Confounding and Effect Modification in the Short-Term Effects of Ambient Particles on Total Mortality: Results from 29 European Cities within the APHEA2 Project

Klea Katsouyanni,[1] Giota Touloumi,[1] Evangelia Samoli,[1] Alexandros Gryparis,[1] Alain Le Tertre,[2] Yannis Monopolis,[1] Giuseppe Rossi,[3] Denis Zmirou,[4] Ferran Ballester,[5] Azedine Boumghar,[2] Hugh Ross Anderson,[6] Bogdan Wojtyniak,[7] Anna Paldy,[8] Rony Braunstein,[9] Juha Pekkanen,[10] Christian Schindler,[11] and Joel Schwartz[12]

We present the results of the Air Pollution and Health: A European Approach 2 (APHEA2) project on short-term effects of ambient particles on mortality with emphasis on effect modification. We used daily measurements for particulate matter less than 10 μm in aerodynamic diameter (PM_{10}) and/or black smoke from 29 European cities. We considered confounding from other pollutants as well as meteorologic and chronologic variables. We investigated several variables describing the cities' pollution, climate, population, and geography as potential effect modifiers. For the individual city analysis, generalized additive models extending Poisson regression, using a smoother to control for seasonal patterns, were applied. To provide quantitative summaries of the results and explain remaining heterogeneity, we applied second-stage regression models. The estimated increase in the daily number of deaths for all ages for a 10 $\mu g/m^3$ increase in daily PM_{10} or black smoke concentrations was 0.6% [95% confidence interval (CI) = 0.4–0.8%], whereas for the elderly it was slightly higher. We found important effect modification for several of the variables studied. Thus, in a city with low average NO_2, the estimated increase in daily mortality for an increase of 10 $\mu g/m^3$ in PM_{10} was 0.19 (95% CI = 0.00–0.41), whereas in a city with high average NO_2 it was 0.80% (95% CI = 0.67–0.93%); in a relatively cold climate the corresponding effect was 0.29% (95% CI = 0.16–0.42), whereas in a warm climate it was 0.82% (95% CI = 0.69–0.96); in a city with low standardized mortality rate it was 0.80% (95% CI = 0.65–0.95%), and in one with a high rate it was 0.43% (95% CI = 0.24–0.62). Our results confirm those previously reported on the effects of ambient particles on mortality. Furthermore, they show that the heterogeneity found in the effect parameters among cities reflects real effect modification, which is explained by specific city characteristics. (EPIDEMIOLOGY 2001;12:521–531)

Keywords: air pollution, ambient particles, mortality, time-series, Poisson regression, geographic comparisons.

During the last decade many epidemiologic studies have found associations between ambient particulate matter (PM) concentrations at below-guideline levels and short-term adverse health effects, including increases in daily mortality.[1–3] The first such studies were regarded with skepticism,[4] but the accumulated evidence was remarkably consistent and robust.[5] An important development in the investigation of the health effects of PM has come from multicenter studies that used a standardized protocol for their data collection and data analysis. Examples of such studies are the Air Pollution and Health: A European Approach (APHEA) project in

From the [1]Department of Hygiene and Epidemiology, University of Athens Medical School, Athens, Greece; [2]Institut de Veille Sanitaire, Paris, France; [3]Fisiologia Clinica CNR, Unit of Epidemiology and Biostatistics, Pisa, Italy; [4]Universite Joseph Fourier Public Health Laboratory Medical School Domaine de la Merci, Grenoble, France; [5]Epidemiology and Statistics Unit, Escola Valenciana d'Estudis per a la Salut, Conselleria de Sanitat, Generalitat Valenciana, Valencia, Spain; [6]Department of Public Health Sciences, St. George's Hospital Medical School, University of London, United Kingdom; [7]National Institute of Hygiene, Department of Medical Statistics, Population Studies Laboratory, Warsaw, Poland; [8]J. Fodor National Public Health Centre—National Institute of Environmental Health, Division of Environmental Health Assessment, Budapest, Hungary; [9]Department of Epidemiology and Preventive Medicine, Tel Aviv University, Israel; [10]National Public Health Institute, Unit of Environmental Epidemiology, Kuopio, Finland; [11]Universitat Basel, Institut fur Sozial-und Praventivmedizin, Switzerland; and [12]Department of Environmental Health, Harvard School of Public Health, Boston, MA.

Address correspondence to: Klea Katsouyanni, Department of Hygiene and Epidemiology, University of Athens Medical School, 75 Mikras Asias Street, 115 27 Athens, Greece.

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Europe[6,7] and the Harvard Six Cities project in the United States.[8] Major interest has been focused on potential factors that put people at increased risk of PM-related mortality and on the characteristics and sources of particles that affect their toxicity, as well as on the potential confounding by various other air pollutants. The impact of the above results has been important for the revisions of air-quality standards in the United States and Europe.[9,10]

The first multicenter studies were not based on extensive networks and were not able to explore confounding and effect modification satisfactorily. Also, in Europe the APHEA project included limited gravimetric measurement of particles. New multicenter studies include the National Morbidity, Mortality, and Air Pollution Study (NMMAPS) study in the United States[11] and the APHEA2 study in Europe. These studies have tried to assess the consistency of the associations and to address questions of sensitive subpopulations, particle characteristics, and confounding.

