00-53

Inhalation Toxicology, 12(Supplement 4):41–73, 2000

0895-8378/00 $12.00 + .00

Veterans study cohort mortality chronic study PM2.5 ozone

THE WASHINGTON UNIVERSITY–EPRI VETERANS' COHORT MORTALITY STUDY: Preliminary Results

Frederick W. Lipfert

Environmental Consultant, Northport, New York, USA

H. Mitchell Perry, Jr.

Department of Veterans Affairs Medical Center and Washington University School of Medicine, Division of Hypertension, St. Louis, Missouri, USA

J. Philip Miller, Jack D. Baty

Washington University School of Medicine, Division of Biostatistics, St. Louis, Missouri, USA

Ronald E. Wyzga

EPRI, Palo Alto, California, USA

Sharon E. Carmody

Department of Veterans Affairs Medical Center and Washington University School of Medicine, Division of Hypertension, St. Louis, Missouri, USA

This article presents the design of and some results from a new prospective mortality study of a national cohort of about 50,000 U.S. veterans who were diagnosed as hypertensive in the mid 1970s, based on approximately 21 yr of follow-up. This national cohort is male with an average age at recruitment of 51 ± 12 yr; 35% were black and 81% had been smokers at one time. Because the subjects have been receiving care at various U.S. Veterans Administration (VA) hospitals, access to and quality of medical care are relatively homogeneous. The health endpoints available for analysis include all-cause mortality and specific diagnoses for morbidity during VA hospitalizations; only the mortality results are discussed here. Nonpollution predictor variables in the baseline model include race, smoking (ever or at recruitment), age, systolic and diastolic blood pressure (BP), and body mass index (BMI). Interactions of BP and BMI with age were also considered. Although this study essentially controls for socioeconomic status by design because of the homogeneity of the cohort, selected ecological variables were also considered at the ZIP code and county levels, some

Received 4 February 2000; sent for revision 6 March 2000; accepted 15 April 2000.

This project was supported by EPRI under W.O. 9160. We thank the U.S. Environmental Protection Agency for supplying air quality data not routinely available through public channels and two anonymous reviewers for helpful comments.

Address correspondence to Dr. Frederick W. Lipfert, Environmental Consultant, 23 Carll Court, Northport, NY 11768, USA. E-mail: flipfert@suffolk.lib.ny.us

of which were found to be significant predictors. Pollutants were averaged by year and county for TSP, PM_{10}, CO, O_3, and NO_2; SO_2 and Pb were considered less thoroughly. Both mean and peak levels were considered for gases. SO_4^{2-} data from the AIRS database and $PM_{2.5}$, coarse particles, PM_{15}, and SO_4^{2-} from the U.S. EPA Inhalable Particulate (IP) Network were also considered. Four relevant exposure periods were defined: 1974 and earlier (back to 1953 for TSP), 1975–1981, 1982–1988, and 1989–1996. Deaths during each of the three most recent exposure periods were considered separately, yielding up to 12 combinations of exposure and mortality periods for each pollutant. Associations between concurrent air quality and mortality periods were considered to relate to acute responses; delayed associations with prior exposures were considered to be emblematic of initiation of chronic disease. Preexposure mortality associations were considered to be indirect (noncausal). The implied mortality risks of long-term exposure to air pollution were found to be sensitive to the details of the regression model, the time period of exposure, the locations included, and the inclusion of ecological as well as personal variables. Both positive and negative statistically significant mortality responses were found. Fine particles as measured in the 1979–1984 U.S. EPA Inhalable Particulate Network indicated no significant (positive) excess mortality risk for this cohort in any of the models considered. Among the positive responses, indications of concurrent mortality risks were seen for NO_2 and peak O_3, with a similar indication of delayed risks only for NO_2. The mean levels of these excess risks were in the range of 5–9%. Peak O_3 was dominant in two-pollutant models and there was some indication of a threshold in response. However, it is likely that standard errors of the regression coefficients may have been underestimated because of spatial autocorrelation among the model residuals. The significant variability of responses by period of death cohort suggests that aggregation over the entire period of follow-up obscures important aspects of the implied pollution–mortality relationships, such as early depletion of the available pool of those subjects who may be most susceptible to air pollution effects.

An important air pollution health effects issue is that of possible sequellae from long-term exposures that might be associated with initiation of chronic diseases, such as chronic obstructive pulmonary disease (COPD), coronary heart disease, and cancer. Recent cohort studies have postulated an important role for air pollution, based on the spatial distribution of ambient air quality, mainly contemporary with the periods of follow-up or previous by a few years at most (Dockery et al., 1993; Pope et al., 1995; Abbey et al., 1999). Two of these studies (Dockery et al., 1993; Pope et al., 1995) figured prominently in the 1997 revisions to the national ambient air quality standards (NAAQS) for particulate matter (PM) by the U.S. Environmental Protection Agency (U.S. EPA, 1996). However, since that time, there has been intense debate within the scientific community about the details, interpretation, and use of such studies for regulatory purposes (Lipfert 1995, 1997; Kunzli & Tager, 1997; Gamble, 1998; Valberg & Watson, 1998; Vedal, 1997). Issues that have been discussed include the appropriate timing of air pollution exposure data, the interpretation of ambient air quality data from central monitoring stations as individual exposures, the potential for socioeconomic confounding when only limited information is available on individual subjects, and the interpretation of responses integrated over a period of follow-up as indicative of the initiation of new cases of chronic disease.

This article presents the study design and some preliminary results on the mortality experience of a national cohort of about 90,000 male U.S.

veterans,* based on approximately 21 yr of follow-up beginning in the mid 1970s, following diagnosis with hypertension. Air pollution exposures could be estimated for about 25–70% of the cohort, depending upon the pollutant and exposure period (1953–1996). The locations of interest spanned the nation and included Puerto Rico. Because the subjects have been receiving care at U.S. Veterans Administration (VA) hospitals, access to care and quality of care are relatively homogeneous and the cohort is thought to represent a sample with relatively uniform socioeconomic status (SES).

The objectives of the study were to:

1. Estimate long-term responses to exposure to a variety of air pollutants on a relatively homogeneous cohort, using proportional hazards modeling.
2. Determine the sensitivity of such estimates to alternative model formulations and to the inclusion of "ecologic" (census-based) variables in addition to personal variables.
3. Determine the sensitivity of such estimates to improvements in the specificity of the estimated air pollution exposures, both spatially and temporally.

The article begins with a description of the cohort and some of the baseline studies that had been done prior to the addition of air pollution to the list of possible risk factors. Early results with a simplified model are described briefly, and contrasts are shown between results obtained with successively more complex models. Conclusions are drawn and suggestions are offered for further research with this interesting cohort.

METHODS AND DATA

Characteristics of the Cohort (Personal Variables)

The observed cohort consisted of about 90,000 U.S. male military veterans who were identified as hypertensive by a large-scale screening program in the mid 1970s at 32 special Veterans Administration (VA) Hypertension Screening and Treatment Program (HSTP) clinics located across the United States. Table 1 gives the characteristics and distribution of subjects by center; the numbers of subjects with complete data for all models were proportionately lower. This cohort differs from a general male population in being limited to hypertensive patients, and it differs from the cohorts that are randomized into large-scale multicenter trials since it contains a broad spectrum of subjects, including many with various comorbidities.

After an earlier study (Veterans Administration Cooperative Study Group on Antihypertensive Agents, 1970) demonstrated that patients with moderate hypertension benefited from treatment, the Hypertension Screening and

*The original cohort comprised about 90,000 subjects. The numbers used in our analyses varied from about 30,000 to 70,000 depending on missing data for the variables used.

TABLE 1. HSTP Cohort Characteristics

Racial group	Frequency	Percent	
Non-Black	58,265	64.7	
Black	31,805	35.3	
Current smoker?	Frequency	Percent	
No	39,039	43.3	
Yes	51,031	56.7	
Ever smoke?	Frequency	Percent	
No	17,123	19.0	
Yes	72,947	81.0	
Continuous variables	*n*	Mean	SD
Systolic BP (mm Hg)	90,070	148.05	23.12
Diastolic BP (mm Hg)	90,070	95.43	13.13
BMI	(Kg/m^2)	26.3	4.5
Age (yr)	90,070	51.2	13.0
Clinic site	Frequency	Percent	
Allen Park, MI	8552	9.5	
Birmingham, AL	5707	6.3	
Buffalo, NY	1599	1.8	
Chicago, IL	3159	3.5	
Cleveland, OH	3952	4.4	
Dallas, TX	1621	1.8	
Dayton, OH	4014	4.5	
East Orange, NJ	1979	2.2	
Houston, TX	1403	1.6	
Indianapolis, IN	314	0.3	
Iowa City, IO	3691	4.1	
Jackson, MS	5109	5.7	
Los Angeles, CA	1142	1.3	
Memphis, TN	3937	4.4	
Milwaukee, WI	594	0.7	
Minneapolis, MN	1251	1.4	
New Orleans, LA	1319	1.5	
Miami, FL	5642	6.3	
Oklahoma City, OK	3138	3.5	
Omaha, NE	596	0.7	
Philadelphia, PA	1789	2.0	
Pittsburgh, PA	4348	4.8	
Richmond, VA	3805	4.2	
Salt Lake City, UT	1747	1.9	
San Francisco, CA	551	0.6	
San Juan, PR	5284	5.9	
Seattle, WA	246	0.3	
St. Louis, MO	4596	5.1	
Topeka, KS	567	0.6	
Tucson, AZ	4018	4.5	
Washington, DC	1222	1.4	
West Haven, CT	3178	3.5	

Treatment Program (HSTP) was established to provide care for the large number of previously untreated veterans with hypertension (Perry et al., 1982). The HSTP clinics screened more than 500,000 veterans from all parts of the United States and began treating about 100,000 of them who had mild and moderate hypertension (screening diastolic blood pressure $\geq$90 to $<$115 mm Hg). The average systolic blood pressure was 148 mm Hg and the average diastolic blood pressure was 96 mm Hg. The difference between the mean diastolic blood pressure for this cohort and for the United States general population was 7 mm Hg (Roberts, 1981), consistent with mild hypertension. Thirty-five percent of the cohort was black, 81% had been smokers at one time and 57% were smokers at screening, 12% had a pulmonary abnormality on physical examination, 9% were diabetic, 19% had a history of heart disease, 7% had a history of stroke, and 56% had a positive cardio-renal family history. These subjects had all been healthy enough to be in the U.S. armed forces at one time. The subjects received all or most of their medical care at a VA facility, suggesting relatively low socioeconomic status. The medical care was similar for the entire cohort since it was standardized in the HSTP clinics (Miller et al., 1994; Perry et al., 1995a).

Systolic (SBP) and diastolic (DBP) blood pressure and all other individual risk factor data (smoking status, age, race, height, body mass index) considered here were obtained as part of the initial pretreatment screening. Vital status was determined from the VA's Beneficiary Identification Records Location System, which has been found to be 90–95% complete (Miller et al., 1994; Perry et al., 1995b; Boyco et al., 2000). Three sequential mortality follow-up periods were considered separately: 1976–1981, 1982–1988, 1989–1996. Since follow-up began at slightly different times among the 32 centers during a period of rapidly improving air quality at some of them, some of the analyses were found to be sensitive to censoring the data to provide a common starting year of 1976.

This cohort has also been matched with the Patient Treatment File, which contains the diagnoses by ICD codes from the hospital discharges from all VA hospitals (not just those involved in the screening of the HSTP cohort); these data would allow specific morbidity outcomes to also be considered. However, this article considers only death from all causes. Table 2 gives the fractions of the cohort that have been diagnosed with specific conditions (some may have more than one condition). A general picture of the relative health of the cohort may be obtained by comparing these fractions with corresponding mortality data for the general public (National Center for Health Statistics, 1986); such comparisons were generally reasonable, taking into account the racial composition of the cohort (about the same proportion of heart attacks but slightly more lung cancer and stroke).

