONSIDERATIONS

The small overdispersion and autocorrelation of the residuals in the final regression models suggested a good fit to standard Poission models, which assume independence of observations. Temporal autocorrelation was diminished further when TSP was included in the model, as data for this pollution parameter were available only for every sixth day. The statistical effect of serial correlation between observations was addressed directly by refitting the final Poisson regression models with modifications to allow for autocorrelation and overdispersion. In contrast with other studies in which autocorrelation of the observations has been reported as important, the use of these analytical procedures made little difference in the results.

COMPARISON WITH PREVIOUS EPIDEMIOLOGICAL STUDIES

Although the specific biological mechanism for acute increases in mortality associated with elevated ozone levels has not been demonstrated, the empirical consistency with which elevated ozone levels are accompanied by acute increases in morbidity measures enhances the plausibility of an association with mortality (Lippmann 1993; Marks 1994). Exposure to ozone has been associated with transient adverse effects in healthy persons, with adverse effects in individuals with respiratory disease, and with increases in hospital and emergency room visits. Elevated atmospheric ozone has been associated with increases in the frequency of hospital and emergency room visits in Ontario, Canada (Bates and Sizto 1983; Bates and Sizto 1987; Lipfert and Hammerstrom 1992; Burnett et al. 1994; Thurston et al. 1994), hospital visits for asthma in New Jersey (Cody et al. 1992), respiratory hospital admissions in New York (Thurston et al. 1992), and hospital admissions for pneumonia in Minnesota (Schwartz 1994b) and Birmingham, Alabama (Schwartz 1993).

The results of our study are broadly consistent with reports indicating positive associations between daily changes in mortality and ozone levels in Los Angeles and New York (Kinney and Ozkaynak 1991, 1992). As in Kinney and Ozkaynak's (1991) study in Los Angeles, we found that total noninjury mortality and cardiovascular mortality were associated with daily ozone levels. In addition, the association in both studies was strongest when ozone concentration was lagged by one day, suggesting the possibility that some biological effect of ozone persists for at least a short time. However, in our study the association of mortality with ozone was diminished by adjusting for exposure to particulate pollutants. Kinney and Ozkaynak adjusted for nitrogen dioxide, but not particulate exposures.

No association with mortality was reported in two other studies of air pollution in which ozone was considered. Our results are in general agreement with a recent study in São Paolo, Brazil, which indicated that daily respiratory mortality among infants was not associated with ozone levels (Saldiva et al. 1994); we found no evidence of excess mortality among children under age five. Our findings are more challenging to reconcile with data reported by Dockery and colleagues (1992). Their study showed no evidence of association between mortality and exposure to ambient ozone; however, the range of ozone concentrations was small (mean concentration 22 ppb), relative to Mexico City, in the areas they studied. Previous epidemiological studies treated areas under consideration as single regions and did not characterize geographical heterogeneity of exposure to air pollutants within them. In addition, they generally included fewer deaths (that is, smaller populations) and therefore had less statistical power than the present study.

The diversity of the epidemiological findings to date highlights some of the challenges that attend research concerning the human health effects of ambient ozone. Al-

though much is known about the transient effects of ozone from experimental studies, it can be difficult to translate conclusions from the simple, controlled conditions of the laboratory to the complex environments in which humans live. Exposures to ozone and other agents occur simultaneously and their effects on health may be intertwined. The complexity and variability of the mixtures in which pollutants coexist in urban environments makes isolating the specific, biologically-active agents responsible for empirical associations between health endpoints and measured air pollutant levels a challenging task. All studies to date have used aggregate estimates of outdoor pollution levels from routine air quality monitoring programs to indicate exposure. Data of this type may not be adequate to disentangle the complexities involved, however.

The mechanisms by which air pollutants, including ozone, might cause mortality generally can not be determined with epidemiological methods. Some epidemiological studies indicate that short-term increases in atmospheric ozone concentration lead to higher rates of serious, nonfatal disease, as indicated by hospital admissions for respiratory and other diseases. Studies of chronic, nonfatal health conditions, such as the development of chronic respiratory conditions, would help to resolve key uncertainties about the importance of human exposures to ozone by defining the middle ground between the known transient effects of ozone and the suggestive results of the few existing studies of ozone in connection with more serious outcomes, including mortality. In addition, epidemiological studies of mortality and ambient ozone exposures have focused on short-term relations. Although short-term human exposures to ozone are known from experimental and epidemiological studies to have a variety of acute, reversible health effects, the effects of long-term exposures have not been studied. Follow-up studies of serious health outcomes in relation to long-term exposures might help to define the consequences of living in environments with chronically elevated ozone levels, such as those that exist in Mexico City and some other urban areas. Neither type of study has been conducted to date.

In contrast to uncertainties about the health effects of ozone, the consistent association of airborne particulates with increased mortality across a number of cities, despite potential differences in the mixture of pollutants and in populations, is impressive. One important difference, along with smoking habits, quality of health care, housing, and supporting infrastructure, is demographic. The crude death rate in Mexico City is much lower than that in the U.S. because the young population is a larger percentage of the whole in Mexico than it is in the U.S. This difference has been observed in other locations in Latin America (Ostro et al. 1996). In a metanalysis, Schwartz (1994a) reported an estimate of the rate ratio of 1.06 (95% CI = 1.04, 1.07) for an increase in TSP mass, which is essentially identical to the rate ratio of 1.05 per 100 $\mu g/m^3$ observed for TSP in this study. This result, similar to those of numerous other studies (Dockery et al. 1992; Schwartz 1993, 1994b,c; Spix et al. 1993), is particularly noteworthy considering the small quantity and possibly poor quality of the particulate data; in contrast to the daily measurements of PM_{10}, TSP data were available only on every sixth day.

CONCLUSIONS

This study provided clear evidence that mortality is related to air pollution levels in Mexico City. The magnitude of the excess mortality associated with air pollution indicators was small but statistically significant after adjustment for temperature and long-term trends. Associations with pollution were strongest on the day before and on the date of death, and among the elderly.

Exposure to ozone was associated with an increase of 3 to 5 percent in total mortality for each 100-ppb increase in ambient ozone concentration. Total suspended particulates and sulfur dioxide were associated with mortality to a similar degree. However, neither ozone nor sulfur dioxide had an effect on mortality that was statistically independent of particulate pollutant levels. The excess mortality independently associated with particulate pollution was similar to that observed in other cities in the U.S. and Europe.