We report here the results of the APHEA2 project on short-term effects of ambient particles on all-age and elderly all-cause mortality with emphasis on confounding factors and effect modifiers. In APHEA2 an extended database is used that includes more (29) cities and more extensive exposure data than the older APHEA project.[6] This database allows a more comprehensive and structured approach at the second stage of the analysis, in which we explore the role of effect modifiers in explaining heterogeneity.

Subjects and Methods

DATA

Location, Outcome, and Exposure

Table 1 shows the descriptive data from the 29 cities included in this analysis. The study period was longer than 5 years (1,826 days) for most cities. The total population in all cities was more than 43 million. We excluded 1 of the 30 cities originally providing data (Bucharest, Romania) because of insufficient days of PM concentration data (missing values 37%). The mean daily total number of deaths (excluding deaths from external causes, *International Classification of Diseases* code ≥800) ranged from 6 to 169 and that for the elderly (>65 years) ranged from 4 to 139. The median levels of black smoke (BS) and PM less than 10 μm in aerodynamic diameter (PM_{10}) concentrations (average of 2 consecutive days) ranged from 9 to 64 and from 14 to 166 $\mu g/m^3$, respectively. BS levels represent concentrations of black particles with an aerodynamic diameter <4.5 μm.[5] These measurements have a long history in Europe, and although standards for BS have been replaced recently by those for PM_{10},[12] the results are dis-

TABLE 1. Descriptive Data on the Study Period, Population, Exposure (PM_{10} and Black Smoke), Outcome (Daily Number of Deaths), and Levels of Other Pollutants (Exposure and Levels of Other Pollutants in $\mu g/m^3$)

Cities	Study Period	Population × 1000	No. of Deaths per Day		PM_{10} (24 Hour) Percentiles		Black Smoke (24 Hour) Percentiles		SO_2 (24 Hour) Percentiles		O_3 (1 Hour) Percentiles		NO_2 (24 Hour) Percentiles	
			Total	>65 Years	50	90	50	90	50	90	50	90	50	90
Athens	1/92–12/96	3,073	73	64	40*	59	64	122	46	89	83	135	74	114
Barcelona	1/91–12/96	1,644	40	32	60	95	39	64	12	14	71	112	69	97
Basel	1/90–12/95	360	9	8	28*	55			9	25	62	117	38	58
Bilbao	4/92–3/96	667	15	11			23	39	23	39			49	64
Birmingham	1/92–12/96	2,300	61	50	21	40	11	22	19	39	56	79	46	65
Budapest	1/92–12/95	1,931	80	57	40*	52			39	59	82	132	76	113
Cracow	1/90–12/96	746	18	13	54*	86	36	101	49	100			44	80
Dublin	1/90–12/96	482	13	10			10	26	21	34				
Erfurt	1/91–12/95	216	6		48	98			26	133	71	132	35	65
Geneva	1/90–12/95	317	6	4	33*	71			9	24	63	124	45	65
Helsinki	1/93–12/96	828	18	14	23*	49			6	16	57	83	33	50
Ljubljana	1/92–12/96	322	7	5			13	42	27	69	71	145	46	70
Lodz	1/90–12/96	828	30	20			30	77	19	56			39	59
London	1/92–12/96	6,905	169	139	25	46	11	22	22	36	43	71	61	86
Lyon	1/93–12/97	416	9	7	39	63			23	42	61	121	63	87
Madrid	1/92–12/95	3,012	61	46	33	59			26	75	52	98	70	107
Marseille	1/90–12/95	855	22	18			34	56	23	38			71	99
Milan	1/90–12/96	1,343	29	23	47*	88			20	82	38	119	94	141
Paris	1/91–12/96	6,700	124	91	22	46	21	45	15	34	38	84	53	74
Poznan	1/90–12/96	582	17	12			23	76	23	72			47	73
Prague	2/92–12/96	1,213	38	30	66	124			36	92	78	144	58	86
Rome	1/92–12/96	2,775	56	44	57*	81			11	23	41	93	88	115
Stockholm	1/90–12/96	1,126	30	25	14	27			4	10	63	91	26	37
Tel Aviv	1/91–12/96	1,141	27	22	43	75			19	39	36	56	70	156
Teplice	1/90–12/97	625	18	13	42	83			46	117	52	103	32	47
Torino	1/90–12/96	926	21	17	65*	129			23	71	88	159	76	118
Valencia	1/94–12/96	753	16	14			40	70	25	38	59	86	66	101
Wroclaw	1/90–12/96	643	15	10			33	97	21	62			27	39
Zurich	1/90–12/95	540	13	10	28*	54			10	28	62	123	40	59

PM_{10} = particulate matter less than 10 μm in aerodynamic diameter; SO_2 = sulfur dioxide; C_3 = ozone; NO_2 = nitrogen dioxide.
* PM_{10} values were estimated using a regression model relating collocated PM_{10} measurements to the black smoke or total suspended particles.

played here both for reasons of continuity and because there is evidence that BS exposure is more relevant to health effects than PM_{10}.[13,14] BS is a better marker of primary combustion products and small particles.[15] Because domestic or industrial burning of coal is minimal in most of the cities studied, BS is more specific for traffic-related particles than PM_{10} and provides a means of addressing the question of particle composition. Sulfur dioxide (SO_2), nitrogen dioxide (NO_2), and ozone (O_3) concentrations are also shown. Measurements of air pollutants were provided by monitoring networks established in each town. European Union (EU) legislation regulates the methods of air pollutant measurements,[12] and recently most Central-Eastern European countries (which includes all cities in the former Communist countries and which are not EU members) have tried to comply with this regulation. Nevertheless, the recent EU daughter directive for PM_{10} measurement[12] (replacing the older one for BS) had not been applied during the time periods studied here and, as a result, there is variability in the method of PM_{10} measurement. We calculated the average daily concentration of each pollutant from as many monitors as possible. We included a monitor in the calculation if certain completeness criteria were fulfilled.[6] Despite the completeness criteria, a few missing values remained and were replaced according to the procedure described below.