Age (at entry) was expected to be the most important predictor of mortality and was treated as a categorical variable, thus allowing for nonlinearities and any potential nonlinearities or differences with respect to the "standard" populations used for age adjustment. In the preliminary screening regressions,

TABLE 2. Basic Model Risk Ratios

Endpoint	Percent with endpoint	Risks of		
		Black race	Current smoking	Ever smoking
Death	58.4	0.97	1.40	1.14
Congestive heart failure	8.5	1.23	1.12	1.08
Cerebrovascular accident	3.4	1.53	1.20	0.95
End-stage renal disease	1.7	2.14	0.95	1.01
Myocardial infarction	15.5	0.85	1.12	1.18
Chronic obstructive pulmonary disease	9.0	0.74	2.00	1.79
Emphysema	4.2	0.48	1.82	2.46
Lung cancer	3.7	1.19	2.63	2.89
Pneumonia	8.8	1.17	1.38	1.16
Digestive-tract cancer	2.3	1.68	0.99	0.98
Any neoplasm	15.4	1.14	1.34	1.14
Cirrhosis of the liver	4.8	0.94	1.93	0.83
Diabetes	14.6	1.22	1.02	0.91
Gingival disease	5.3	1.18	1.58	0.98
Osteoarthrosis	5.7	1.03	1.04	0.99
Prostatic hyperplasia	8.2	1.06	0.85	1.001

the cohort was divided into 4 age bins, separated by 10 yr. In subsequent regression models, the cohort was grouped into deciles by age, which were separated by only 2–3 yr in the midrange of the data. BP and body mass index (BMI) were considered categorically in seven levels, also to allow for nonlinear responses; their interactions with age were also considered. Subjects' heights were treated as a continuous variable in the final model.

Air Quality Database

Preliminary screening analyses were performed by specifying average and peak air pollution levels in the communities of each of the 32 VA centers for 1982, which was taken as a convenient year within the period of follow-up. However, treatment at a given VA center does not always imply residence near that center, especially outside of large metropolitan areas. More detailed exposure information was thus obtained by averaging air quality data by year for each county of residence at the time of entry to the study. Detailed analyses of the matching between air quality data and subjects were made for TSP and O_3 data for 1982. For TSP, there were 1379 counties with 67,537 subjects; by center, the number of subjects per county ranged from 14 (Indianapolis) to 112 (Detroit), with an average of 49. For 1982 O_3, there were data for 573 counties comprising 54,292 subjects; subjects per county ranged from 4 in San Juan to 307 in Miami, with an average of 92. Given the expected variations in air quality for these pollutants between central cities and suburbs, matching at the county level substantially reduces the errors in estimated exposures incurred by averaging across an entire metropolitan area.

The traditional criteria pollutants considered included TSP, PM_{10}, CO, O_3, and NO_2; SO_2 and Pb were considered less thoroughly. Based on the results of screening analyses and a priori expected responses, the detailed studies of CO and O_3 employed the 95th percentile levels for each county, as a robust long-term estimate of peak levels. Also, it should be noted that the annual average is not a suitable metric for a seasonal pollutant like O_3. SO_4^{2-} data from the AIRS database (glass-fiber filters) and $PM_{2.5}$, coarse particles, PM_{15}, and SO_4^{2-} from the U.S. EPA Inhalable Particulate (IP) Network (Teflon filters) were also considered (personal communication, J. Sune, U.S. EPA). Both types of SO_4^{2-} data were used, since the IP data are thought to be more reliable through their use of nonreactive filter media (Teflon), but the AIRS data have been used in previous studies (Pope et al., 1995; Lipfert et al., 1988; Lipfert, 1992) with which comparisons would be useful. The IP data used here comprise more counties with monitors (103) than were used in previous studies (Pope et al., 1995; Lipfert et al., 1988).

Four separate exposure periods were defined: 1974 and earlier (back to 1953 for TSP; U.S. Department of Health, Education, and Welfare, 1958), 1975–1981, 1982–1988, and 1989–1996; these periods were selected as compromises between reduced sample sizes and reasonable temporal gradients within periods. However, the IP data could only be divided into two periods, 1979–1981 and 1982–1984; the first period corresponds to the data used in the previous studies (Pope et al., 1995; Lipfert et al., 1988, 1992). No data were available on personal exposures to air pollution; the assumption is made that the temporal patterns in countywide average ambient data based on residence at entry to the study are representative throughout each subject's life. The salient statistics of the air quality data are given in Table 3; their intercorrelations are discussed in some detail later.

It must be recognized that all potentially harmful pollutant species are not measured routinely and thus cannot be included in epidemiology studies of this type. For this reason, those pollutants that are included should be considered as indices of the overall urban pollution mix. Further, the nature of this mix has changed significantly during the period evaluated in this study. For example, internal combustion engines were responsible for only about 35% of the total NO_x emitted before 1970, whereas the current share is about 45% or more (U.S. EPA, 1995). Similarly, shares of PM emissions contributed by metals, minerals, and fuel combustion have declined from about 10%, 35%, and 25%, respectively, to about 2%, 3%, and 17% currently.

Ecological Variables

Research has shown that health and longevity may be affected by neighborhood or "contextual" socioeconomic variables as well as by personal attributes (Wannamethee & Shaper, 1997; Smith et al., 1996). In addition, climate and elevation (altitude) can have physiological effects as well as indirect effects on exposure to outdoor air pollution. These hypotheses were tested by running models with and without such variables, without including the var-

TABLE 3. Statistics of the Air Quality Data Base

Species	Metric	Filter	Period	Subjects	Mean	Median	SD	Min.	Max.
TSP	Mean, μg/m^3	GF	1953–74	64,764	96	94	26	11	372
TSP	Mean, μg/m^3	GF	1975–78	65,551	74	72	17	14	181
TSP	Mean, μg/m^3	GF	1982–88	63,519	59	57	11	12	139
PM_{10}	Mean, μg/m^3	T	1989–96	59,053	39	29	6	11	93
SO_4^{2-}	Mean, μg/m^3	GF	1960–74	51,284	11.21	11.77	3.85	1.65	23.94
SO_4^{2-}	Mean, μg/m^3	GF	1975–81	54,974	10.88	10.89	3.55	1.42	23.79
O_3	95%ile, ppm		1960–74	44,179	0.132	0.119	0.044	0.056	0.431
O_3	95%ile, ppm		1975–81	57,040	0.140	0.136	0.038	0.048	0.472
O_3	95%ile, ppm		1982–88	55,453	0.094	0.089	0.018	0.031	0.170
O_3	95%ile, ppm		1989–96	56,710	0.085	0.085	0.012	0.040	0.138
CO	95%ile, ppm		1960–74	49,593	10.82	9.31	5.15	0.94	35.30
CO	95%ile, ppm		1975–81	55,053	7.64	7.04	2.94	0.43	22.38
CO	95%ile, ppm		1982–88	54,336	3.42	3.33	0.95	0.30	15.20
CO	95%ile, ppm		1989–96	53,566	2.36	2.30	0.67	0.30	7.10
NO_2	Mean, ppb		1960–74	36,869	30.32	28.19	14.24	5.00	64.88
NO_2	Mean, ppb		1975–81	49,887	27.22	27.75	8.54	2.65	58.37
NO_2	Mean, ppb		1982–88	47,242	23.65	22.60	6.51	2.70	46.00
NO_2	Mean, ppb		1989–96	46,397	21.45	21.60	6.14	1.00	42.50
Data from the Inhalable Particulate Network									
$PM_{2.5}$	Mean, μg/m^3	T	1979–81	26,067	24.24	24.33	5.59	5.60	42.3
CP	Mean, μg/m^3	T	1979–81	26,067	20.81	20.26	5.37	3.60	64.3
PM_{15}	Mean, μg/m^3	T	1979–81	26,067	45.05	44.30	9.84	9.74	101.7
$PM_{2.5}$	Mean, μg/m^3	T	1982–84	29,177	22.01	22.06	5.03	7.67	40.8
CP	Mean, μg/m^3	T	1982–84	29,177	20.53	19.41	5.23	5.03	53.1
PM_{15}	Mean, μg/m^3	T	1982–84	29,177	42.54	44.22	7.79	13.6	85.2
SO_4^{2-}	Mean, μg/m^3	T	1979–81	29,192	7.45	8.29	2.29	0.71	12.9
SO_4^{2-}	Mean, μg/m^3	T	1982–83	29,061	6.68	6.96	2.53	0.71	14.5

Note. CP = PM_{15}–$PM_{2.5}$. Filters: GF = glass fiber; T = Teflon.

ious pollution variables. Variables considered at the ZIP-code level included average measures of education, income, and racial mix. Variables considered at the county level included altitude, annual average heating degree-days (as a measure of climate), percentage of Hispanics, and other socioeconomic indicators. Variables available at the ZIP-code level were considered first, one at a time. "Years of education" was considered in five levels, with the lowest (<10 yr) as referent. With stepwise selection, the highest three levels were significant; each indicated lower mortality risk with more education. This variable was thus considered as a continuous measure in subsequent runs. Census tract poverty, defined as the proportion in the tract with less than 124% of the official poverty level, was considered similarly, with 7 levels. All were significant, showing increased risk with more neighborhood poverty, but the increase was not strictly monotonic. The census tract racial mix was considered in terms of the percentage of black population (7 levels, with the lowest [0.5%] as referent). The next lowest level indicated a beneficial relationship, while higher proportions of black population showed increased risk. When all four of these variables were run simultaneously (stepwise), education (continuous), income

at 75% of the poverty level (continuous), and 2 of the 6 levels of percent black entered the model. County-level socioeconomic and demographic variables (including percent Hispanic) made no additional contribution. Heating degree-days were significant, but altitude was not.

Regression Methods and Models

The regression analysis was conducted in stages using models of increasing complexity. Screening regressions were performed using a model similar to what had been used with this cohort prior to this study (Miller et al., 1994; Perry et al., 1995b). This model included terms for age (4),* SPB (7), DBP (7), BMI (7), interactions with age, race (2), current smoking (2), ever smoked (2), and 1982 average air quality for each of the 32 centers. Subsequently, we defined a "baseline" model that used deciles for age [i.e., age (10)] and air quality for each county for four different exposure periods. The final model added each subject's height and the ecological variables [education, income <75% of poverty, percent black (7), degree days] to the baseline model.

With the baseline and final models, deaths during each of the three most recent exposure periods were considered separately, yielding up to 12 combinations of exposure and mortality periods for each pollutant. Associations between concurrent air quality and mortality periods were considered to relate to acute responses, associations with prior exposure were considered to be emblematic of initiation of chronic diseases, and preexposure mortality associations could only be indirect, that is, noncausal, and the result of intercorrelations or spurious association.

Measures of Risk

Studies of long-term health risks of air pollution vary in their choices of metrics to describe their findings. Many of the older studies use "mean effect," which corresponds to the excess (relative) risk at the mean pollutant level (Lipfert, 1994). Some of the extant prospective cohort studies have expressed their findings in terms of the extreme pollution levels across the data set, that is, maximum risk relative to minimum risk (Dockery et al., 1993; Pope et al., 1995). This approach tends to exaggerate the average expected risks and is impractical when several hundred counties are involved that differ in terms of the relative importance of the various pollutants considered. In this study, the mortality risks were based on the mean concentrations of pollutants less estimated background weighted by the number of subjects in each county. This metric is more robust over the ranges of the pollution variables involved. Background is estimated as the mean concentration less 3 standard deviations. In the few cases for which this value was negative (indicating a skewed distribution), the background was taken as zero.