The composition of ambient air pollution is extremely complex and variable over time and space, and so are the conditions under which people are exposed to it. Although laboratory or statistical methods can be used to estimate an effect of one pollutant while artificially holding the levels of others constant, the scientific validity of such attempts to isolate the effect of a single pollutant requires careful consideration. Such a model does not appear realistic when people are exposed to complex mixtures, and it may be impossible to attribute the true effects of air pollution to any single agent.

In light of these challenges, we could not resolve whether high ambient ozone levels would have an important effect on mortality when particulate pollutant levels were reduced. However, with the large population exposed to ambient air pollution in Mexico City and other metropolises throughout the world, the small but significant associations we observed between mortality and air pollution indices are of public health concern. This study provides further support for efforts to control air pollution levels, especially particulate concentrations.

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APPENDIX A. Supplemental Data

Table A.1. Population Size by Delegacion, Mexico City, 1990[a]

Delegacion	Total	Men	Women
Distrito Federal			
Azcapotzalco	474,688	228,420	246,268
Coyoacan	640,066	302,047	338,019
Cuajimalpa de Morelos	119,669	58,333	61,336
Gustavo A. Madero	1,268,068	612,459	655,609
Iztacalco	448,322	215,749	232,573
Iztapalapa	1,490,499	730,466	760,033
Magdalena la Contreras	195,041	93,603	101,438
Milpa Alta (excluded)	3,654	1,710	31,944
Alvaro Obregon	642,753	307,118	335,635
Tlahuac	206,700	102,060	104,640
Tlalpan	484,866	234,335	250,531
Xochimilco	271,151	133,679	137,472
Benito Juarez	407,811	179,713	228,098
Cuauhtemoc	595,960	277,812	318,148
Miguel Hidalgo	406,868	184,949	221,919
Venustiano Carranza	519,628	247,458	272,170
State of Mexico (not included in analysis)			
Atizapan	5,339	2,646	2,693
Ecatepec	1,218,135	600,410	617,725
Huixquilucan	131,926	62,406	69,520
Naucalpan de Juarez	786,551	387,272	399,279
Nezahualcoyotl	1,256,115	615,947	640,168
Tlalnepantla de Baz	702,807	343,974	358,833
Tultitlan	246,464	121,678	124,786

[a] Source: Instituto Nacional de Estadística, Geografía e Informática.

Table A.2. Characteristics of Air Pollution Monitoring System in Mexico City

Pollutant	Method	Frequency of Measurement
Ozone (ppb)	Ultraviolet photometry (thermoelectron)	Hourly
Carbon monoxide (ppb)	Nondispersive infrared photometry (NDR thermoelectron)	Hourly
Sulfur dioxide (ppb)	Pulsant fluorescence (thermoelectron)	Hourly
Nitrogen oxides (ppb)	Chemiluminescence (thermoelectron)	Hourly
Total suspended particles ($\mu g/m^3$)	Gravimetric (high-volume sampler)	Every 6 days
Particulate matter with aerodynamic diameter < 10 μm ($\mu g/m^3$)	Gravimetric measurement (Andersen)	Daily

Table A.3. Missing and Assigned Ozone Values by Year and Monitor

Year	Monitor Station	Maximum Consecutive Days with Missing Values	Total Number of Days with Missing Values	Assigned Values
1990	Azcapotzalco	365	365	0
	Tlanepantla	29	101	0
	Xalostoc	40	98	0
	C. de la Estrella	20	58	57
	Pedregal	22	39	39
	Plateros	12	51	50
	Merced	4	12	11
	Hangares	365	365	0
1991	Azcapotzalco	155	231	0
	Tlanepantla	21	48	43
	Xalostoc	25	87	79
	C. de la Estrella	10	35	26
	Pedregal	7	20	15
	Plateros	8	41	32
	Merced	18	89	81
	Hangares	10	50	40
1992	Azcapotzalco	15	51	50
	Tlanepantla	13	105	0
	Xalostoc	8	48	47
	C. de la Estrella	17	53	53
	Pedregal	4	44	44
	Plateros	7	39	38
	Merced	15	77	76
	Hangares	20	78	77

Table A.4. Correlation Matrix of Different Ozone Indices

	1-Hour Maximum	24-Hour Average	Moving Average	8 a.m.–6 p.m. Average	3-Day Cumulative Average
1-Hour Maximum	1.0000				
24-Hour Average	0.7715	1.0000			
Moving Average	0.9280	0.8806	1.0000		
8 a.m.–6 p.m. Average	0.9143	0.8943	0.9801	1.0000	
3-Day Cumulative Average	0.6929	0.7748	0.7796	0.7898	1.0000

Table A.5. Poisson Regression Results for Total Mortality: Central Mexico City, 1991–1992

Variable	Coefficient	Standard Error	z	P>|z|	95% CI
Ozone maximum	0.0000437	0.0004543	0.096	0.923	−0.0008466, 0.0009341
Temperature	−0.0232563	0.007594	−3.062	0.002	−0.0381403, −0.0083723
TSP	0.0002457	0.0004184	0.587	0.557	−0.0005742, 0.0010657
Prepost[a]	−0.0437138	0.0666652	−0.656	0.512	−0.1743751, 0.0869475
Constant	3.716907	0.1337629	27.787	0.000	3.454736, 3.979077

[a] Prepost = dummy variable for the two periods of ozone measurements; $n = 70$.

Table A.6. Rate Ratios for Total Mortality in Relation to 100-ppb Increase in 1-Hour Ozone Maximum, 0-Day Lag, by Area, Adjusted for a Spline Function of Time and TSP, Mexico City, 1990–1992[a]

Adjusted for	Region	Number of Days	Rate Ratio[b]	95% CI
Smoothing spline	Southwest	211	0.980	0.942, 1.030
	Southeast	206	0.990	0.932, 1.062
	Central	191	1.020	0.980, 1.072
	Northeast	211	1.030	0.951, 1.105
	Northwest	206	1.072	0.990, 1.150
	All	1025	1.010	0.990, 1.041
Smoothing spline and TSP	Southwest	211	0.990	0.914, 1.010
	Southeast	206	0.990	0.932, 1.062
	Central	191	1.010	0.961, 1.072
	Northeast	211	1.010	0.932, 1.105
	Northwest	206	1.051	0.980, 1.139
	All	1025	1.010	0.980, 1.030

[a] Restricted to days when TSP data were available.