A missing value on day i of year k from monitor j was replaced by a weighted average of the values of the other monitoring stations as follows:

$$\hat{x}_{ijk} = \bar{x}_{i.k} \times (\bar{x}_{.jk}/\bar{x}_{..k})$$

where $\bar{x}_{i.k}$ is the mean value on day i of year k among all monitors reporting, $\bar{x}_{.jk}$ is the mean value for monitor j in year k, and $\bar{x}_{..k}$ is the overall mean level in year k.

In ten cities (Athens, Basel, Budapest, Cracow, Erfurt, Geneva, Milano, Rome, Torino, and Zurich), PM_{10} measurements were not available for the whole time period but were estimated using a regression model relating collocated PM_{10} measurements to the BS (for Athens and Cracow) or total suspended particles measurements (for Budapest and Erfurt) or as a percentage of total suspended particles (based on measurements, for the other cities).

Confounders

We used the daily average temperature and relative humidity to control for potential confounding effects of meteorologic variables. All available information on influenza epidemics was recorded, and unusual events (for example, heat waves) were also taken into account. We adjusted for day of the week, national and school holidays, seasonality, and long-term trends. The potential confounding effects of the daily levels of other pollutants (Table 1) were investigated, as described below. The correlation coefficients between PM_{10} and NO_2 ranged from 0.12 to 0.75; between PM_{10} and ozone from −0.38 to +0.38; between PM_{10} and SO_2 from 0.14 to 0.78; and between BS and each of these pollutants from 0.11 to 0.65, −0.55 to −0.04, and 0.41 to 0.77, respectively, in the different cities.

Potential Effect Modifiers

Substantial heterogeneity in the estimated effect parameters has been observed previously.[7,16–18] It was therefore important to collect information on several variables hypothesized to be potential effect modifiers. These variables are "city characteristics" (that is, one value per city, which characterizes a particular situation, such as its climate or air pollution sources). The potential effect modifiers for which information was recorded are classified into the following four categories.

(1) Air pollution level and mix. This category includes the average levels of PM (PM_{10} and BS) and that of other pollutants for the whole study period as well as the ratio of PM_{10} and BS to NO_2. The former address the question of whether the effect size depends on the level of exposure *per se* or on the level of exposure to other pollutants. The ratio of PM to NO_2 indicates the extent to which PM comes from traffic, because NO_2 is mainly traffic generated. Therefore, a lower PM/NO_2 ratio reflects a higher proportion of traffic-generated PM.

(2) Climatic variables. It has often been proposed that the air pollution effects estimated are modified by climate,[19] and this theory is supported by seasonal and geographic differences observed previously.[7,16–18] To characterize a city's climate, the mean temperature and relative humidity over the whole study period were recorded. The mean annual daily temperature ranged in our cities from 5.9°C (Helsinki) to 17.8°C (Athens) and the mean relative humidity from 48.9% (Marseilles) to 82.3% (Dublin).

(3) Health status of the population. It is also thought that air pollution affects certain subgroups of the population to a greater extent. Older persons and those suffering from chronic cardiorespiratory disease are obvious candidates. As indicators of their size, the age-adjusted mortality and lung cancer mortality rates for each city's population were used as well as the percentage of persons over 65 years of age and smoking prevalence. The directly standardized annual all-cause mortality rate per 100,000 ranged in our cities from 579 (Lyon) to 1,231 (Lodz). Fifteen cities had values below 800; nine between 800 and 1,000; and five above 1,000. The annual lung cancer mortality rate ranged between 28 and 92 deaths per 100,000 person-years; the proportion of the population >65 years of age between 9% and 21%; and smoking prevalence from 22% to 55%.

(4) Geographic area. It has been observed before[7] (on the basis of fewer cities) that the effect size differed by geographic area. To investigate this further, we classified the cities into three categories: Central-Eastern (which included all cities in the former Communist countries: Budapest, Cracow, Erfurt, Ljubljana, Lodz, Poznan, Prague, Teplice, and Wroclaw), Southern (those with latitude less than 45°: Athens, Barcelona, Bilbao, Madrid, Marseille, Rome, Tel Aviv, and Valencia), and North Western (all other cities). Alternatively we used latitude and longitude.

ANALYSIS

We used a hierarchic modeling approach. First, we fitted regression models in each city separately to allow specific control for seasonal effects, weather, and other potential confounders. We used the results of the individual city analysis in turn in a second-stage analysis to provide overall estimates and to investigate potential effect modifiers.