Among the extant cross-sectional studies of air pollution and mortality, typical population-based studies (Lipfert et al., 1998; Lipfert, 1992, 1994) have reported excess risks ranging from 2 to 8%, while the more recent

*Numbers in parentheses are numbers of levels (categories) considered.

prospective cohort studies (Dockery et al., 1993; Pope et al., 1995) have reported substantially higher levels, from 8 to 25% (Lipfert et al., 1995). These higher levels, when compared to typical daily risks of air pollution from time-series studies of around 2 to 6% (Lipfert et al., 1995), have prompted some observers to interpret the prospective cohort findings as indicative of chronic responses.

Geographic Patterns of Response

Geographic patterns in individual risk were examined by computing mortality residuals with no air pollutants in the model, for each of the 32 VA treatment centers. Possible effects of spatial autocorrelation have not been considered in this phase of the investigation; thus, significance levels may have been overstated in the proportional hazards regression models that were used. However, use of county-level air quality data captures at least part of the typical city–suburb spatial gradients for TSP, CP, CO, and O_3; thus, spatial autocorrelation would be expected to be most severe for regionally distributed pollutants such as SO_4^{2-} and $PM_{2.5}$ (and to some extent, O_3) (Lipfert, 1995).

RESULTS

Correlations Among the Air Quality Variables

Because the numbers of subjects in each county differ substantially, correlations have been weighted accordingly. First, we consider correlations between like pollutants for different exposure periods, as shown in Table 4a (unless otherwise specified, "SO_4^{2-}" refers to data from the U.S. EPA AIRS database, which is also the source of all data other than "IP" measures). The AIRS SO_4^{2-} data were insufficient for the locations of interest in this study after 1982, so that only the first two exposure periods are considered for this

TABLE 4a. Correlations between Successive Exposure Periods (Number of Observations)

		Exposure periods		
Parameter	Grouping	2nd vs. 1st	3rd vs. 2nd	4th vs. 3rd
TSP (4th = PM_{10})	Pairwise (61,811 to 67,962)	0.855	0.755	0.732
	Listwise (61,170)	0.863	0.748	0.734
CO	Pairwise (50,797 to 56,767)	0.367	0.670	0.872
	Listwise (49,878)	0.362	0.624	0.877
O_3	Pairwise (45,229 to 56,442)	0.489	0.877	0.942
	Listwise (43,244)	0.496	0.902	0.919
NO_2	Pairwise (44,575 to 51,177)	0.809	0.781	0.913
	Listwise (34,329)	0.814	0.835	0.908
SO_4^{2-}	(53,354)	0.835		
IP SO_4^{2-}	(29,782)		0.864	
Fine IP ($PM_{2.5}$)	(26,721)		0.690	
Coarse IP	(26,721)		0.403	
Total IP (PM_{15})	(26,721)		0.531	

pollutant. There are only minor differences between pairwise (based on all observations available for each pair of variables) and listwise (based only on observations having data for all variables in the list) correlations here, indicating stability over these relatively small changes in dataset size. The table shows that the third (1982–1988) and fourth (1989–1996) exposure periods are highly correlated ($R > .7$) for all pollutants, but that there are important differences between the earlier periods for CO and O_3. The correlations between successive periods decrease over time for TSP and PM_{10}, suggesting a widening rather than narrowing spatial distribution. Changing from TSP (1982–1988) to PM_{10} (1989–1996) did not seem to matter much in this regard. The correlations for (AIRS) SO_4^{2-} were high for all periods, suggesting that it may be difficult to distinguish delayed from concurrent responses for this species. These high correlations are likely manifestations of the relatively homogeneous regional sulfate distribution in the eastern United States. The

TABLE 4b. Correlations between Pollutants for Each Exposure Period (Number of Observations)

	1960–74	1975–81	1982–88	1989–96
TSP vs. CO (PM_{10})	0.320 (50,662)	0.031 (57,876)	0.289 (56,912)	0.309 (55,295)
TSP vs. O_3 (PM_{10})	−0.179 (45,234)	0.247 (58,376)	0.126 (56,315)	0.286 (55,444)
TSP vs. NO_2 (PM_{10})	0.517 (30,452)	0.557 (48,569)	0.411 (45,912)	0.715 (43,970)
TSP vs. SO_4^{2-} (PM_{10})	0.555 (54,085)	0.358 (57,910)	−0.188 (17,310)	0.190 (9586)
TSP vs. IP SO_4^{2-}		0.313 (29,905)	−0.169 (29,768)	
TSP vs. fine		0.635 (26,727)	0.185 (29,888)	
TSP vs. coarse		0.707 (26,727)	0.391 (29,888)	
TSP vs. PM_{15}		0.748 (26,727)	0.383 (29,888)	
CO vs. O_3	0.004 (41,470)	0.109 (56,186)	0.158 (53,730)	0.397 (53,002)
CO vs. NO_2	0.690 (30,452)	0.249 (48,569)	0.413 (45,912)	0.492 (43,970)
CO vs. SO_4^{2-}	0.469 (46,623)	−0.155 (55,354)	−0.518 (15,579)	−0.551 (8996)
CO vs. IP SO_4^{2-}		0.356 (29,717)	0.075 (29,215)	
CO vs. fine		0.624 (26,543)	0.296 (29,335)	
CO vs. coarse		0.498 (26,543)	0.135 (29,335)	
CO vs. PM_{15}		0.626 (26,543)	0.284 (29,335)	
O_3 vs. NO_2	0.229 (30,452)	0.558 (48,569)	0.629 (45,912)	0.621 (43,970)
O_3 vs. SO_4^{2-}	0.025 (41,616)	0.294 (54,727)	0.352 (15,912)	−0.384 (9164)
O_3 vs. IP SO_4^{2-}		0.171 (29,793)	0.033 (28,788)	
O_3 vs. fine		0.310 (26,621)		0.155 (28,908)
O_3 vs. coarse		0.015 (26,621)	−0.190 (28,908)	
O_3 vs. PM_{15}		0.185 (26,621)	−0.031 (28,908)	
NO_2 vs. SO_4^{2-}	0.676 (30,452)	0.347 (48,569)	0.447 (28,080)	0.553 (28,080)
SO_4^{2-} vs. IP SO_4^{2-}		0.530 (29,700)	0.760 (10,443)	
SO_4^{2-} vs. fine		0.518 (26,527)	0.732 (10,559)	
SO_4^{2-} vs. coarse		0.277 (26,527)	0.009 (10,559)	
SO_4^{2-} vs. PM_{15}		0.445 (26,527)	0.540 (10,559)	
IP SO_4^{2-} vs. fine		0.747 (26,740)	0.757 (29,782)	
IP SO_4^{2-} vs. coarse		0.296 (26,740)	−0.094 (29,782)	
IP SO_4^{2-} vs. PM_{15}		0.588 (26,740)	0.427 (29,782)	
Fine vs. coarse		0.606 (26,741)	0.144 (29,902)	
Fine vs. PM_{15}		0.901 (26,741)	0.745 (29,902)	
Coarse vs. PM_{15}		0.891 (26,741)	0.767 (29,902)	

correlations between 1979–1981 and 1982–1984 periods for inhalable particulates (IP) were surprisingly low (IP SO_4^{2-} was an exception), given the fact that these data all came from the same monitoring program and generally from the same stations within counties.

Next, we consider correlations between pollutants, which might act to obscure the true pollution–mortality relationships (Table 4b). Since there was close correspondence between pairwise and listwise correlations when the numbers of observations involved were also similar, only the pairwise values are given here. Pollutant combinations with relatively high correlations include AIRS SO_4^{2-} versus IP SO_4^{2-}, SO_4^{2-} versus fine particles, and PM_{15} versus its constituents (fine and coarse particles). Fine and coarse particles were moderately correlated in the first period ($R = .6$) but not in the second ($R = .14$). The correlation between TSP/PM_{10} and NO_2 was strongest for PM_{10} (4th period). Ozone had little or no correlation with TSP, coarse particles, SO_4^{2-}, and CO. Important shifts over time include CO versus SO_4^{2-} (changed from positive to negative), TSP versus O_3 (changed from negative to positive), CO versus O_3 (increased from nil to positive), and TSP versus SO_4^{2-} (decreased over time, negative in 1982–1988). The only strong negative relationships are between CO and AIRS SO_4^{2-} in the later exposure periods. The modest relationships between AIRS SO_4^{2-} and IP SO_4^{2-} are of special interest. The main difference is the type of filter used in the sampler, which creates artifact SO_4^{2-} in the AIRS samplers (Lipfert, 1994). Thus, the IP data are believed to be more accurate. Although in these correlations AIRS and IP SO_4^{2-} are only measured in the same county, not necessarily at the same site, long-term spatial distributions of SO_4^{2-} are believed to be sufficiently smooth to rule out this source of variability.

Regression Results With Nonpollutant Variables

One measure of the credibility of a mortality study is the extent to which the models produce reasonable estimates of previously established risk factors. We use the final model with a dummy variable for each VA center to examine the overall credibility of the model. This model employed 233 terms; 162 of them were interactions of the categorized SBP, DBP, and BMI variables with age. The most significant variables were SBP, DBP, BMI, and their interactions with age, current smoking, average education level in the subject's ZIP code, ever smoking, race, living in a high-poverty census tract, subject's height, and the clinic where the subject had been screened. The need for such a complex model was supported by the findings of nonlinearities, for example, in BMI, and in the large number of interaction terms that were significant, often at the .0001 level. The risk of current cigarette smoking (1.43) was somewhat lower than has been reported elsewhere, but other studies have not accounted for as many additional factors. The mortality risk of short stature was highly significant, at about 2%/cm. This is consistent with some of the findings in the literature (Cook et al., 1994; Watt et al., 1995), although the effect of stature on longevity seems to vary by cause of death (Samaras & Elrick, 1999). Patients

from the Buffalo VA Center enjoyed a 14% lower risk of dying (relative to St. Louis, the referent city), while the risk was 19% higher in Salt Lake City. The finding of positive effects of heating degree days on mortality (more deaths in northern climates) is consistent with the effects of cold on cardiovascular health (Eurowinter Group, 1997) and with less potential for outdoor exercise. The main effects of BMI were U-shaped and roughly consistent with the recent findings of Calle et al (1999). The effect of race was not significant, which suggests that race per se is not a factor after the physiological terms have been controlled for. Although the percentage of Hispanics in the county of residence was not a significant predictor for the nation, the lowest mortality risks were seen in San Juan, which is consistent with findings of lower rates of cardiovascular mortality in Hispanics (Ng-Mak et al., 1999).

The finding of higher mortality in colder climates also has implications with respect to the effects of air pollution. In colder climates, one would expect more time to be spent indoors, with less opportunity for exposure to outdoor air pollution and perhaps more exposure to indoor pollutants. The regression coefficient for degree days was robust (the effect was about 1% increase in mortality per thousand degree days) for all pollutants except the IP variables, for which it lost significance and became negative.

Preliminary Screening Regression Results

Univariate (survival as a function of pollution alone) and multivariate (survival as a function of pollution and other covariates) screening regressions were performed with 1982 ambient air quality for criteria pollutants, averaged for each VA center. The results were mixed, with both positive and negative significant relationships, as shown in Table 5. There were changes in sign and in significance between univariate and multivariate models; future regressions

TABLE 5. Results from Screening Regressions Using Model 1 and 1982 Air Quality Averaged by VA Center

Pollutant	Univariate model	Multivariate model
Mean concentrations		
CO	NS (+)	NS (−)
NO_2	NS (−)	NS (−)
O_3	S (−)	NS (−)
Pb	S (−)	S (−)
SO_2	S (−)	NS (−)
TSP	S (+)	S (+)
Peak concentrations		
CO	S (−)	NS (−)
NO_2	NS (−)	NS (+)
O_3	NS (+)	S (+)
SO_2	S (−)	NS (−)

Note. NS, $p > .05$; S, $p \leq .05$. Plus and minus refer to direction of mortality risk.

were restricted to multivariate models. Only 2 of the 10 pollutants were consistently significant in the multivariate model: TSP and O_3. Lead (Pb) and SO_2 were consistently negative and were not considered further. Peak O_3 performed better than average O_3 and was thus used in the subsequent analyses, as was peak CO.