[b] Mortality rate ratio estimated by Poisson regression; model contains a smoothing spline function or a smoothing spline function and TSP, in addition to ozone. Model for all regions combined also includes an indicator variable for region.

Table A.7. Rate Ratios for Total Mortality in Relation to 100-ppb Increase in 1-Hour Ozone Maximum, Lagged 1 to 4 Days, Adjusted for TSP and a Spline Function of Time[a]

Lag Time (days)	Rate Ratio[b]	95% CI
0	1.010	0.980, 1.030
1	1.020	0.990, 1.041
2	1.010	0.980, 1.030
3	0.980	0.961, 1.010
4	1.010	0.980, 1.030

[a] Overall estimates for Mexico City, 1990–1992, including area as a fixed effect.

[b] Mortality rate ratio estimated by Poisson regression; model contains 6-knot cubic spline, TSP, and an indicator variable of region, in addition to ozone.

Table A.8. Rate Ratios for Respiratory Mortality in Relation to 100-ppb Increase in 1-Hour Ozone Maximum, Lagged 1 to 4 Days, Adjusted for TSP and a Spline Function of Time[a]

Lag Time (days)	Rate Ratio[b]	95% CI
0	1.041	0.970, 1.127
1	1.041	0.970, 1.116
2	0.951	0.887, 1.030
3	1.020	0.951, 1.105
4	1.041	0.970, 1.127

[a] Overall estimates for Mexico City, 1990–1992, including area as a fixed effect.

[b] Mortality rate ratio estimated by Poisson regression; model contains 6-knot cubic spline, TSP, and an indicator variable of region, in addition to ozone.

Table A.9. Rate Ratios for Respiratory Mortality in Relation to 100-ppb Increase in 1-Hour Ozone Maximum, Lagged 1 to 4 Days, Adjusted for TSP and Temperature[a]

Lag Time (days)	Rate Ratio[b]	95% CI
0	0.980	0.905, 1.051
1	1.041	0.970, 1.116
2	0.951	0.878, 1.020
3	1.020	0.951, 1.105
4	1.020	0.942, 1.090

[a] Overall estimates for Mexico City, 1990–1992, including area as a fixed effect.

[b] Mortality rate ratio estimated by Poisson regression; model contains temperature, TSP, and an indicator variable of region, in addition to ozone.

Table A.10. Rate Ratios for Cardiovascular Mortality in Relation to 100-ppb Increase in 1-Hour Ozone Maximum, Lagged 1 to 4 Days, Adjusted for TSP and a Spline Function of Time[a]

Lag Time (days)	Rate Ratio[b]	95% CI
0	1.010	0.961, 1.072
1	1.030	0.980, 1.083
2	1.010	0.961, 1.062
3	1.000	0.942, 1.051
4	1.000	0.942, 1.051

[a] Overall estimates for Mexico City, 1990–1992, including area as a fixed effect.

[b] Mortality rate ratio estimated by Poisson regression; model contains 6-knot cubic spline, TSP, and an indicator variable of region, in addition to ozone.

Table A.11. Rate Ratios for Cardiovascular Mortality in Relation to 100-ppb Increase in 1-Hour Ozone Maximum, Lagged 1 to 4 Days, Adjusted for TSP and Temperature[a]

Lag Time (days)	Rate Ratio[b]	95% CI
0	1.000	0.951, 1.062
1	1.041	0.980, 1.094
2	1.030	0.970, 1.083
3	1.010	0.961, 1.062
4	1.000	0.942, 1.051

[a] Overall estimates for Mexico City, 1990–1992, including area as a fixed effect.

[b] Mortality rate ratio estimated by Poisson regression; model contains temperature, TSP, and an indicator variable of region, in addition to ozone.

Table A.12. Rate Ratios for Mortality of Children Under Age 5 in Relation to 100-ppb Increase in 1-Hour Ozone Maximum, Lagged 1 to 4 Days, Adjusted for TSP and a Spline Function of Time[a]

Lag Time (days)	Rate Ratio[b]	95% CI
0	0.970	0.905, 1.041
1	0.970	0.914, 1.041
2	0.990	0.923, 1.062
3	1.010	0.942, 1.072
4	1.020	0.951, 1.083

[a] Overall estimates for Mexico City, 1990–1992, including area as a fixed effect.

[b] Mortality rate ratio estimated by Poisson regression; model contains 6-knot cubic spline, TSP, and an indicator variable of region, in addition to ozone.

Table A.13. Rate Ratios for Mortality of Children Under Age 5 in Relation to 100-ppb Increase in 1-Hour Ozone Maximum, Lagged 1 to 4 Days, Adjusted for TSP and Temperature[a]

Lag Time (days)	Rate Ratio[b]	95% CI
0	0.961	0.905, 1.030
1	0.970	0.905, 1.030
2	0.970	0.905, 1.030
3	0.990	0.932, 1.062
4	1.010	0.951, 1.083

[a] Overall estimates for Mexico City, 1990–1992, including area as a fixed effect.

[b] Mortality rate ratio estimated by Poisson regression; model contains temperature, TSP, and an indicator variable of region, in addition to ozone.

Table A.14. Rate Ratios for Mortality in Relation to 100-ppb Increase in 1-Hour Ozone Maximum, with 0-Day Lag and Adjusted for a Spline Function of Time[a]

Cause of or Age Group for Mortality Data	Rate Ratio[b]	95% CI
Spline Function		
Total mortality	1.022	1.007, 1.037
Respiratory	1.027	0.982, 1.074
Cardiovascular	1.023	0.993, 1.055
< 5 years of age	0.995	0.957, 1.036
> 65 years of age	1.028	1.008, 1.049
Spline Function and TSP		
Total mortality	1.009	0.974, 1.044
Respiratory	1.066	0.960, 1.184
Cardiovascular	1.030	0.958, 1.108
< 5 years of age	1.013	0.922, 1.113
> 65 years of age	1.021	0.973, 1.072
Spline Function, TSP, and Sulfur Dioxide		
Total mortality	1.009	0.973, 1.045
Respiratory	1.072	0.964, 1.195
Cardiovascular	1.027	0.953, 1.106
< 5 years of age	1.026	0.932, 1.131
> 65 years of age	1.017	0.969, 1.069

[a] Mexico City, 1990–1992.