INDIVIDUAL CITY DATA ANALYSIS

We analyzed the data for each city separately according to a predefined standardized methodology, which resulted in a city-specific model. All data were analyzed in one location (Athens) by three statisticians. We applied generalized additive models (GAM) extending Poisson regression to model the nonlinear effects of the covariates, using a local nonparametric loess smoother to control for seasonal patterns and long-term trends, allowing for overdispersion.[20]

A broad range of smoothing parameters for time removed the basic seasonality from the data. To choose among these, we used diagnostic tools including partial autocorrelation plots and plots of residuals over time to determine the smoothing parameter (that is, the fraction of the data used for smoothing). We had decided in advance that the smoothing window should not be below 2 months to avoid eliminating short-term patterns actually due to the exposure under study. After seasonal and long-term trends were controlled for, we incorporated meteorologic variables into the model. We investigated smoothed functions of the same day and of lags up to 2 days or averaged over 0 to 2 days of daily mean temperature and relative humidity. Same-day values were always included. The inclusion of lagged weather variables and the choice of smoothing parameters for all of the weather variables were done by minimizing Akaike's information criterion.[20] Finally, we added dummy variables to the model to control for day of the week, holidays, or unusual events if necessary.

Information on daily influenza counts was not available for all cities. On the basis of results from a sensitivity analysis (manuscript in preparation), we decided to control for influenza using a dummy variable taking the value 1 for days when the 7-day moving average of the daily respiratory number of deaths was greater than the 90th percentile of its distribution and 0 otherwise. Thus, influenza control was uniform for all cities.

The air pollution variables were put into the model last. Previous results have indicated that in areas with high particle concentrations, log-transformed measurements of particles best represented the mortality-particle relation.[21] To facilitate the second-stage analysis, we decided to use only linear terms, and thus the analysis was restricted to days with BS or PM_{10} concentrations below 150 $\mu g/m^3$. We decided *a priori* to use the average of lags 0 and 1 for BS and PM_{10} measurements. This decision was based on previous studies having shown those lags to be the most relevant.[22] It also avoids potential bias, which could result from selectively reporting those lags associated with the largest effect estimates. We also fitted two-pollutant models to adjust for the confounding effects of SO_2, O_3, and NO_2. Carbon monoxide measurements were not used, because there were many cities with incomplete measurements or without carbon monoxide measurements. If serial correlation remained in the residuals of the final models, autoregressive terms were added. All analyses were done using S-Plus.[23]

SECOND-STAGE ANALYSIS

We applied a second-stage analysis to provide a quantitative summary of all individual city results and to explain heterogeneity, if present. We assumed that the city-specific estimates b_i were normally distributed around an overall estimate, assuming heterogeneity. To examine this heterogeneity we assumed $b_i \sim N(\beta_0 + \gamma z_i, \Omega)$ where β_0 is the mean of the b_i values, z_i is a vector of effect modifiers in city i, γ is the vector of regression coefficients for the effect modifiers, and Ω is the covariance. Such hierarchic models are becoming more common in epidemiology.[24]

To investigate the role of potential effect modifiers, we applied univariate (for one-pollutant models) or multivariate (for two-pollutant models) regression models. We estimated fixed-effects pooled regression coefficients by weighted ecologic regression of city-specific estimates on potential effect modifiers (at city level) with weights inversely proportional to their city-specific variances. If substantial heterogeneity among city results (beyond the variation associated with the effect modifiers) remained, random-effects regression models were applied. In these latter models, it was assumed that the individual coefficients are a sample of independent observations from the normal distribution with mean equal to the random-effects pooled estimate and variance equal to the between-cities variance. We estimated the between-cities variance from the data, using the maximum likelihood method described by Berkey *et al*,[25] and this variance was added to the city-specific variances.

For multivariate second-stage regression models, we applied the method described by Berkey *et al.*[26] In contrast to the usual univariate second-stage regression, in which results from each pollutant are analyzed separately, the multivariate model provides more accurate estimates by incorporating the correlation among pollutants within each city. Specific S-Plus functions (available on request) were written to fit the univariate and multivariate second-stage regression models.

Results

Figure 1 shows the percentage increase in the daily number of deaths associated with 10 $\mu g/m^3$ increase in PM_{10} measurements for each city as well as the pooled estimates. Because there was substantial heterogeneity in the single-city results, pooled estimates using random-effects models are also shown. The estimated increases (per 10 $\mu g/m^3$ increase in PM_{10}) for single cities ranged from -0.6% to 1.5%. The combined increase in the

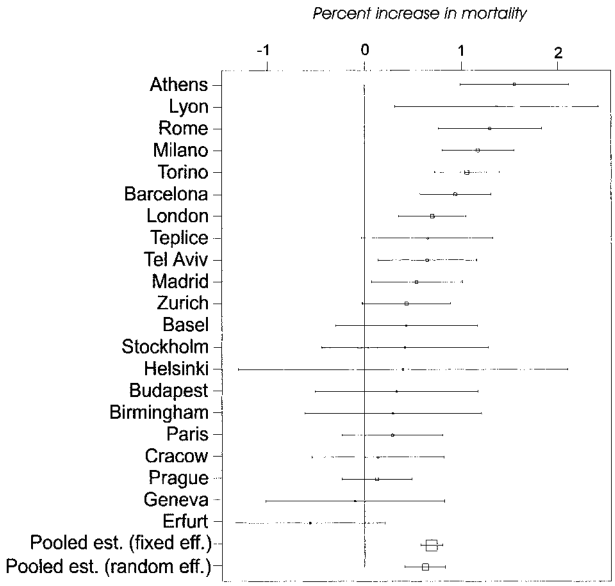

FIGURE 1. Percentage increase in the total daily number of deaths (excluding deaths from external causes) and their 95% confidence intervals associated with an increase of 10 $\mu g/m^3$ in the levels of particulate matter less than 10 μm in aerodynamic diameter in each city. The size of the point representing each increase is inversely proportional to its variance.