Baseline Model Results

The baseline model was run both in the traditional mode, that is, with single periods for mortality follow-up and for exposure, and as a 3 × 4 matrix as described earlier. The latter mode allows the timing of exposure to be examined relative to the timing of death. The results are displayed in Table 6, which displays the exposure–mortality matrices for each pollutant (columns headed "deaths, 19xx"), plus some summary and explanatory statistics to help interpret this information. Beginning at the left of the table, correlations are given between pollution concentrations for successive exposure periods. The next six columns are the regression coefficients and fractional risks for each segment of the follow-up period. Cells within each matrix are identified as either "concurrent" (heavy boxes along the matrix diagonal), "delayed" (no identification), or "indirect" (shaded). The columns labeled "averages" (third to fifth from right) summarize each of these three categories by averaging the risks (up to 6 cells for "delayed," up to 3 cells for "concurrent," and up to 3 cells for "indirect"). The two columns at right under the heading "single period" present regression results from separate model runs for which mortality for the entire follow-up period was regressed against each exposure period, for the purpose of comparison with the segmented mortality analysis and with previous cohort studies (Dockery et al., 1993; Pope et al., 1995; Abbey et al., 1999). Within a column of this table, the cohort remains unchanged but the pollutants differ; however, since missing data vary by pollutant, there are also small changes in the population being considered. Within a row of the table, the pollutant remains constant, but the cohort is successively depleted with the passage of time.

Reading across the table from the top left, responses to historic TSP, averaged from 1953 to 1974, are seen to diminish with successive follow-up segments of the cohort. Reading down the left-most column, responses to successive exposure periods are seen to increase, such that the largest predictor of deaths that occurred between 1976 and 1981 was PM_{10} measured from 1989 to 1996. This must be deemed an indirect or noncausal association.

In general, Table 6 shows reasonably uniform responses within columns for each pollutant, especially for NO_2, and somewhat less uniform responses between columns (there are consistent decreases in response from early to late mortality periods). We examined a few changes in interpollutant correlations between columns (Table 4a) and found them to be minimal, suggesting that the depletion of the cohort by death did not change the basic relationships among pollutants, although such depletion may have affected the cohort's overall response to air pollution.

TABLE 6. Pollution Effects on Mortality by Exposure and Mortality Period

exposure period		deaths, 1976–81		deaths, 1982–88		deaths after 1988		averages of response categories			single period	
TSP, PM10	corr**	coeff*	effect	coeff*	effect	coeff*	effect	category	mean effect	std dev++	coeff*	effect
up to 1975		*0.966*	*0.072*	0.31	0.023	−0.38	−0.028				*0.42*	*0.031*
1975–81	0.86	*1.440*	*0.069*	0.554	0.027	*−1.310*	*−0.063*	*delayed*	0.005	0.043	*0.41*	*0.020*
1982–88	0.76	2.360	0.080	1.25	0.042	−0.09	−0.003	*concurrent*	*0.066*	0.018	0.75	0.025
89–96 (PM10)	0.73	*9.930*	*0.174*	*6.57*	*0.115*	*4.92*	*0.086*	*indirect*	*0.123*	0.039	*4.92*	*0.086*
SO4		coeff*	effect	coeff*	effect	coeff*	effect	category	mean effect	std dev++	coeff*	effect
up to 1975		*17.27*	*0.191*	*11.68*	*0.129*	*7.01*	*0.077*	*delayed*	*0.124*	0.050	*8.49*	*0.094*
1975–81	0.83	*17.39*	*0.185*	*15.42*	*0.164*	*5.67*	*0.060*	*concurrent*	*0.185*	n/a	*12.10*	*0.129*
1979–81 (IP)	0.53	−2.24	−0.015	*−12.08*	*−0.082*	*−23.76*	*−0.162*	*delayed*	−0.099	0.046	4.81	0.033
1982–84 (IP)	0.86	4.93	0.033	−5.12	−0.034	−7.58	−0.052	*concurrent*	−0.025	0.009		
								indirect	0.033	n/a		
PM2.5		coeff*	effect	coeff*	effect	coeff*	effect	category	mean effect	std dev++	coeff*	effect
1979–81		−2.54	−0.043	*−7.06*	*−0.120*	*−11.38*	*−0.193*	*delayed*	*−0.173*	0.038	1.52	0.026
1982–84	0.69	1.14	0.017	*−5.29*	*−0.080*	*−12.16*	*−0.206*	*concurrent*	*−0.061*	0.018	0.95	0.014
								indirect	0.017	n/a		
PM15–PM2.5		coeff*	effect	coeff*	effect	coeff*	effect	category	mean effect	std dev++	coeff*	effect
1979–81		−2.12	−0.034	−0.69	−0.011	−0.74	−0.012	*delayed*	−0.069	0.082	1.66	0.027
1982–84	0.40	*−10.34*	*−0.163*	−5.91	−0.093	*−11.54*	*−0.185*	*concurrent*	−0.063	0.029	−1.54	−0.024
								indirect	*−0.163*	n/a		
PM15		coeff*	effect	coeff*	effect	coeff*	effect	category	mean effect	std dev++	coeff*	effect
1979–81		−1.48	−0.044	−2.42	*−0.072*	*−5.63*	*−0.166*	*delayed*	*−0.168*	0.079	0.99	0.029
1982–84	0.53	*−4.33*	*−0.101*	*−4.54*	*−0.106*	*−8.96*	*−0.265*	*concurrent*	*−0.075*	0.031	−0.29	−0.007
								indirect	*−0.101*	n/a		
NO2		coeff#	effect	coeff#	effect	coeff#	effect	category	mean effect	std dev++	coeff#	effect
up to 1975		*3.31*	*0.101*	*2.24*	*0.069*	*2.11*	*0.065*				n/a	
1975–81	0.81	*5.47*	*0.139*	*3.75*	*0.095*	*3.05*	*0.077*	*delayed*	*0.076*	0.019		
1982–88	0.78	*5.02*	*0.098*	2.85	0.055	2.38	0.046	*concurrent*	*0.075*	0.046		
1989–96	0.91	*7.63*	*0.140*	*4.02*	*0.074*	1.72	0.031	*indirect*	*0.104*	0.027		
95%ile O3		coeff#	effect	coeff#	effect	coeff#	effect	category	mean effect	std dev++	coeff#	effect
up to 1975		*−0.740*	*−0.098*	−0.374	−0.049	*−0.542*	*−0.072*				*−0.79*	*−0.104*
1975–81	0.49	*0.901*	*0.103*	*0.903*	*0.103*	−0.096	−0.011	*delayed*	−0.011	0.072	*0.51*	*0.058*
1982–88	0.88	*2.770*	*0.150*	*2.813*	*0.152*	*1.135*	*0.061*	*concurrent*	*0.098*	0.046	*1.19*	*0.064*
1989–96	0.94	*4.230*	*0.152*	*4.106*	*0.148*	1.078	0.039	*indirect*	*0.150*	0.002	*2.31*	*0.083*
95%ile CO		coeff#	effect	coeff#	effect	coeff#	effect	category	mean effect	std dev++	coeff#	effect
up to 1975		*0.0043*	*0.047*	−0.0002	*−0.002*	*−0.0041*	*−0.045*				−0.000	−0.004
1975–81	0.37	*−0.0170*	*−0.131*	*−0.0217*	*−0.167*	*−0.0240*	*−0.185*	*delayed*	*−0.078*	0.085	*−0.013*	*−0.099*
1982–88	0.67	−0.0294	−0.081	*−0.0484*	*−0.134*	*−0.0424*	*−0.117*	*concurrent*	*−0.123*	0.013	*−0.028*	*−0.077*
1989–96	0.87	*−0.0590*	*−0.115*	*−0.0581*	*−0.113*	*−0.0536*	*−0.104*	*indirect*	*−0.103*	0.016	*−0.046*	*−0.090*

*fractional mortality per mg/m3
**w/previous period
#fractional mortality per ppm
++ among exposure/mortality periods

bold italic = $p < 0.05$

death before exposure | concurrent response

Note. "Effect" = fractional risk based on mean value of pollutant less estimated background.

In the context of previous studies, the magnitudes of most of the mean responses for the "concurrent" relationships for TSP, PM_{10}, O_3, and NO_2 seem reasonable, although the SO_4^{2-} responses vary. There is a strong contrast between results for the AIRS and for the IP sulfate variables. AIRS SO_4^{2-} was significant (positive) with large mean responses in all three follow-up periods, while IP SO_4^{2-} was mainly negative, significantly so for the "delayed" cells of Table 6. Since AIRS SO_4^{2-} data are known to be biased by filter artifacts (Lipfert, 1994), our a priori expectation was that responses to the IP data would be more credible. However, there are also differences in the sets of counties that had data for both pollutants.

Few if any "delayed" relationships are larger than their "concurrent" counterparts in Table 6. However, delayed relationships occur mostly in the later years of follow-up, when depletion of the cohort may be a factor. Note that these "delayed" estimates tend to be lower than those reported for previous prospective cohort studies (Dockery et al., 1993; Pope et al., 1995; Lipfert, 1995).

Negative relationships, of which some were significant, were found for the IP variables (fine and coarse fractions, PM_{15}) and for CO (except for pre-1975 exposure and 1976–1981 deaths). An inverse relationship was seen between the CO and the O_3 responses; cells in Table 6 with positive results for CO had negative entries for O_3, and vice versa. There are statistically significant indirect (death preceding apparent exposure) responses. Although some of these could be due to the high correlations between exposure periods, most of the indirect estimates are larger then the potentially causal ones.

Final Model Results

Subjects' heights* and the ecological variables were added to the baseline model to comprise the final model, and the analyses shown in Table 6 were replicated to allow detailed comparisons (Table 7). The effect of including the ecological variables differed substantially by pollutant. Because of the significant contributions of the ecological variables in ways that agreed with expectations, the estimates shown in Table 7 are regarded as the more credible.

Minimal changes due to the ecological variables were seen for peak O_3, NO_2, peak CO, $PM_{2.5}$, PM_{15}, and IP SO_4^{2-}. Except for the indirect responses, responses to TSP and PM_{10} were reduced, with loss of statistical significance. The largest changes were seen in AIRS SO_4^{2-}, for which the concurrent response in the earliest period dropped by an order of magnitude with respect to the baseline model, and the delayed responses changed sign.

Responses to NO_2 are consistent across all three follow-up periods (five of the six estimates are significant), and the delayed response is not significantly different from the concurrent response; this may be due in part to the fact that

*A limited investigation of the effect on the pollution estimates of adding only height to the baseline model showed generally minimal differences.