[b] Mortality rate ratio estimated by Poisson regression; model contains listed variables, and an indicator variable of region, in addition to ozone.

Table A.15. Collinearity Diagnostics in a Poisson Regression Model Including Minimum Temperature, Ozone, TSP, and Sulfur Dioxide

Component	1	2	3	4	5
Eigenvalues	0.020	0.064	0.070	0.154	4.692
Conditional numbers	15.321	8.558	8.162	5.522	1.000
Constant	0.967	0.003	0.027	0.001	0.001
Ozone maximum	0.004	0.820	0.167	0.005	0.004
Sulfur dioxide	0.034	0.422	0.540	0.000	0.004
Temperature	0.633	0.000	0.143	0.221	0.003
TSP	0.456	0.029	0.226	0.285	0.004

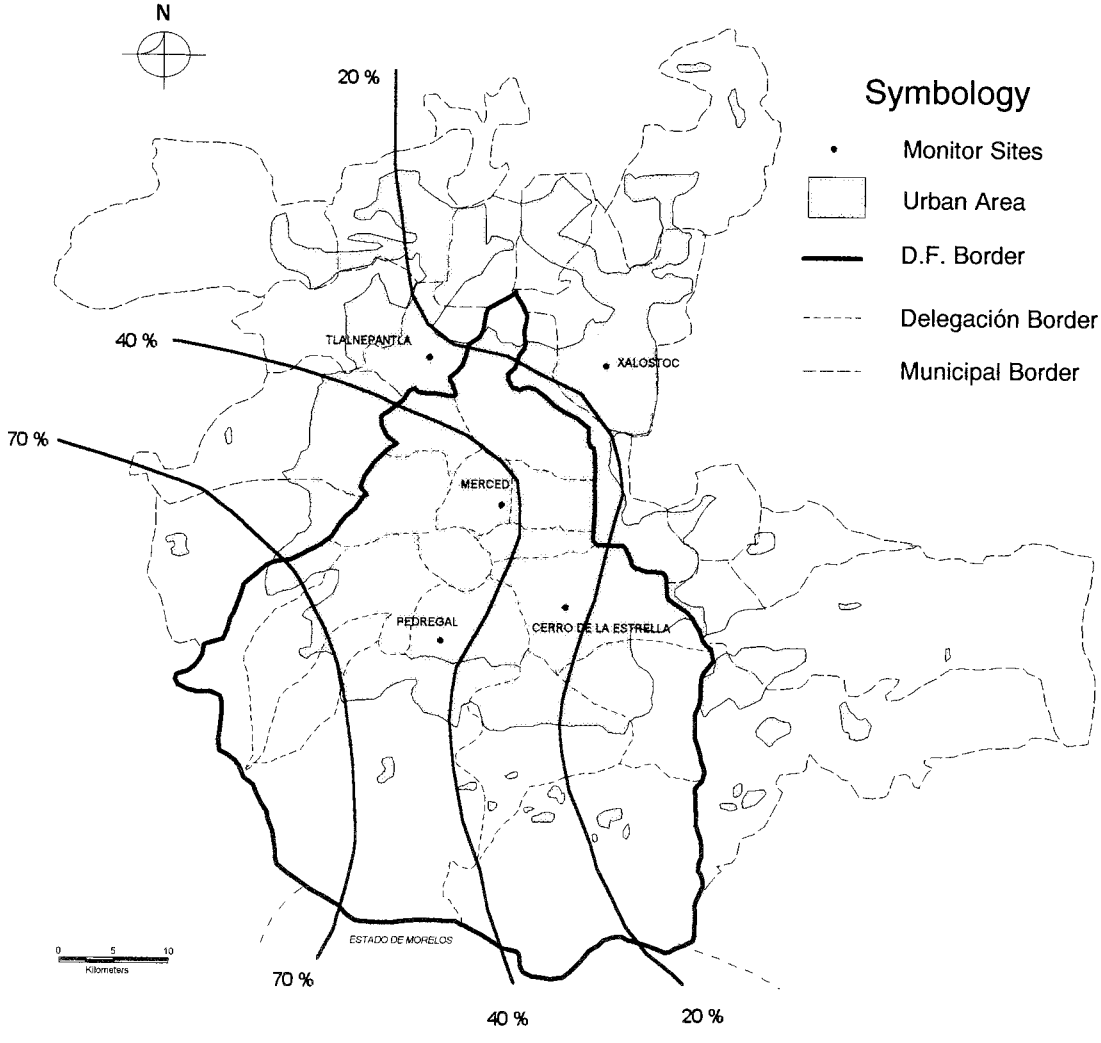

Figure A.1. Isopleths showing the spatial distribution of days above the ozone standard in Mexico City metropolitan area, 1990.