total number of deaths associated with 10 $\mu g/m^3$ increase in the daily PM_{10} concentrations was 0.7% [95% confidence interval (CI) = 0.6–0.8%] under the fixed-effects model and 0.6% (95% CI = 0.4–0.8%) under the random-effects model. Figure 2 shows the corresponding

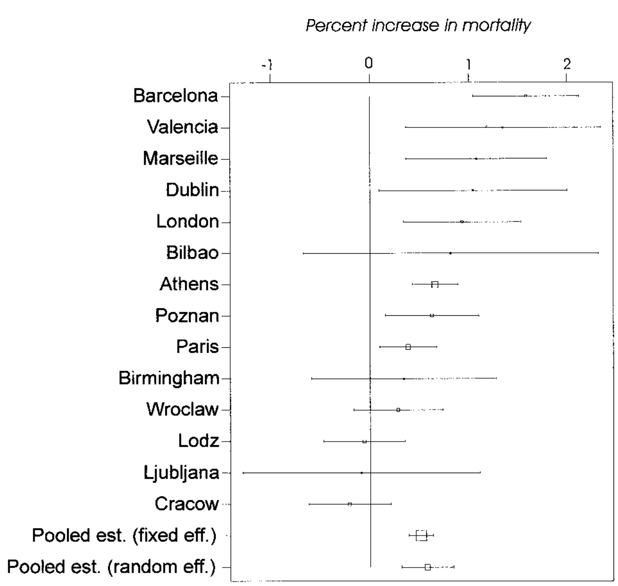

FIGURE 2. Percentage increase in the total daily number of deaths (excluding deaths from external causes) and their 95% confidence intervals associated with an increase of 10 $\mu g/m^3$ in the levels of black smoke in each city. The size of the point representing each increase is inversely proportional to its variance.

individual city and pooled increase in daily deaths associated with a 10 $\mu g/m^3$ increase in BS. The figures for each city ranged from −0.2% to 1.6% (χ^2 for heterogeneity = 46.9, degrees of freedom = 13), and the combined estimate for the same increase under the fixed-effects model was 0.5% (95% CI = 0.4–0.6%) and under the random-effects model 0.6% (95% CI = 0.3–0.8%). When we considered only deaths among the elderly (>65 years of age), the corresponding percentage increase for PM_{10} was 0.8% (95% CI = 0.7–0.9%) under the fixed-effects model and 0.7% (95% CI = 0.5–1.0%) under the random-effects model, whereas for BS it was 0.6% (95% CI = 0.5–0.8%) and 0.7% (95% CI = 0.4–0.9), respectively.

To test the sensitivity of the above results for estimated PM_{10} series, we excluded the ten cities for which the PM_{10} series were not originally complete. The combined estimated increase remained similar; that is, a 0.7% increase in deaths was associated with a 10 $\mu g/m^3$ increase in PM_{10}, both under the fixed-effects and the random-effects models (corresponding 95% CI = 0.6–0.9% and 0.5–0.9%, respectively).

Table 2 shows results from two-pollutant models combined using multivariate second-stage regression, adjusting in turn for the confounding effects of SO_2, O_3, and NO_2. PM_{10} associations with total mortality were not substantially confounded by O_3 or SO_2 concentrations. In contrast, the estimated combined increase in mortality for 10 $\mu g/m^3$ increase in PM_{10} was reduced by 48% when adjusting for NO_2. BS associations with total mortality were slightly confounded by SO_2 levels and substantially confounded by the levels of NO_2 and O_3. When adjusting for NO_2, the estimated increase in total mortality associated with 10 $\mu g/m^3$ increase in BS concentrations was reduced by 55%, whereas, when adjusting for O_3, it became larger by 52%. In all of the multivariate second-stage models results, there remained substantial heterogeneity in the other pollutant-adjusted coefficients for PM_{10} and BS.

We investigated the observed heterogeneity in the effect estimates of both PM_{10} and BS, taking into account the potential effect modifiers through second-stage regression models. Table 3 shows the change in the PM_{10} regression coefficient and its 95% CI when an effect modifier was included in the second-stage regression model. It also shows the resulting estimated PM_{10} effect (that is, the increase in the total daily number of deaths, per 10 $\mu g/m^3$ increase in daily PM_{10} concentrations) for a city characterized by a value in the effect modifier equal to the 25th (low) and 75th (high) percentile of the distribution of this particular effect modifier. Among the potential effect modifiers, only those explaining more than 10% of the heterogeneity are presented. Several variables appeared to be effect modifiers.