TABLE 7. Pollution by Exposure and Mortality Period with Ecological Variables

exposure period		deaths, 1976–81		deaths, 1982–88		deaths after 1988		averages of response categories				single period	
TSP, PM10	corr**	coeff*	effect	coeff*	effect	coeff*	effect	category	mean effect	std err++		coeff*	effect
up to 1975		−0.351	−0.026	***−0.81***	***−0.060***	***−1.49***	***−0.111***					−0.18	−0.013
1975–81	0.86	0.078	0.004	−0.680	−0.033	***−2.490***	***−0.120***	*delayed*	−0.059	0.043		0.41	0.020
1982–88	0.76	***2.060***	***0.070***	1.08	0.037	−0.20	−0.007	*concurrent*	0.033	0.023		***0.94***	***0.032***
89–96 (PM10)	0.73	***7.060***	***0.124***	***4.33***	***0.076***	3.43	0.060	*indirect*	***0.090***	0.024		***3.92***	***0.069***
SO4		coeff*	effect	coeff*	effect	coeff*	effect	category	mean effect	std err++		coeff*	effect
up to 1975		2.20	0.024	−0.02	−0.000	***−8.1***	***−0.090***	*delayed*	−0.025	0.061		−0.10	−0.001
1975–81	0.83	1.74	0.019	4.25	0.045	***−9.78***	***−0.104***	*concurrent*	0.019	n/a		***4.93***	***0.053***
1979–81 (IP)	0.53	−6.62	−0.045	***−18.45***	***−0.126***	***−32.47***	***−0.221***	*delayed*	***−0.141***	0.060		1.82	0.012
1982–84 (IP)	0.86	3.05	0.020	−9.57	−0.064	−11.15	−0.076	*concurrent*	−0.054	0.009		***6.68***	***0.045***
								indirect	0.020	n/a			
PM2.5		coeff*	effect	coeff*	effect	coeff*	effect	category	mean effect	std err++		coeff*	effect
1979–81		−5.28	−0.090	***−10.07***	***−0.171***	***−15.35***	***−0.261***	*delayed*	***−0.205***	0.040		0.27	0.005
1982–84	0.69	0.236	0.004	***−6.11***	***−0.092***	***−10.78***	***−0.183***	*concurrent*	***−0.091***	0.001		−0.06	−0.001
								indirect	0.004	n/a			
PM15–PM2.5		coeff*	effect	coeff*	effect	coeff*	effect	category	mean effect	std err++		coeff*	effect
1979–81		−4.27	−0.069	−1.99	−0.032	***−9.20***	***−0.148***	*delayed*	***−0.127***	0.071		0.68	0.011
1982–84	0.40	***−11.00***	***−0.173***	***−7.91***	***−0.124***	***−12.64***	***−0.203***	*concurrent*	***−0.096***	0.028		***−3.64***	***−0.057***
								indirect	***−0.173***	n/a			
PM15		coeff*	effect	coeff*	effect	coeff*	effect	category	mean effect	std err++		coeff*	effect
1979–81		−3.03	−0.090	***−3.79***	***−0.112***	***−7.65***	***−0.226***	*delayed*	***−0.209***	0.073		0.30	0.009
1982–84	0.53	***−4.46***	***−0.104***	***−5.99***	***−0.139***	***−9.73***	***−0.288***	*concurrent*	***−0.114***	0.025		−1.54	−0.036
								indirect	***−0.104***	n/a			
NO2		coeff*	effect	coeff*	effect	coeff*	effect	category	mean effect	std err++		coeff*	effect
up to 1975		***2.36***	***0.072***	***2.18***	***0.067***	***2.38***	***0.073***					***−0.33***	−0.010
1975–81	0.81	***3.66***	***0.093***	***2.72***	***0.069***	***2.91***	***0.074***	*delayed*	***0.064***	0.015		***1.43***	0.036
1982–88	0.78	2.5	0.049	1.49	0.029	1.66	0.032	*concurrent*	0.045	0.034		***−0.20***	−0.004
1989–96	0.91	3.81	0.070	1.64	0.030	0.741	0.014	*indirect*	0.049	0.016		***0.07***	0.001
95%ile O3		coeff*	effect	coeff*	effect	coeff*	effect	category	mean effect	std err++		coeff*	effect
up to 1975		***−0.670***	***−0.088***	−0.250	−0.033	−0.292	−0.039					***−0.54***	***−0.072***
1975–81	0.49	***0.898***	***0.102***	***0.881***	***0.100***	−0.087	−0.010	*delayed*	−0.002	0.063		***0.56***	***0.063***
1982–88	0.88	***2.540***	***0.137***	***2.710***	***0.146***	1.106	0.060	*concurrent*	***0.094***	0.046		***1.25***	***0.068***
1989–96	0.94	***4.030***	***0.145***	***3.840***	***0.138***	0.962	0.035	*indirect*	***0.140***	0.004		***2.39***	***0.086***
95%ile CO		coeff*	effect	coeff*	effect	coeff*	effect	category	mean effect	std err++		coeff*	effect
up to 1975		0.0013	0.014	−0.0022	−0.024	***−0.0061***	***−0.065***					−0.001	−0.015
1975–81	0.37	***−0.0128***	***−0.099***	***−0.0186***	***−0.143***	***−0.0203***	***−0.156***	*delayed*	***−0.072***	0.061		***−0.008***	***−0.061***
1982–88	0.67	−0.0007	−0.002	***−0.0246***	***−0.068***	***−0.0216***	***−0.060***	*concurrent*	***−0.061***	0.034		−0.009	−0.025
1989–96	0.87	−0.0106	−0.021	−0.0136	−0.027	−0.0078	−0.015	*indirect*	***−0.016***	0.011		−0.009	−0.017

*fractional mortality per mg/m3
**w/previous period
#fractional mortality per ppm
++ among exposure/mortality periods

bold italic = p < 0.05

death before exposure | concurrent response

Note. "Effect" = fractional risk based on mean value of pollutant less estimated background.

the mean concentrations of NO_2 changed relatively little during the follow-up period and were highly correlated among segments. With the exception of NO_2, most of the significant responses after 1988 are negative, and there is a general tendency for lower regression coefficients with increasing follow-up time (with the exception of O_3, for which the highest value occurred in the 1982–1988 period). The only significant responses for SO_4^{2-} were negative, for both AIRS and IP data sets; this represents an important change from Table 6 for the AIRS SO_4^{2-} data. The summary columns in Table 7 show positive average concurrent responses for TSP, AIRS SO_4^{2-}, NO_2, and O_3, but only the value for O_3 was significant overall. The single-period responses were consistent with the segmented analysis for PM_{10} (which was measured late in the follow-up period and thus represented mainly an "indirect" response), peak O_3 (single-period responses were lower than those for the earlier periods), and CO (all responses were negative).

Because of the strong showing for peak O_3 in the middle of the follow-up period, we conducted a simple test for the linearity of response to the 1975–1981 pollution data. This was done by dividing the data set into tertiles and evaluating the relative risk for counties in the upper two tertiles compared to the lowest one. The results are shown in Figure 1. Only the top tertile showed excess risks, such that the dose-response plot shows a clear threshold, plotted here at the midpoint of the tertile (the lower limit of this group was 0.15 ppm). Although only the result for the 1982–1988 mortality period was significant ($p = .018$), results for the two periods shown are not significantly

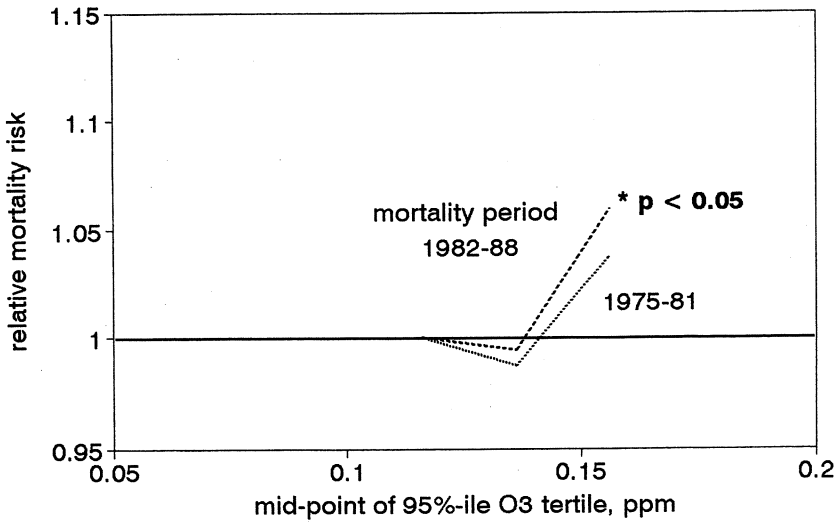

FIGURE 1. Results of tests of linearity of 1975–1981 peak O_3 as a predictor of 1975–1981 and 1982–1988 mortality, based on pollutant tertiles and the final model.

different. Note from Table 7 that the reduced regression coefficient and loss of statistical significance of peak O_3 in 1989–1996, for which the mean concentration was reduced to 0.085 ppm, is also consistent with the presence of a threshold.

The results of running the model with a dummy variable for each VA center were used to construct a map of excess mortality risk relative to St. Louis (the referent center), in the absence of controlling for air pollution (Figure 2). The high mortality areas are seen to be in the south central United States (Houston, Dallas, and New Orleans), in addition to Salt Lake City and Los Angeles (note that this map presents data that have been adjusted for the effect of degree days, as discussed earlier). This is consistent with the strong responses to ozone that were seen in Tables 6 and 7. In contrast, the residuals in the northeastern and north-central United States were mixed, with significantly low values in Buffalo, Indianapolis, and New Haven, CT, and moderate risks in other cities in this region. These trends were found to be reasonably consistent across all three mortality periods.

Figure 2 may be useful in trying to understand some of the interrelationships among pollutant responses, for example, the inverse relationship between responses to peak CO and O_3. Figure 2 shows that mortality risks in Houston and Dallas are generally higher than those in Pittsburgh and Philadelphia. The AIRS database indicates that the Texas cities were somewhat higher in O_3 and lower in CO than the Pennsylvania cities, thus providing a rough check.

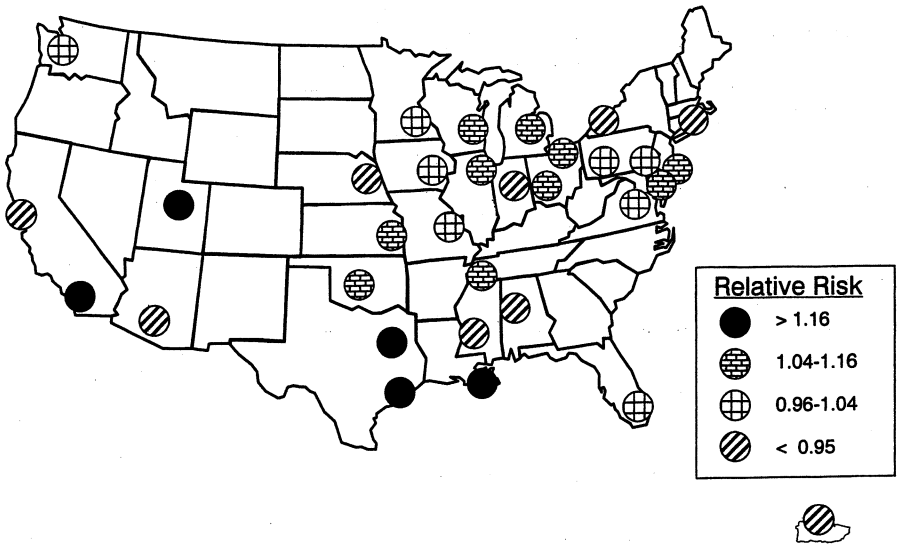

FIGURE 2. Map of VA centers showing excess risks estimated without air pollution in the (final) model.