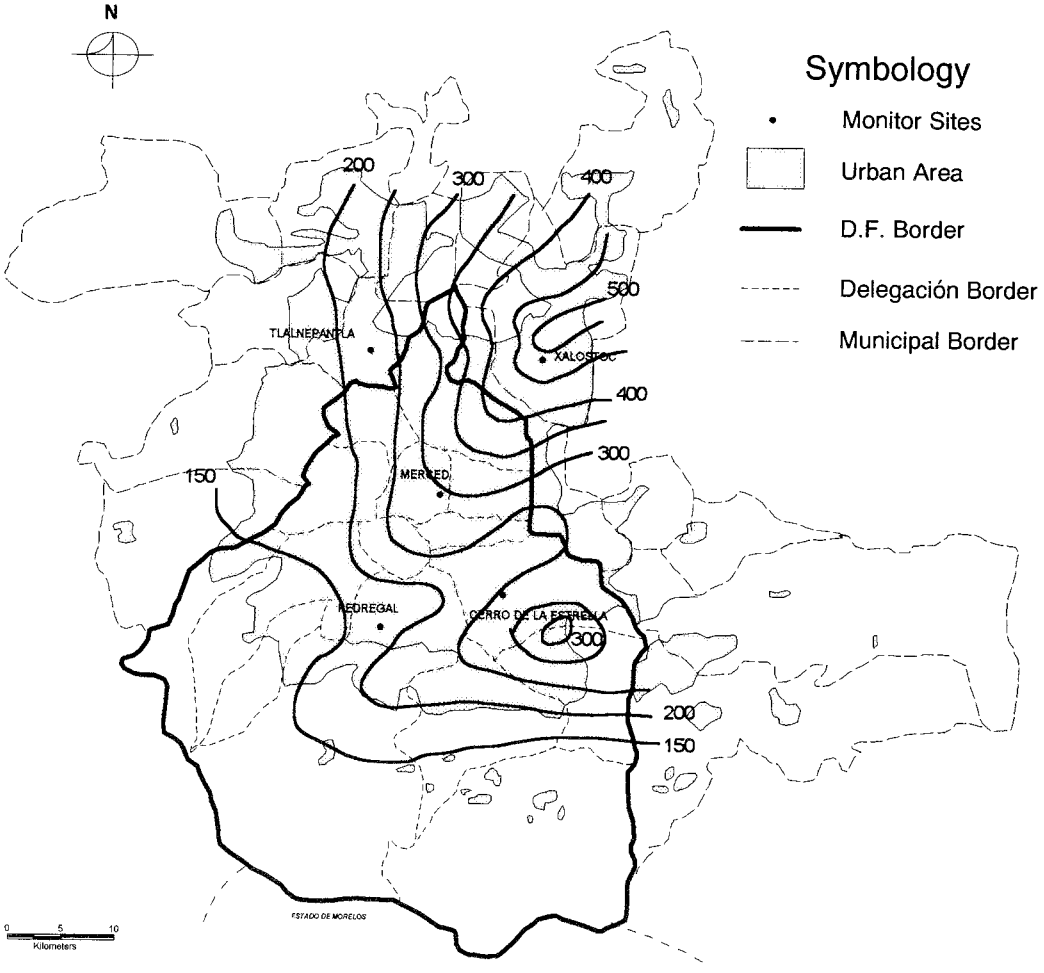

Figure A.2. Isopleths showing spatial distribution of TSP in Mexico City metropolitan area. Annual geometric mean.

APPENDIX B. Quality of Mortality Data

The quality of mortality data was assessed in two different ways for the purposes of this study: recoding and analysis of the content of a sample of death certificates, and checking for possible misclassification among geographic regions.

We assessed the extent of spatial misclassification by comparing the region of residence to the region where death occurred (Table B.1). Most deaths (about 70 percent) occurred in the region of residence. However, some 30 percent occurred in a different region, suggesting mobility across areas. Substantial mobility potentially could lead to misclassification of exposure, given that the exposure metric for the contaminants was assigned by area of residence. Residents of the Central region tended to die outside their region of residence somewhat less frequently than did people residing in other parts of the city. However, when residents of other regions died outside their residential area, the deaths most frequently occurred in the Central region.

The ideal assessment of the quality of cause-of-death information would be a comparison of the diagnoses stated on death certificates with those determined at autopsy. Because the frequency of autopsies in Mexico City is very low, this was not possible. Another technique is to compare the diagnosis with medical files. However, we were not allowed to search medical records in a representative sample. As an alternative, the quality of the information on death certificates was assessed in a random sample of 571 certificates from 1991 and 1994 (Table B.2). These two years were selected in order to assess trends in the quality of death certification over the study period. Variables for this evaluation included place of death (home, hospital, other), whether medical attention was received (yes or no), and the profession of death certifier (treating physician, medical examiner, other physician, or unknown). We applied the ICD-9 rules for coding the underlying cause of death in terms of the order and timing of pathologies stated in the death certificate to evaluate the internal coherence of diagnosis.

In addition to problems related to medical certification of cause of death, misclassification also might occur during the certificate coding process. We evaluated potential misclassification in our random sample of death certificates by comparing codes assigned by the most experienced Mexican specialist in ICD-9 coding with those assigned by the regular process followed in Mexico.

In contrast with previous reports, we found that almost half of the deaths did not occur in the hospital. However, most individuals did receive medical attention during their final illness. The majority of deaths (57 percent) were certified by a physician, typically hospital house staff, who had not treated the patient. Another 37 percent of deaths were certified by the treating physician, 3 percent were certified by medical examiners, and certifier information was missing for 2 percent.

Analysis of the internal coherence indicated that approximately 80 percent of the death certificates sampled could be coded using ICD-9 general rules, which is indicative of relatively good quality of certification. When we compared the existing codes for the underlying cause of death with the codes assigned by our expert, 140 of the 571 certificates were at variance. Given the grouped analysis of causes previously defined, most of the variation is irrelevant to this study. However, 12 percent of these variations would change the categories of disease of interest. The second reviewer was most likely to code to "other causes" rather than respiratory or cardiovascular diseases.

Table B.1. Percent Distribution of Deaths by Region of Residence and Region Where Death Occurred, Mexico City, 1988–1992

	Region Where Death Occurred						
Region of Residence	Southeast	Southwest	Central	Northeast	Northwest	Other	Total
Southeast	72.1	1.2	19.3	1.2	6.2	0.2	100
Southwest	10.2	62.1	22.1	1.4	3.9	0.3	100
Central	0.6	3.2	76.3	4.4	8.9	4.5	100
Northeast	3.1	1.1	12.5	70.6	12.5	0.1	100
Northwest	5.3	0.5	13.7	4.6	75.6	0.2	100

Table B.2. Selected Characteristics of a Sample of 571 Death Certificates, Mexico City 1991 and 1994

Characteristic	Number	Percent
Place of death		
Medical unit	306	53.6
Home	246	43.1
Other place	12	2.1
No information	7	1.2
Received medical attention during last disease		
Yes	541	94.7
No	25	4.4
No information	5	0.9
Person who certified the death		
Treating physician	213	37.3
Medical examiner	17	3.0
Other physician	328	57.4
No information	13	2.3
Total	571	100.0

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PUBLICATIONS RESULTING FROM THIS RESEARCH

Borja-Aburto VH, Loomis DP, Shy CM, Bangdiwala S. 1995. Air pollution and daily mortality in Mexico City (abstract). Epidemiology 6(Suppl):S64.

Borja-Aburto VH, Loomis DP, Shy CM, Bangdiwala SI, Rascon-Pacheco RA. 1996. Ozone, suspended particulates, and daily mortality in Mexico City. Am J Epidemiol (in press).