Of the pollutants considered, NO_2 was the most important effect modifier; in a city with low long-term average NO_2 concentration, the estimated increase in daily mortality, associated with an increase of 10 $\mu g/m^3$ in PM_{10}, was 0.19%, whereas in a city with high NO_2 it

TABLE 2. Pooled* Estimates for the Increase in the Total Daily Number of Deaths Associated with PM_{10} and Black Smoke Increase of 10 gm/m^3 (Average of Lags 0 and 1) Adjusting Alternatively for Other Pollutants in Two Pollutant Models

Other Pollutant	PM_{10} Increase %				Black Smoke Increase %			
	FE Model		RE Model		FE Model		RE Model	
	%	95% CI	%	95% CI	%	95% CI	%	95% CI
None	0.68	0.6–0.8	0.62	0.4–0.8	0.51	0.4–0.6	0.58	0.3–0.8
SO_2	0.59	0.5–0.7	0.50	0.3–0.7	0.42	0.3–0.6	0.57	0.1–1.0
O_3	0.74	0.6–0.9	0.73	0.5–0.9	0.71	0.5–0.9	0.88	0.5–1.3
NO_2	0.35	0.2–0.5	0.41	0.2–0.7	0.26	0.1–0.4	0.26	0.0–0.6

FE = fixed effects; RE = random effects; PM_{10} = particulate matter less than 10 μm in aerodynamic diameter; SO_2 = sulfur dioxide; O_3 = ozone; NO_2 = nitrogen dioxide.
* The combined estimates were calculated using a multivariate second-stage regression program.

was 0.80%. The other pollutants considered were not important. The ratio of PM_{10} to NO_2 was also important, with a lower ratio associated with a larger PM_{10} effect. These were followed by temperature, humidity, age-standardized mortality, the proportion of the elderly, and geographic area. In contrast, lung cancer mortality and smoking prevalence were not important. When the best effect modifier from each category (that is, NO_2 levels, temperature, and standardized mortality) was included with the others in a second-stage model with three effect modifiers, most of the heterogeneity was explained and the remaining heterogeneity was substantially reduced. Figure 3 shows the scatter plots of the individual city effect parameters for PM_{10} by the levels of the most important effect modifiers.

In Table 4, the second-stage regression results for BS effect estimates are shown. Geographic area, NO_2 concentrations, and temperature were the most important effect modifiers. In a second-stage regression model with four effect modifiers (as described above for PM_{10}, plus geographic area), most of the heterogeneity was explained. Figure 4 shows the scatter plots of the effect parameters for BS by the levels of the most important effect modifiers.

The results of second-stage regression models for the effect parameters among deaths in the elderly showed a practically identical pattern, both for BS and PM_{10} effects, with the coefficients changing at the second or third significant digit.

Because NO_2 was a confounder in the PM-mortality association, we also tried multivariate second-stage regression models with the estimated effect parameters of PM and NO_2 for each city as dependent variables and average long-term NO_2 concentrations as a potential effect modifier. This approach gave results on modification of the effect parameters of the PM exposure indicators (PM_{10} and BS) by NO_2 after adjusting for the confounding effects of NO_2. NO_2 level continued to act as an effect modifier after we adjusted for confounding of its daily fluctuations on the PM effect parameters in each city. Thus, in a city with low NO_2 concentration, the adjusted estimated increase in mortality associated with a 10 μg/m^3 increase in PM_{10} was 0.11% and in a

TABLE 3. Results of Second-Stage Regression Models Investigating the Role of Potential Modifiers* of the Estimated Effects of PM_{10} on the Daily Number of Total Natural Deaths

Effect Modifier Included in the Model†	Units or Groups	Effect Modifier *b*-Coefficient‡		Estimated Increase at the 25th Percentile§		Estimated Increase at the 75th Percentile§	
		Coefficient	95% CL	Estimate	95% CL	Estimate	95% CL
Mean 24-hour NO_2 for the study period	10 μg/m^3	0.000199	0.000126, 0.000272	0.19	0.00, 0.41	0.80	0.67, 0.93
Mean PM_{10}/NO_2	0.10	−0.0000563	−0.0000962, −0.0000163	0.83	−0.76, 2.45	0.58	0.44, 0.72
Mean 24-hour temperature for the study period	5°C	0.000466	0.000280, 0.000651	0.29	0.16, 0.42	0.82	0.69, 0.96
Mean relative humidity for the study period	5%	−0.000241	−0.000357, −0.000126	0.89	0.74, 1.05	0.38	0.19, 0.57
Age-standardized annual mortality rate per 100,000	100 deaths	−0.000123	−0.000194, −0.000052	0.80	0.65, 0.95	0.43	0.24, 0.62
Proportion of individuals age > 65 years	5%	0.02964	0.01028, 0.04900	0.54	0.38, 0.69	0.76	0.63, 0.90
NW = 0/CE = 1		−0.000502	−0.000817, −0.000187	0.73	0.49, 0.97	0.22	0.00, 0.50
NW = 0/S = 1		0.000926	−0.000079, 0.000481	0.73	0.49, 0.97	0.87	0.68, 1.06

PM_{10} = particulate matter less than 10 μm in aerodynamic diameter; NO_2 = nitrogen dioxide; CL = confidence limit; NW = North Western; CE = Central Eastern; S = Southern.
* These are variables characterizing each city. Only effect modifiers reducing the heterogeneity by >10% are presented.
† The effect modifiers were included alternatively in the models.
‡ From fixed-effects models. This coefficient indicates the difference in the estimated PM_{10} coefficient (which is here the dependent variable) resulting from an increase in the effect modifier of the size given in the Units or Groups column.
§ Increase in the daily number of deaths associated with an increase of 10 μg/m^3 in the daily PM_{10} concentrations, estimated for a city with levels of the corresponding effect modifier equal to the 25th and 75th percentiles of its distribution.