Two-Pollutant Regression Results

A limited investigation was made of joint regressions of selected pairs of pollutants and time periods, using the final model. The objectives were to evaluate the effects of pollutant collinearity and to check robustness of the single-pollutant response when subjects are removed because of missing data for the second pollutant. The results are shown in Table 8, which compares the single-pollutant responses ("separate") with the joint responses. In the presence of collinearity (indicated by the correlation coefficients shown), one would expect some interchange of response between the two pollutants. Joint regressions also reduce the numbers of observations that may be considered

TABLE 8. Two-Pollutant (Joint) Regression Results: Fractional Risks Based on Mean Value of Pollutant Less Estimated Background

	(a) Results for the entire period of follow-up			
	Separate	*R*	Joint	*n* (Joint regression)
1. 1975–81 Exposures				
NO_2	0.035	.35	0.039	48,569
AIRS SO_4^{2-}	**0.053**		**0.072**	
Sum	0.089		0.111	
NO_2	0.036	.56	−0.013	48,569
Peak O_3	**0.063**		**0.086**	
Sum	0.099		0.073	
2. 1982–88 Exposures				
TSP	**0.032**	.63	0.030	56,315
Peak O_3	**0.068**		**0.062**	
Sum	**0.100**		0.092	
IP SO_4^{2-}	**0.045**	.03	0.028	28,788
Peak O_3	**0.068**		**0.124**	
Sum	**0.113**		0.152	
3. 1989–96 Exposures				
PM_{10}	**0.069**	.29	**0.052**	55,444
Peak O_3	**0.086**		**0.076**	
Sum	**0.155**		**0.127**	

	(b) Segmented analysis, averaged over all exposure years					
	Concurrent responses		Delayed responses		Indirect responses	
	Separate	Joint	Separate	Joint	Separate	Joint
Peak O_3	**0.094**	**0.122**	−0.002	0.034	**0.140**	0.178
NO_2	0.045	−0.036	**0.064**	0.030	0.049	−0.052
Sum	0.139	0.086	0.062	0.064	0.189	0.126

Note. Boldface indicates $p < 0.05$. O_3–NO_2 correlations, .23 to .62. Number of subjects, 30,452 to 48,569.

simultaneously, because of missing data; the numbers of subjects having data on both pollutants are shown in the table. The largest reduction was imposed by the IP dataset.

As an initial approach to this question, we used a single period of follow-up (Table 8a) for the 1975–1981 exposure period; we found only minimal differences between separate and joint regressions for (NO_2, AIRS SO_4^{2-}) and for (NO_2, peak O_3). The separate responses were roughly additive, and the relative importance of the pollutants did not change with joint regression. This was also the case for (TSP, peak O_3) for 1982–1988 exposure period and for (PM_{10}, peak O_3) in 1989–1996, but not for the combination of IP SO_4^{2-} and peak O_3 in 1982–1988. In this last case, IP SO_4^{2-} lost importance and peak O_3 gained importance in the joint regression, in spite of the negligible correlation between them. The large increase in response to peak O_3 was thus likely due to the combination of locations that also had data on IP SO_4^{2-}. These results suggest that responses to peak O_3 are reasonably robust to joint regression modeling and the concomitant reductions in the numbers of counties considered.

The investigation was extended to the segmented follow-up analysis for the combination of peak O_3 and NO_2, the two pollutants with the most consistent responses in Table 7. The separate and joint regression results are compared in Table 8b, on the basis of average concurrent, delayed, and indirect responses. Here, only the delayed separate responses appear to be additive. For the joint regression of concurrent responses, the O_3 response increased while the NO_2 response became negative, such that the total joint response was about the same as the separate O_3 response. This was also the case with the indirect responses. In the joint regression of delayed responses, the O_3 and NO_2 shares were about the same (neither was significant) and the total was the same as the separate delayed response to NO_2 (which was significant).

This limited investigation thus suggests that peak O_3 is the dominant pollutant for concurrent responses, while the smaller delayed response may be shared by O_3 and NO_2. As in Table 7, additional insight is gained from the segmented analysis, including the caution implied by the finding of large significant indirect responses.

DISCUSSION

The "conventional wisdom" about the acute mortality effects of air pollution at the low ambient levels we currently enjoy is that death may be hastened for some fraction of the frail elderly that happen to already be compromised at the time of exposure, thus rendering them more susceptible (Lipfert, 1994, 1997). Such effects may be more severe for the lower socioeconomic elements of society, since their mortality rates tend to be higher, they may be less likely to enjoy whole-house air conditioning (which reduces the penetration of outdoor air), and they may live in neighborhoods closer to local sources of air pollution. Thus, relative to the general or middle class public who have

been studied previously (Dockery et al., 1993; Pope et al., 1995; Abbey et al., 1999), somewhat larger effects should be expected for this cohort, because of its high levels of smoking, low SES, and male gender (some studies have identified males as being more susceptible to air pollution). However, in general, these expectations have not been realized. Later we discuss the findings across all models and with special reference to the final model, as shown in Table 7.

Three caveats should be expressed about comparisons among the various cells for each pollutant in Tables 6 and 7. First, the different pollutants, both among species and among time periods within species, may represent different locations because of missing data. Second, the relatively high fraction of mortality within this cohort may have depleted it of susceptible individuals in the later periods of follow-up. Finally, all of the personal characteristics of each subject were determined only at entry to the study. It is quite likely that many of those characteristics will have changed during the 21 years of follow-up. This may a reason to regard the results for the 1976–1981 period as the most credible.

Comparisons Across Models

Tables 6 and 7 are intended to be comprehensive and to facilitate detailed comparisons among the 12 cells of the exposure period–mortality period matrices. As stated earlier, we consider the results of Table 7 to be the more credible. Table 9 summarizes this detailed information and displays the overall features of the analysis, such as responses to the inclusion of county-level ecological variables (in addition to air quality), single versus segmented periods of mortality follow-up, and the timing of exposure relative to death. The entries in the "single period" columns of Tables 6 and 7 were averaged across the four exposure periods to create the corresponding columns in Table 9. The pollutants are listed in decreasing order of mean response to concurrent exposure.

Beginning at the left of Table 9, we compare responses for concurrent exposure and mortality periods with respect to the inclusion of ecological variables and with respect to the single-period responses. The concurrent responses were larger than the single-period responses for AIRS SO_4^{2-}, TSP, O_3, and NO_2; they were smaller for the other species and significantly negative for $PM_{2.5}$ and PM_{15}. The delayed responses (mortality associated with prior exposure periods) were smaller (more negative) than their concurrent counterparts for all pollutants except NO_2, for which there was little difference between the two mortality follow-up periods. Including the ecological variables also reduced the mean concurrent responses (they became more negative), which was also the case for indirect responses except for CO.

The strength of this analysis lies in its analytical design and the ability to compare the 12 cells of each exposure–mortality matrix. In contrast, the single-period analysis represents an aggregated approach to exposure. When the follow-up periods are short, say a few years, the exposure aggregation

TABLE 9. Reconciliation of Average Responses, Expressed as Fractional Risks at Mean Value of Pollutant Less Background

	1. Concurrent responses		2. Delayed responses		3. Indirect responses		4. Single mortality period	
Pollutant	Table 7 with ecol var	Table 6 no ecol var	Table 7 with ecol var	Table 6 no ecol var	Table 7 with ecol var	Table 6 no ecol var	Table 7 with ecol var	Table 6 no ecol var
Peak O_3	**0.094**	**0.098**	−0.002	−0.011	**0.140**	**0.150**	**0.036**	**0.025**
NO_2	0.045	**0.075**	**0.064**	**0.076**	0.049	**0.104**	0.006	n/a
TSP, PM_{10}	0.033	**0.066**	−0.059	0.005	**0.090**	**0.123**	0.027	**0.041**
SO_4 (AIRS)	0.019	**0.185**	−0.025	**0.124**	n/a	n/a	0.026	**0.112**
SO_4 (IP)	−0.054	−0.025	**−0.141**	−0.099	0.020	0.033	0.029	0.033
Peak CO	**−0.061**	**−0.123**	**−0.072**	**−0.078**	−0.016	**−0.103**	−0.030	**−0.068**
$PM_{2.5}$	**−0.091**	**−0.061**	**−0.205**	**−0.173**	0.004	0.017	0.002	0.020
PM_{15}	**−0.114**	**−0.075**	**−0.209**	**−0.168**	**−0.104**	**−0.101**	−0.013	0.011
PM_{15}–$PM_{2.5}$	−0.096	−0.063	−0.127	−0.069	**−0.173**	**−0.163**	−0.023	−0.001

Note. Bold, $p < .05$. Ecol var, ecological variable. n/a, not applicable.

error may be small but the study will generally lack power because of smaller numbers of deaths. For longer follow-up periods, say 10 yr or more, it becomes important to consider the timing of death relative to exposure, in order to preclude associating mortality with subsequent exposure. In the present study, the "indirect" cells of the matrix tend to occur earlier in the follow-up period, while the "delayed" cells tend to occur later. Since there is one "concurrent" cell for each mortality period, they are distributed evenly throughout the period of follow-up, but the use of specific exposure periods improves the precision of the exposure estimates. For example, in Table 9 with ecological variables in the model, there is only one significant response for the single mortality period but four are significant for the segmented analysis (concurrent responses), which is consistent with the more precise definition of exposure in the latter. This would apply to both positive and negative responses.

In comparing indirect (earlier) responses with delayed (later) responses and the general trend toward lower responses in the later years, two other factors must be considered: The most susceptible members of the cohort will have died first, and given the high total mortality rate over the 24 yr, the pool of susceptible subjects may have become depleted. This hypothesis is consistent with considering air pollution as exacerbating existing disease rather than creating new cases. Second, the personal characteristics of subjects (including residence locations) may have changed over the years, leading to greater error in the independent variables in the later periods and likely biasing those estimates towards the null. This paradigm would also identify the top left cell of each matrix as the most reliable indicator of delayed responses; in Table 7, this cell is only significant (positive) for NO_2, but that response is only marginally larger than the concurrent response and could be attributed to the correlation between exposure periods (.81).

For the single period of follow-up without ecological variables in the model, responses are significantly positive for SO_4^{2-} (as measured on glass-fiber filters and reported by AIRS), but not for the IP SO_4^{2-} data (measured on Teflon filters), for TSP (PM_{10} in the last period), or for peak ozone. The response to peak CO was significantly negative. Adding the ecological variables to this model reduced the mean responses, substantially for AIRS SO_4^{2-}, for all species except peak O_3 and peak CO (this comparison was not made for NO_2). A previous cohort study (Pope et al., 1995) that used similar air quality data found mean risks of 0.077 for AIRS SO_4^{2-} and 0.117 for $PM_{2.5}$ (Lipfert, 1995). The latter result is much higher than any $PM_{2.5}$ response found in the present study; the response to AIRS SO_4^{2-} is midway between the single-period results in Tables 6 and 7.

Effects of Ecological Variables

The effects of the ecological variables in reducing the mean pollution responses may simply be attributed to collinearity between the two types of variables. For example, the subject-weighted correlations between degree days and AIRS SO_4^{2-} (1960–1974, 1975–1981), IP SO_4^{2-} (1979–1981, 1982–

1983), and 1982–1984 $PM_{2.5}$ were .77, .86, .67, .36, and .28, respectively, reflecting higher SO_4^{2-} and $PM_{2.5}$ levels in more northern locations. However, only the AIRS SO_4^{2-} mortality estimates were substantially affected by including the ecological variables. When collinear variables compete in such situations, the relative degrees to which they represent the actual agents of biological action affect the stability of their coefficients; in this study, all of the ecological variables must be considered surrogates (including the air quality variables, which are likely to differ from actual personal exposures). With respect to collinearity between degree days and air quality, it should be noted that the degree-day estimates were very stable in the single-period regressions, but fell into two groups: For the "IP" pollutants (n = 26,067 to 29,192),* the mean estimate of the degree-day regression coefficient was −.0067 with a standard error of .0011; for the remaining pollutants (n = 36,869 to 65,551), the mean estimate was .011 with a standard error of .0006. This provides some indication of heterogeneity among the counties having data on specific air pollutants. In contrast, the model estimates for personal attributes such as current smoking were quite stable for all the data sets defined by pollutant data availability.