ABBREVIATIONS

CI	confidence interval
DDF	Departamento Distrito Federal
DF	Distrito Federal
EPA	U.S. Environmental Protection Agency
ICD	International Classification of Diseases
IWFLS	iteratively weighted and filtered least-squares analysis
ppb	parts per billion
ppm	parts per million
RR	rate ratio
TSP	total suspended particulates
PM_{10}	particulate matter < 10 μm in diameter

INTRODUCTION

Fossil fuel combustion by motor vehicle and industrial sources produces a number of atmospheric pollutants, including ozone, volatile organic compounds, sulfur and nitrogen oxides, and particles as well as secondary particulate matter such as acid aerosols (U.S. Environmental Protection Agency 1991, 1993). Because many of these pollutants have the potential to cause health effects, the U.S. Environmental Protection Agency (EPA)* sets standards for a variety of pollutants under Section 109 of the Clean Air Act of 1991, which provides for the establishment of National Ambient Air Quality Standards (NAAQS) to protect the public health. This Section also requires periodic review and, if appropriate, revision of the NAAQS and of the air quality criteria on which they are based.

Currently, the EPA Administrator is considering new standards for ozone and particulate matter that will be finalized in mid-1997 (Nichols 1996). For ozone, the Administrator is considering the recommendation of the EPA staff that the current one-hour standard be replaced with an eight-hour standard in the range of 70 to 90 parts per billion (ppb). For particulate matter, the Administrator is giving preliminary consideration to a new standard that would regulate the coarse and fine particles that compose the fraction of particulate matter having an aerodynamic diameter of less than or equal to 10 microns (PM_{10}).

It is well known that severe air pollution episodes, such as those that occurred in the Meuse Valley in Belgium in 1930, in Donora, PA in 1948, and in London in 1952, were associated with an increased number of deaths (Firket 1936; Schrenk et al. 1949; Martin 1964; Brimblecombe 1987). More recently, a number of epidemiologic studies suggested that less severe increases in some indices of air pollution, especially particulate matter, are also associated with an increase in mortality (Wyzga 1978; Ostro 1984; Hatzakis et al. 1986; Ozkaynak and Thurston 1987; Shumway et al. 1988; Fairley 1990; Kinney and Ozkaynak 1991; Pope et al. 1992; Schwartz and Dockery 1992; Schwartz 1993). Some investigators have interpreted the results of these studies as showing that low levels of particulate matter have a causal role in these increases in mortality (Pope et al. 1992; Schwartz and Dockery 1992; Schwartz 1993).

In light of concerns about the association of increased mortality with air pollution, the Health Effects Institute funded epidemiologic studies on the health effects of exposure to ambient ozone and particulate matter. As part of the ozone program, the HEI funded a project by Dr. Loomis and his colleagues to test the hypothesis that ozone exposure is associated with increased mortality during episodes of high ambient ozone levels in Mexico City. This Commentary describes the results of that study and their relationship to other epidemiologic studies that show an association of increased mortality with air pollution.

During the review process, the HEI Health Review Committee and the investigators had the opportunity to exchange comments and to clarify issues in the Investigators' Report and in the Review Committee's Commentary. The following is intended to aid the sponsors of the HEI and the public by highlighting both the strengths and limitations of the study and by placing the Investigators' Report into scientific perspective.

EPIDEMIOLOGIC STUDIES OF THE HEALTH EFFECTS OF OZONE EXPOSURE

The epidemiologic data on the health effects of prolonged exposure to ozone are limited (U.S. Environmental Protection Agency 1988, 1991, 1993; Lippmann 1989). Kilburn and coworkers (1985) reported reduced pulmonary function in the wives and daughters of shipyard workers in an area of high ambient ozone concentrations. Detels and colleagues conducted a prospective cohort study in which the lung function of residents of communities characterized by different levels of oxidants and other air pollutants were measured. Those most heavily exposed to oxidant pollution had decreased lung function at the beginning of the study and an accelerated decline of lung function over time (Detels et al. 1981, 1987; Tashkin et al. 1990). However, extensive loss to follow-up, imprecise exposure characterization, and other methodologic difficulties have made interpretation of the data difficult.

Most information on the health effects of short-term exposure to ozone are from studies done in exposure chambers or with field observations that were designed to measure acute responses to elevated ozone levels (reviewed by U.S. Environmental Protection Agency 1988, 1991, 1993, 1995; Lippmann 1989). These studies have shown that exposure to ambient ozone at levels as low as 80 to 120 ppb for several hours can produce an acute, reversible reduction in pulmonary function in some healthy, exercising adults and children. Short-term ozone exposure also can cause an

* A list of abbreviations appears at the end of the Investigators' Report for your reference.

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increase in certain markers of airway inflammation as well as changes in airway reactivity (Seltzer et al. 1986; Kehrl et al. 1987; Horstman et al. 1989; Devlin et al. 1991).

Some recent epidemiologic studies have found statistically significant associations between daily increases in mortality and elevated ozone levels. In a Los Angeles County, CA study, in which the effects of temperature and nitrogen dioxide levels were controlled for statistically, daily mortality rates from cardiovascular causes and from all causes not related to injury were associated with elevated ozone levels, but on the day after the ozone measurements (a one-day lag). Additional annual regression analyses demonstrated the consistency of these results over time (Kinney and Ozkaynak 1991). When this analysis was extended to New York City, the association was even stronger (Kinney and Ozkaynak 1992). However, epidemiologic studies conducted in St. Louis, MO and Tennessee found no association of mortality with low-level ozone exposures (Dockery et al. 1992). Also, some researchers have found mortality to be more closely associated with other pollutants, such as particulates, in the atmospheric mixture than with oxidants (Pope et al. 1992; Schwartz and Dockery 1992; Schwartz 1993).

As a result of these suggestive but somewhat inconsistent results, the HEI Research Committee thought that a study of whether an association exists between elevated ozone levels and daily mortality in Mexico City (where ozone levels are high and confounding by weather variables is minimized) would provide an opportunity to further evaluate this association and add to the number of locations studied.