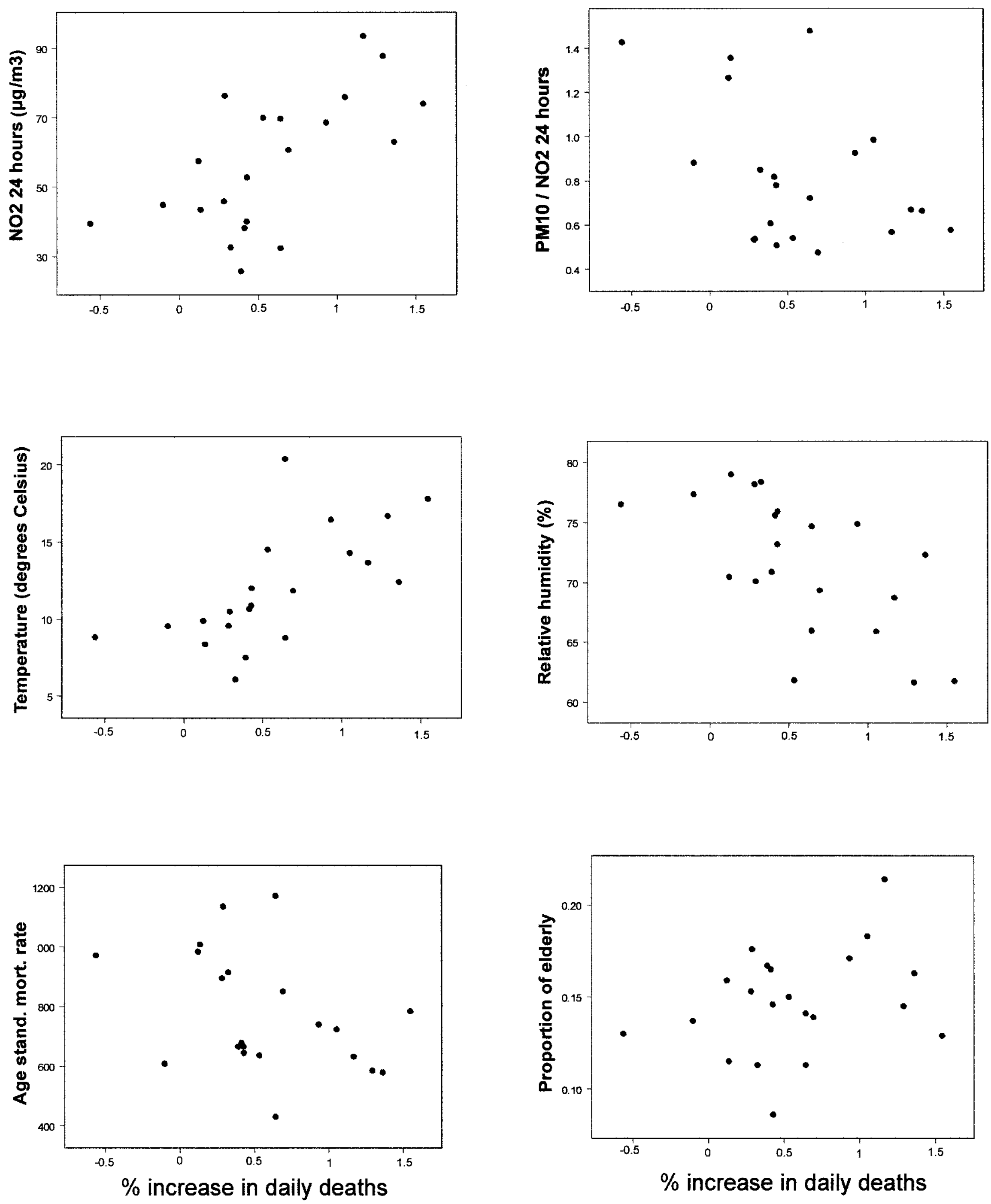

FIGURE 3. Percentage increase in the total daily number of deaths (excluding deaths from external causes) associated with an increase of 10 $\mu g/m^3$ in the levels of particulate matter less than 10 μm in aerodynamic diameter in each city, according to the levels of selected effect modifiers.

city with high NO_2 it was 0.51%, with the corresponding figures for BS being 0.11% and 0.38%.