There is also the question of the significant negative responses to air pollution. We note that they occur in each column of Table 9 and throughout Tables 6 and 7; thus, they are unlikely to be purely chance occurrences or due to one particular aspect of the model. However, these negative responses should not be interpreted as "beneficial" effects of air pollution. The only conclusory statements that may be made are along the lines of: "The members of this cohort who resided in counties with higher values of pollutant X tended to survive longer than those residing where concentrations were lower." For example, the trend toward lower risks in locations with higher SO_4^{2-} levels may be seen from Figure 2, which shows that patients from Buffalo, New Haven, and Indianapolis (cities with generally higher SO_4^{2-} levels) all have less risk than patients from most of the centers in the West. The implication is thus that the additional predictor variables required to explain these gradients must be missing from our model, even though this model is perhaps more complex than most. This caveat also affects any causal attributions that might be hypothesized from the positive relationships. Thus, it is impossible to judge whether the final model used here is adequate or whether the use of additional mortality predictors, such as variables for diet and/or exercise,† might have affected the pollution results even more.

A further consideration is that of spatial autocorrelation or clustering of effects in specific geographic locations. For example, Figure 2 suggests that such a cluster or "hot spot" might exist in Louisiana and parts of Texas. While

*n, number of subjects with data. Note that 23 of the main counties for the 32 VA centers had data from the IP dataset.

†However, lack of exercise has been shown to increase blood pressure (Slattery & Jacobs, 1988; also see Cleroux et al., 1999), which may thus be a surrogate for exercise habits and was controlled in this study.

the scope of this portion of the project did not permit a formal analysis of spatial autocorrelation effects, we note that increasing the standard errors of the pollution estimates by as much as a factor of 2 would not render all of the anomalous findings (negative and/or indirect responses) nonsignificant. Thus, while consideration of spatial autocorrelation might result in loss of significance for some of the estimates, it is unlikely to change the general conclusions of the study.

Responses to Particulate Matter

Here we consider particulate matter in various particle size ranges but without regard to chemistry. TSP has shown significant responses in all of the models, but in Table 7 it was significant (positive) only as an indirect association (1976–1981 deaths vs. 1982–1988 TSP). The average concurrent response found here (0.033), although not significant, is consistent with effects seen in time-series studies (Lipfert & Wyzga, 1995) and in previous population-based cross-sectional studies (Lipfert, 1992). There are no indications of persistent or delayed responses due to prior exposures. PM_{10} showed the largest positive responses, but they were both in indirect cells in the matrix; the concurrent response to PM_{10} was consistent with the previous period for TSP. It is possible that the indirect responses may simply reflect random variation and collinearity among time periods. At the right-hand side of Table 7, the results for a single mortality period compare quite well with the average across the three separate periods. The standard errors of the IP responses may have been inflated somewhat because of the fewer numbers of observations (Table 3); consideration of spatial autocorrelation would likely increase them further. The results of all four of these parameters ($PM_{2.5}$, CP, PM_{15}, and SO_4^{2-}) were quite similar: generally negative throughout, especially in the last period. In general, the averages across all three periods do not agree with the single-period responses. There are about 10% more subjects in the 1982–1984 period, which would argue that those results might be given more weight. Again, there was no evidence of (positive) delayed response. Previous analyses of size-classified PM have shown stronger (positive) responses for fine particles than for coarse (Pope et al., 1995; Lipfert, 1995) (owing in part to the greater uncertainties involved in the measurement of coarse particles; Lipfert & Wyzga, 1998). We see no evidence of this ranking in any of the models considered here.

Responses to Sulfate

After incorporating the ecological variables (Table 7), we found no evidence that sulfate particles, which are smaller in size and sometimes acidic, are any more toxic than ordinary PM. The significant negative responses in the last period are unlikely to have been due to chance; they are consistent with the lower mortality risks in this cohort in northeastern locations (higher SO_4^{2-}) relative to the south-central and western areas (lower SO_4^{2-}), as seen in Figure 2. The responses to IP SO_4^{2-} were generally more negative than those for AIRS, suggesting the filter artifacts of AIRS measurements may have

biased those results high or that the subset of counties that had IP data is fundamentally different from the rest of the nation.

Responses to Nitrogen Dioxide

Responses to NO_2 in this study were mixed. NO_2 was not significant in the screening regressions or for the entire follow-up period, but it appeared to be the strongest and most consistent pollutant in the segmented analysis. NO_2 was the only pollutant that showed minimal variation across mortality follow-up periods, including delayed responses, five out of six of which were statistically significant. The delayed responses to NO_2 were also somewhat larger than the concurrent responses. NO_2 also showed slightly smaller and nonsignificant responses in the "indirect" cells; the main differences between NO_2 responses with and without ecological variables are the reduced and nonsignificant indirect responses for the latter. Previous cross-sectional studies that found mortality associations with NO_2 or NO_x included the Harvard Six Cities Study (Dockery et al., 1993; single-period mean response = 0.19) and an ecological study that was based on concentrations estimated from a mathematical dispersion model rather than measurements (Lipfert et al., 1988; concurrent mean responses in the range 0.05–0.07). The latter results are quite consistent with the present findings. However, ozone dominated in joint regressions with NO_2 (Table 8) for concurrent responses and shared the joint delayed response. These results suggest that further studies of potential long-term mortality effects of NO_2 and O_3 would be appropriate, including studies with other cohorts.

Responses to Ozone

Responses to ozone have also been qualitatively consistent for all models, but only for peak O_3. When 1975–1981 O_3 was tested for linearity, a clear threshold was seen slightly above the previous federal 1-h standard (0.12 ppm), as shown in Figure 1. This result, which should be confirmed with more detailed studies, suggests that the present standard may be protective of public health from the standpoint of premature mortality.

It should be noted that the spatial distribution of O_3 differs between average and peak metrics, since urban and near-urban areas tend to have wider distributions (higher peaks and lower means) than more distant rural areas, which may show the opposite. The mean of all 8 positive responses in Table 7 was 0.092 ± 0.038. Responses to ozone are stronger for concurrent exposure than for prior exposures. The mean response to peak O_3 in Table 7 is about double what was seen in an (unpublished) population-based mortality study of mean O_3, around 1980 (Lipfert, 1992). As with TSP, the results for a single mortality period compare quite well with the average across the three separate mortality periods.

Responses to Carbon Monoxide

Responses to peak CO were uniformly negative for all but the "delayed" response to 1960–1974 CO, for which the mean 95th percentile concentra-

tion was 11 ppm. However, the CO results were generally more scattered than those for TSP or O_3, although none of the "indirect" categories was significant in Table 7. The entries in Table 9 are reasonably consistent across columns, and the "indirect" responses in Table 7 were not significant. CO tends to be higher in northern locations and in densely populated cities, but population density was not significant as an ecological predictor. At present, we have no explanation for the significant negative responses to peak CO, but it is apparent that this response is quite robust. It is possible that consideration of spatial autocorrelation might increase the standard errors of these (and of other) responses, but the consistency of the negative responses to CO in all of the models considered makes it unlikely that they are all due to chance.

Summary of Pollution Responses

As shown in Table 9, responses to AIRS SO_4^{2-} are quite consistent for each model type but are substantially reduced by the inclusion of ecological variables. Responses to TSP (PM_{10}) are reasonably consistent except for the absence of "delayed" responses, in spite of high pollutant correlations between periods. Responses to sulfate from the IP network differ greatly from those for AIRS SO_4^{2-}; this is because some different cities are involved and because the latter measurements are substantially affected by filter artifacts,. Responses to peak O_3 resemble those to TSP (PM_{10}), especially with regard to the absence of delayed responses; however, TSP–O_3 correlations are low. Responses to $PM_{2.5}$ and PM_{15} differ greatly between the single period and the segmented periods; this is thus a prime example of the value of the segmented analysis in revealing such details. The single-mortality-period responses without ecological variables are qualitatively similar to what has been reported before ($SO_4^{2-} > PM_{2.5} > PM_{15}$), but the segmented analyses show that responses to all of the IP variables are negative, some significantly so. The coarse-particle responses are reasonably consistent except for the indirect responses. Responses to peak CO are consistently negative throughout; the only substantial negative pollutant correlations with CO are for AIRS SO_4^{2-}. Responses to NO_2 are consistent for all three segmented periods but differ from the single-period result. Table 9 thus suggests that O_3 and NO_2 are the most important pollutants and that the concurrent responses are the most credible. The two-pollutant modeling suggests that peak O_3 is more important than NO_2.

Hypertension Considerations

Recent developments in air pollution epidemiology have focused on cardiovascular parameters. Since this cohort comprised diagnosed hypertensives, a possible response pathway might involve relationships between blood pressure and air pollution. The literature on this topic is sparse; Coppola et al. (1989) exposed 12 healthy nonsmoking volunteers to automobile exhaust fumes in a chamber for 30 min; an increase in COHb was observed, but no significant changes in heart rate or blood pressure were seen. In a larger group of healthy and asthmatic volunteers (Linn et al., 1985), exposure to

4 ppm of NO_2 reduced systolic blood pressure. However, Linn et al. (1999) found a weak transient positive relationship between blood pressure and daily outdoor PM_{10} levels in Los Angeles (but not with personal exposure to PM or with central station outdoor NO_2 or O_3). There has been a long-standing association between lead and blood pressure (Hu et al., 1996; Korrick et al., 1999), and it is possible that NO_2 is acting as a surrogate for lead in this study, since vehicle exhaust is a major source of both pollutants. However, this hypothesis is not consistent with the strong negative associations with CO or with the screening regression results for Pb. Note that the best lead metric for predicting blood pressure is the concentration in bone (Hu et al., 1996); atmospheric concentrations may thus be a poor surrogate, leading to attenuated response or even transference of causality because of the resulting exposure measurement error. We thus see no consistent evidence linking exposure to air pollution with development of hypertension.

Causal Interpretations of the Associations

Statistical significance alone is not a sufficient criterion for a causal interpretation of the findings. First, until spatial autocorrelation is accounted for, the significance levels shown here are likely to be inflated. Second, we have not been able to control for all possible confounders, notably diet and exercise. Finally, special attention must be given to significant negative associations between pollution and mortality, which may be indications of confounding or an incomplete model specification. Obviously, such problems could affect the positive associations as well. In a cross-sectional analysis, the gradients pertain first and foremost to the characteristics of places; extension of those findings to the air pollution exposures of one-time residents of those places may or may not be justified. However, we have shown that this model produces credible results for age, blood pressure, smoking, and body mass index, which makes it difficult to reject the findings relative to pollution merely because they differ from expectations.

Needs for Further Research

There are several relevant topic that have not yet been addressed with this cohort. First, the robustness of the results in Table 7 to alternative definitions of subcohorts must be shown, along with responses for a common dataset that allows all pollutants to be evaluated for the same counties. Another issue is the linearity of the implied dose-response functions, both positive and negative. This issue could be addressed by treating selected pollutants as categorical rather than continuous variables. Another is the potential for interactions between pollutants and age, to be handled in the same way as other interactions. It may be useful to analyze selected subsets, such as by race, smoking status, or degree of hypertension. By considering the distribution of air quality by race over time, some contributions to the issue of environmental justice may be possible. Finally, there is a set of morbidity data that could be subjected to similar analyses, and there should be additional follow-up data

available in the future. In all cases, studies should include identification of influential observations and corrections for spatial autocorrelation.