JUSTIFICATION FOR THE STUDY

Because of the concerns relating to the potential health effects of ozone, the HEI Research Committee issued RFA 91-1 in 1991, titled "Epidemiologic Studies of the Health Effects of Long-Term Ozone Exposure," requesting proposals for epidemiologic research encompassing methodologic research and the study of the effects of ozone on diverse disease endpoints. In response to this RFA, Drs. Dana Loomis, Shrikant Bangdiwala, and Carl Shy of the University of North Carolina and Dr. Víctor Borja-Aburto of the Instituto Nacional de Salud Pública in Cuernavaca, Mexico submitted an application titled "Ozone Exposure and Daily Mortality in Mexico City: A Time-Series Analysis."

The rationale for the proposed study was to investigate the association of mortality with increased ambient ozone exposure by performing a time-series analysis of daily measurements of air pollutants and mortality in Mexico City during 1990–1992. The investigators proposed this location because (1) daytime ozone levels in Mexico City frequently exceed the current U.S. EPA standard (120 ppb) by a factor of 2 or 3 during most of the year; (2) outdoor ozone concentrations may be a more reliable measure of personal exposure than in most U.S. cities because indoor heating and air conditioning are rare; (3) studying a large population over several years would provide more statistical power to detect small exposure-induced effects; (4) the mild climate, in which the maximal temperature and pollution levels generally do not occur on the same day, would reduce the potential for data confounding by temperature; and (5) the health of the population under study is relatively poorer than in industrialized countries and, therefore, the ozone-induced health effects may be different.

In light of these considerations, although RFA 91-1 was directed toward epidemiologic studies of the long-term effects of ozone, the HEI Research Committee determined that this study had the potential to add important information on the effects of ozone. Therefore, the Committee approved Dr. Loomis' study, which started in March 1993. This two-year project had total expenditures of $105,690. The investigators submitted their report in April 1995 and revisions to this report were submitted in October 1995. The HEI Health Review Committee accepted their revised report in November 1995.

OBJECTIVES AND STUDY DESIGN

The major objective of this study was to determine variations in daily mortality and their correlation with ozone concentrations over time in Mexico City. This type of daily time-series analysis reduces confounding by factors such as occupational exposures and socioeconomic status because they are not expected to show concurrent variation with ozone over time. However, it is still necessary to consider confounding by factors that are correlated in time with increased ambient ozone levels and that may influence mortality independently of ozone. Thus, weather characteristics, such as temperature and humidity, and the concentrations of other pollutants, such as particulate matter and sulfur dioxide, need to be considered as potential confounders when studying the effects of ozone. If an association between ozone exposure and excess daily mortality in Mexico City were found, then the study was designed to determine (1) if the effects of ozone exposure on excess mortality were combined with the effects of other pollutants, weather variables, or both (2) if the association varied by age group, and (3) if ozone exposure had any influence on respiratory and cardiac causes of death.

The Instituto Nacional de Estadística, Geografía e Informática of Mexico provided mortality data on computer diskettes. Only the deaths of residents of the Distrito Federal, which includes approximately 50% of the Mexico City Metropolitan area, that actually occurred within the district were considered. The Departamento del Distrito Federal supplied air quality and weather data from a monitoring network of 33 stations that measure gasses and an array of meteorologic parameters. Due to incomplete monitoring data, the investigators based their exposure measurements for ozone on 9 of these monitoring stations with the most complete data. The particulate data measured by a network of 19 stations were supplemented by measurements of PM_{10} from 1 monitor that operated on weekdays from 1991 through 1992 in the central area of Mexico City. Dr. Irma Rosas of Centro de Ciéncas de la Atmósphera from the Universidad Nacional Autónoma de México provided the PM_{10} data.

TECHNICAL EVALUATION

ATTAINMENT OF STUDY OBJECTIVES

The investigators conducted a valuable study of mortality during episodes of increased air pollution in Mexico City. They were successful in achieving their main objective of evaluating whether there was an association between excess mortality and ambient ozone levels in Mexico City. They were also successful in studying the association of mortality with the pollution mixture and controlling for confounding variables. In addition, they were able to study the association of excess mortality with ozone in individuals over 65 years of age. However, the small number of deaths from respiratory and cardiovascular disease resulted in conditions that did not supply enough statistical power for the analysis of an association between cause of death and ambient ozone levels.

METHODS AND STUDY DESIGN

The methods and study design were generally appropriate to address the goals of the investigation. Each death record used by the investigators included age, gender, date of death, date of death registration, county (delegacion) of death, county of residence, and cause of death. The investigators reduced the data to total and cause-specific number of deaths per day for five geographic areas of Mexico City. They used the number of daily deaths as the outcome measure because the size of the population did not change during the years under consideration. The investigators used this information appropriately. It is noteworthy that the death rate reported by the investigators for Mexico City during this time period is low (approximately 17 deaths/day/million people) compared with that reported in other major cities worldwide, a fact that the investigators attribute to the young age structure of the population. The investigators discussed the potential for misclassification of deaths in Appendix B of their report.

Measurements of exposure to ozone, sulfur dioxide, nitrogen oxides, and carbon monoxide were based on the nine monitoring stations with the most complete information for the five geographic areas. It would have been helpful to have more information on how these sites were interrelated. Data for these pollutants as well as temperature and relative humidity were available on an hourly basis. Total suspended particles (TSP) were measured only every sixth day, which limited the ability to study the potential effects of particulate matter. The potential effect of measurement error was addressed by the investigators in the Discussion section of their Report.

The investigators used Poisson regression techniques and refit all of their final models using the Generalized Estimating Equation of Liang and Zeger (1993) in order to account for serial correlation of the levels of pollutants. They used these regression techniques to study the correlation of increased mortality with ozone in a single pollutant model and with ozone, sulfur dioxide, and TSP in a combined pollutant model.

RESULTS AND INTERPRETATION

The investigators found increases in deaths in Mexico City associated with episodes of increased air pollution, both on the same day and on the following day. Although the magnitude of these increases in deaths per 100-ppb increase in ozone was relatively small (1% to 2%), the increases were statistically significant when Poisson regression models were used to adjust for temperature and long-term trends. When ozone was considered alone in the analytical models, the rate ratio for increased mortality associated with an increment of 100 ppb in the one-hour maximum ozone concentration was 1.029 (95% confidence interval equals 1.015 to 1.044); that is, deaths increased 2.9%. Using an eight-hour moving average around the daily maximum ozone concentrations showed a stronger correlation (rate ratio of 1.048, 95% confidence interval of 1.025 to 1.070). Excess mortality was greater for individuals over 65 years of age. Separate analyses of the effects of ozone for different areas of the city showed similar results; however, they were not statistically significant, most likely due to the smaller population sizes.

In interpreting these results, it is noteworthy that increases in other pollutants also were associated with increased mortality. The rate ratio was 1.075 (95% confidence interval of 1.024 to 1.126) for increased mortality resulting from a 100-ppb increase in sulfur dioxide. The rate ratio was 1.054 (95% confidence interval of 1.035 to 1.072) for increased mortality resulting from a 100-g/m^3 increase in TSP. Moreover, as the investigators note in their report, when ozone, TSP, and sulfur dioxide were considered simultaneously, only the association between TSP and increased mortality remained statistically significant with a rate ratio of 1.054 (95% confidence interval of 1.034 to 1.13) for increased mortality resulting from a 100-g/m^3 increase in TSP. Since ozone had no effect on mortality when other air pollutants were considered simultaneously, the effects observed in this study cannot be attributed to this pollutant.

Recent epidemiologic studies suggest that relatively small, short-term increases in indices of particulate air pollution are associated with increased daily mortality (Pope et al. 1992; Schwartz and Dockery 1992; Schwartz 1993). The results of these studies have generated controversy because of their potential sensitivity to measurement error and the statistical and modeling approaches used (Thomas 1994; Li and Roth 1995; Lipfert and Wyzga 1995; Thurston and Kinney 1995), the lack of complementary data from toxicologic studies (Utell and Frampton 1995), and the possible confounding by weather and climatic factors or by other air pollutants (Li and Roth 1995; Moolgavkar et al. 1995a,b). Also, some studies have implicated other pollutants, including ozone and carbon monoxide, as being associated with mortality (Hexter and Goldsmith 1971; Bates and Sizto 1989; Lippmann 1989; Kinney and Ozkaynak 1991). However, in its review of approximately 40 time-series mortality studies, the EPA staff has concluded that particulate matter is the air pollutant most closely associated with increased mortality (U.S. Environmental Protection Agency 1996).

To help resolve questions about the validity of the statistical procedures used in other selected studies, the HEI funded a reanalysis of some of the epidemiologic data using different modeling and statistical approaches (Samet et al. 1995; Samet et al. 1996). These analyses demonstrated that the association between individual pollutants and increased mortality is complex. Specifically, in Philadelphia for the years 1974–1988 (the data set that was reanalyzed in detail), mortality increased as levels of particulate air pollution increased, but levels of TSP, sulfur dioxide, nitrogen dioxide, and carbon monoxide were moderately correlated with each other, making it impossible, in this data set, to identify a single pollutant in this group most strongly correlated with increased mortality (Samet et al. 1996). In addition, ozone levels were correlated only moderately with those of the other pollutants and this correlation was seasonally variable with ozone having independent effects on mortality. Therefore, it has been difficult to disentangle the effects of ozone from those of particulate matter in this data set.

Surprisingly, in spite of the highly ozone-polluted atmosphere in Mexico City (approximately 75% of the days had ozone levels in excess of 120 ppb), Dr. Loomis and colleagues did not find an independent effect of increased levels of ozone on mortality. These results are consistent with those of Dockery and coworkers in United States locations with lower-level ozone exposures (Dockery et al. 1992). In contrast, as noted above, elevated levels of ozone had independent effects on mortality in Philadelphia, a city with much lower levels of ozone pollution (averaging approximately 20 ppb), during the 1974–1988 time period (Samet et al. 1996). In light of the complexity and geographic variability of the pollutant mixture to which individuals are exposed, and the differences in the strength of the associations between levels of individual air pollutants and increased mortality, it may be difficult to determine whether the increased mortality associated with low levels of ambient air pollution is due to an independent effect of any one pollutant in Mexico City or other locations.

IMPLICATIONS FOR FUTURE RESEARCH

The major outstanding questions remaining in Mexico City and elsewhere are (1) what are the underlying causes of the observed increase in mortality that are associated with elevated air pollution, and (2) what are the contributions of individual pollutants to this effect?

The underlying causes of the observed excess mortality could be studied in a number of ways. For example, the pathophysiological effects of air pollution episodes on groups of individuals with specific medical conditions, such as coronary disease and asthma or other respiratory diseases, could be measured. Also, the hypothesis that air pollution episodes cause individuals to die one or a few days earlier than they would have otherwise, called the "harvesting effect", could be evaluated by comparing excess mortality on high-pollution days with excess mortality on the days immediately following the pollution episodes.

In order to address the contributions of individual pollutants to mortality, the increases in mortality associated with each of the pollutants separately and the combined pollutant mixture in Mexico City could be compared to

results obtained in other cities with similar and different pollutant profiles. Specifically, the fact that TSP remained statistically significantly associated with excess mortality in the multipollutant model in Mexico City indicates that the effect of TSP on mortality in this location should be studied further. In this manner, the contributions of the individual pollutants and the overall mixture to the increase in mortality could be better understood. However, in light of the complexity of this phenomenon, insights into the association of air pollution with increased mortality may be more likely gained by assessing the correlations of individual pollutants with increased deaths in multiple locations having differing pollutant mixtures rather than by using regression models to analyze data from a single location.

CONCLUSIONS

Dr. Loomis and colleagues used regression analysis techniques to study the correlation of increased concentrations of selected air pollutants with increased mortality in Mexico City. When ozone was the only air pollutant considered in the model, the rate ratio for increased mortality associated with a 100-ppb increment in the one-hour maximum ozone concentration was 1.029. However, other pollutants were also related to increased mortality. When TSP was independently considered in the model, the rate ratio for increased mortality associated with a 100-$\mu g/m^3$ increment in TSP was 1.054. When sulfur dioxide was considered alone, the rate ratio for increased mortality associated with a 100-ppb increment in sulfur dioxide was 1.075. When all three pollutants were included in the model, only the association of TSP with mortality was statistically significant.

In summary, although the investigators found an increase in mortality during periods in which ambient levels of ozone were elevated, these effects cannot necessarily be attributed to ozone alone because the effect was not statistically significant when other air pollutants were included in the analysis. Overall, the results of this study conducted in Mexico City appear largely consistent with what has been seen in other locations worldwide, namely that short-term increases in particulate air pollution are associated with increased daily mortality. However, further research is needed to disentangle the effects of the various pollutants and to gain insights into the association of individual pollutants with morbidity and mortality.

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