CONCLUSIONS

The results from this study that have been obtained thus far show that the most consistent plausible associations with mortality were for exposures concurrent with the period of follow-up. Peak ozone was the only pollutant with consistent positive concurrent responses; the presence of a threshold at about 0.14 ppm was suggested. NO_2 was the only pollutant for which concentrations measured before enrollment were consistently associated with mortality; these delayed responses were consistently significant (positive) throughout the period of follow-up, but the delayed responses were not significantly different from the concurrent responses. However, before any of these results can be accepted at face value, linearity issues should be investigated in more detail and the regression analysis protocol investigated here should be tested with another cohort.

The study found some responses that were consistent with previous studies (Dockery et al., 1993; Pope et al., 1995; Abbey et al., 1999), but only in the absence of ecological covariates in the model or when responses were aggregated across the entire period of follow-up. The study also found many inconsistent and anomalous results for some pollutants (NO_2 is a notable exception), such as statistically significant effects of air pollution with the "wrong" sign and significant risks of exposure after death, with and without such ecological covariates. Most of these findings were the result of a more detailed consideration of exposure timing than has been used in previous cohort studies, and they suggest that even this relatively complex model might benefit by including additional predictors, for example, for dietary and lifestyle factors.

The technique of examining the temporal coherence between exposure and response within the overall period of follow-up has been shown to be useful and to provide insights not otherwise available. One of these insights is the general decline of mortality responses to air pollution with increasing follow-up time. This trend could suggest depletion of the cohort of its most susceptible subjects, a concentration-response threshold, increasing uncertainty about the exposures and characteristics of the cohort, or all of these. A bona fide chronic effect of prior air pollution exposure would be expected to be manifested throughout the period of follow-up, especially as the cohort ages, not just at the beginning. It thus follows that other such cohort studies should also examine the ramifications of the timing of air pollution exposure.

In terms of the project's original objectives, we conclude the following:

1. The largest and most consistent mortality responses of this cohort were associated with peak ozone concentrations; however, these responses include deaths prior to the exposure period that remain to be fully explained

and that require further study. Delayed responses to air pollution exposure appear to be no larger than concurrent responses and were only evident with NO_2.
2. Census-based ecologic variables were significant predictors of the risk of death, in addition to personal characteristics; inclusion of such variables reduced the estimated contributions of some of the air pollution variables.
3. Improving the specificity of air pollution exposures affected the sign, magnitude, and identification of the corresponding mortality risk factors.

REFERENCES

Abbey, D. E., Nishino, N., and McDonnell, W. F. 1999. Long-term inhalable particles and other air pollutants related to mortality in nonsmokers. *Am. J. Respir. Crit. Care Med.* 159:373–382.

Boyco, E. J., Koepsell, T. D., Gaziano, J. M., Horner, R. D., and Feussner, J. R. 2000. U.S. Department of Veteran Affairs Medical Care System as a resource to epidemiologists. *Am. J. Epidemiol.* 151:307–314.

Calle, E. E., Thun, M. J., Petrelli, J. M., Rodriguez, C., and Heath, C. W., Jr. 1999. Body-mass index and mortality in a prospective cohort of U.S. adults. *N. Engl. J. Med.* 341:1097–1105.

Cleroux, J., Feldman, R. D., and Petrella, R. J. 1999. Lifestyle modifications to prevent and control hypertension. 4. Recommendations on physical exercise training. *CMAJ* 160(9 suppl.):S21–28.

Cook, N. R., Hebert, P. R., Satterfield, S., Taylor, J. O., Buring, J. E., and Henneken, C. H. 1994. Height, lung function, and mortality from cardiovascular disease among the elderly. *Am. J. Epidemiol.* 139:1066–1076.

Coppola, L., Giunta, R., Grassia, A., Misso, L., Verrazo, G., Violano, P. F., Grandillo, F., and Tirelli, A. 1989. Air pollution by gasoline exhaust fumes: effect on platelet function and blood viscosity. *Med. Lav.* 80:187–191.

Dockery, D. W., Pope, C. A. III, Xu, X., Spengler, J. D., Ware, J. H., Fay, M. E., Ferris, B. G. Jr., and Speizer, F. E. 1993. An association between air pollution and mortality in six U.S. cities. *N. Eng. J. Med.* 329:1753–1759.

Eurowinter Group. 1997. Cold exposure and winter mortality from ischaemic heart disease, cerebrovascular disease, respiratory disease, and all causes in warm and cold regions of Europe. *Lancet* 349:1341–1346.

Gamble, J. F. 1998. $PM_{2.5}$ and mortality in long-term prospective cohort studies: Cause–effect or statistical associations? *Environ. Health Perspect.* 106:535–549. Also see subsequent correspondence in *Environ. Health Perspect.* 107:A392–A394 (1999).

Hu, H., Aro, A., Payton, M., Korrick, S., Sparrow, D., Weiss, S. T., and Rotnitzky, A. 1996. The relationship of bone and blood lead to hypertension. The Normative Aging Study. *J. Am. Med. Assoc.* 275:1171–1176.

Korrick, S. A., Hunter, D. J., Rotnitzky, A., Hu, H., and Speizer, F. E. 1999. Lead and hypertension in a sample of middle-aged women. *Am. J. Public Health* 89:330–335.

Kunzli N., and Tager, I. B. 1997. The semi-individual study in air pollution epidemiology: A valid design as compared to ecological studies. *Environ. Health Perspect.* 105:1078–1083.

Linn, W. S., Solomon, J. C., Trim, S. C., Spier, C. E., Shamoo, D. A., Venet, T. G., Avol, E. L., and Hackney, J. D. 1985. Effects of exposure to 4 ppm nitrogen dioxide in healthy and asthmatic volunteers. *Arch. Environ. Health* 40:234–239.

Linn, W. S., Gong, H., Jr., Clark, K. W., and Anderson, K. R. 1999. Day-to-day particulate exposures and health changes in Los Angeles area residents with severe lung disease. *J. Am. Waste Manage. Assoc.* 49:PM-108–115.

Lipfert, F. W. 1992. Community Air Pollution and Mortality: Analysis of 1980 Data from U.S. Metropolitan Areas. Report prepared for U.S. Department of Energy, Brookhaven National Laboratory, November. BNL 48446.

Lipfert, F. W. 1994a. *Air pollution and community health*. New York: Van Nostrand Reinhold.

Lipfert, F. W. 1994b. Filter artifacts associated with particulate measurements: Recent evidence and effects on statistical relationships. *Atmos. Environ.* 28:3233–3249.

Lipfert, F. W. 1995. Estimating air pollution–mortality risks from cross-sectional studies: Prospective vs. ecologic study designs. In *Particulate matter: Health and regulatory issues*, Proc. of International Specialty Conference, Pittsburgh, PA, April, pp. 78–102. AWMA Publ. VIP 49.

Lipfert, F. W. 1997. Air pollution and human health: Perspectives for the '90s and beyond. *Risk Anal.* 17:137–146.

Lipfert, F. W., and Wyzga, R. E. 1995. Air pollution and mortality: Issues and uncertainties. *J. Am. Waste Manage. Assoc.* 45:949–966.

Lipfert, F. W., and Wyzga, R. E. 1998. Statistical considerations in determining the health significance of constituents of airborne particulate matter. *Proc. AWMA Conf. $PM_{2.5}$: A Fine Particle Standard*, Long Beach, CA, January.

Lipfert, F. W., Malone, R. G., Daum, M. L., Mendell, N. R., and Yang, C.-C. 1988. A Statistical Study of the Macroepidemiology of Air Pollution and Total Mortality. Report BNL-52122. Brookhaven National Laboratory, April.

Miller, J. P., Perry, H. M., Jr., Rossiter, J. E., Baty, J. D., Carmody, S. E., and Sambhi, M. P. 1994. Regional differences in mortality during 15-year follow-up of 11,936 hypertensive veterans. *Hypertension* 23:431–438.

National Center for Health Statistics. 1986. *Vital Statistics of the United States, 1981*, vol. II, *Mortality*, part A. DHHS Pub. No. (PHS) 86-1101. Washington, DC: U.S. Government Printing Office.

Ng-Mak, D. S., Dohrenwend, B. P., Abraido-Lanza, A. F., and Turner, J. B. 1999. A further analysis of race differences in the national longitudinal mortality study. *Am. J. Public Health* 89:1748–1751.

Perry, H. M., Jr., Schnaper, H. W., Meyer, G., and Swatzell, R. 1982. Clinical program for screening and treatment of hypertension in veterans. *J. Nat. Med. Assoc.* 74:433–444.

Perry, H. M., Jr., Miller, J. P., Baty, J. D., Sambhi, M. P., Rutan, G., Moskowitz, D. W., and Carmody, S. E. 1995a. Early predictors of 15-year end-stage renal disease in hypertensive patients. *Hypertension* 25:587–594.

Perry, H. M., Miller, J. P., Fornoff, J. R., Baty, J. D., Sambhi, M. P., Rutan, G., Moskowitz, D. W., and Carmody, S. E. 1995b. Early predictors of 15-year end-stage renal disease in hypertensive patients. *Hypertension* 25:587–594.

Pope, C. A. III, Thun, M. J., Namboodiri, M. M., Dockery, D. W., and Evans, J. S. 1995. Particulate air pollution as a predictor of mortality in a prospective study of U.S. adults. *Am. J. Respir. Crit. Care Med.* 151:669–674.

Roberts, J. 1981. Hypertension in Adults 25–74 Years of Age, United States, 1971–75. Vital and Health Statistics: Series 11, Data from the National Health Survey; No. 221. DHHS Publication No. (PHS) 81-1671, April. Washington, DC: U.S. Government Printing Office.

Samaras, T. T., and Elrick, H. 1999. Height, body size, and longevity. *Acta Med. Okayama* 53:149–169.

Slattery, M. L., and Jacobs, D. R., Jr., 1988. Physical fitness and cardiovascular mortality, the U.S. Railroad study. *Am. J. Epidemiol.* 127:571–580.

Smith, G. D., Wentworth, D., Neaton, J. D., Stamler, R., and Stamler, J. 1996. Socioeconomic differentials in mortality risk among men screened for the multiple risk factor intervention trial: II. Black men. *Am. J. Public Health* 86:497–504.

U.S. Department of Health, Education, and Welfare. 1958. Air Pollution Measurements of the National Air Sampling Network, Analysis of Suspended Particulate Samples Collected 1953–1957. Cincinnati, OH: Taft Sanitary Engineering Center.

U.S. Environmental Protection Agency. 1995. National Air Pollution Emission Trends, 1900–1994. EPA-454/R-95-011, Research Triangle Park, NC: U.S. EPA.

U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards. 1996. Review of the National Ambient Air Quality Standards for Particulate Matter: Policy Assessment of Scientific and Technical Information. Research Triangle Park, NC: U.S. EPA.

Valberg P. A., and Watson, A. Y. 1998. Alternative hypotheses linking outdoor particulate matter with daily morbidity and mortality. *Inhal. Toxicol.* 10:641–662.

Vedal, S. 1997. Ambient particles and health: Lines that divide, *J. Am. Waste Manage. Assoc.* 47:551–581.

Veterans Administration Cooperative Study Group on Antihypertensive Agents. 1970. Effects of treatment on morbidity in hypertension. II. Results in patients with diastolic blood pressure averaging 90 through 114 mm Hg. *J. Am. Med. Assoc.* 213:1143–1152.

Wannamethee, S. G., and Shaper, A. G. 1997. Socioeconomic status within social class and mortality: A prospective study in middle-aged British men. *Int. J. Epidemiol.* 26:532–541.

Watt, G. C., Hart, C. L., Hole, D. J., Smith, G. D., Gillis, C. R., and Hawthorne, V. M. 1995. Risk factors for cardiorespiratory and all cause mortality in men and women in urban Scotland: 15 Year follow up. *Scot. Med. J.* 40:108–112.