Discussion

This study, based on the most extensive database available in Europe until today, confirmed the short-term effects of ambient particle concentrations on the daily number of deaths found in previous studies[7,11,16–18,27–31] and provided new results on confounding and effect modification by a number of variables. We emphasize that even though other pollutants are potential confounders and effect modifiers of the PM_{10}-mortality association, they are also, largely, indices of a complex process shaped by emissions, secondary reactions, the

TABLE 4. Results of Second-Stage Regression Models Investigating the Role of Potential Modifiers* of the Estimated Effects of Black Smoke (BS) on the Daily Number of Total Natural Deaths

Effect Modifier Included in the Model†	Units or Groups	Effect Modifier *b*-Coefficient‡		Estimated Increase at the 25th Percentile		Estimated Increase at the 75th Percentile	
		Coefficient	95% CL	Estimate	95% CL	Estimate	95% CL
Mean 24-hour NO_2 for the study period	10 $\mu g/m^2$	0.0001858	0.000094, 0.000278	0.26	0.08, 0.45	0.73	0.55, 0.91
Mean BS/NO_2	0.10	−0.0000456	−0.0000847, −0.0000068	0.67	0.52, 0.82	0.45	0.30, 0.60
Mean 24-hour temperature for the study period	5°C	0.000359	0.000182, 0.000536	0.23	0.03, 0.42	0.70	0.53, 0.86
Mean relative humidity for the study period	5%	−0.000126	−0.000210, −0.000043	0.44	0.30, 0.59	0.32	0.13, 0.51
Age-standardized annual mortality rate per 100,000	100 deaths	−0.000113	−0.000189, −0.000037	0.64	0.48, 0.81	0.38	0.22, 0.55
Proportion of individuals age >65 years	5%	0.04013	0.01104, 0.06923	0.48	0.34, 0.62	0.70	0.51, 0.90
NW = 0/CE = 1		−0.000392	−0.000753, −0.000031	0.51	0.27, 0.75	0.12	0.00, 0.33
NW = 0/S = 1		0.000327	−0.000022, 0.000675	0.51	0.27, 0.75	0.84	0.64, 1.04

CL = confidence limit; NO_2 = nitrogen dioxide; NW = North Western; CE = Central Eastern; S = Southern.
* These are variables characterizing each city. Only effect modifiers reducing the heterogeneity by >10% are presented.
† The effect modifiers were included alternatively in the models.
‡ From fixed-effects models. This coefficient indicates the difference in the estimated BS coefficient (which is here the dependent variable) resulting from an increase in the effect modifier of the size given in the Units or Groups column.
§ Increase in the daily number of deaths associated with an increase of 10 $\mu g/m^3$ in the daily PM_{10} concentrations, estimated for a city with levels of the corresponding effect modifier equal to the 25th and 75th percentiles of its distribution.

location of fixed-site monitors, and measurement error related to their representativeness of the average population exposure.

We found that both PM_{10} and BS were predictors of daily deaths across Europe, with similar size of the effect estimates. The analyses were restricted to days with concentrations below 150 $\mu g/m^3$ and hence cannot be interpreted as reflecting the effects of a few high days. This study was based on a much larger database compared with a related previous project (APHEA1) that used data from 12 cities[7] and included mostly BS measurement of particles with very limited gravimetric data. The statistical methods applied here differ from those used before, and a sensitivity analysis comparing methods has been reported.[32] The results found here for BS effects are consistent with those reported from the previous project[32] in which the overall estimated increase per 10 $\mu g/m^3$ increase in 1-day BS level was 0.6% (95% CI = 0.5–0.7%), when analysis was restricted to days with BS concentrations <150 $\mu g/m^3$.

Within the U.S. NMMAPS project,[11,31] which has just been concluded, the analysis of data from the 90 largest U.S. cities found that PM_{10} levels were associated with a 0.5% increase in the total daily number of deaths per 10 $\mu g/m^3$. The effect reported from NMMAPS is slightly smaller than the one found in APHEA2. The APHEA2 estimate is based on a 2-day average PM_{10} concentration (average of lags 0 and 1), whereas the NMMAPS is based on a 1-day level, and it has consistently been found that exposures based on more than 1-day averages are associated with larger effect estimates.[16–18,22,33]

Since the early reports of associations between ambient particles and daily deaths, questions have arisen about the potential for those effects to be confounded by other air pollutants. We have addressed that issue in our analyses using two-pollutant models. We found no evidence for the effects of PM_{10} to be confounded by SO_2 or ozone. BS effects were not confounded by SO_2 either but were higher with simultaneous control for ozone. These results are supported by the similar findings of Schwartz,[34] who has recently reported on a multicity analysis of ten U.S. locations, and Samet *et al*[11] and Schwartz *et al*,[20] who examined two- and three-pollutant models in the 20 largest U.S. cities. On the basis of these large studies, we believe that confounding by SO_2 or ozone can be dismissed as an explanatory factor for observed associations with particles. In contrast, we did find evidence that both the PM_{10} and BS associations were moderately confounded by NO_2. These results are different from those reported in the United States, where Samet *et al*[11,31] find no evidence of confounding by NO_2. The most obvious explanation for this finding lies in the difference in relative source contribution between European and U.S. cities. In the United States, there are few diesel cars. In contrast, in many European cities, diesel cars approach 50% of all cars. Therefore, motor vehicles are a larger source of urban particles in Europe than in the United States, where they are the predominant source of urban NO_2. Hence, it may be more difficult to distinguish between NO_2 and particles in Europe than in the United States. If particle measures were only standing for NO_2, however, then the results of Samet *et al*[11,31] would be unexpected. Hence, it would be unwise to interpret these results as indicating that half of the particle effects are really the result of NO_2. If we consider NO_2 to be correlated better with traffic-generated particles (as opposed to particles from other sources), then the NO_2-adjusted effect estimates may reflect, to a larger extent, the effects of particles from sources other than traffic. This issue is discussed further below.

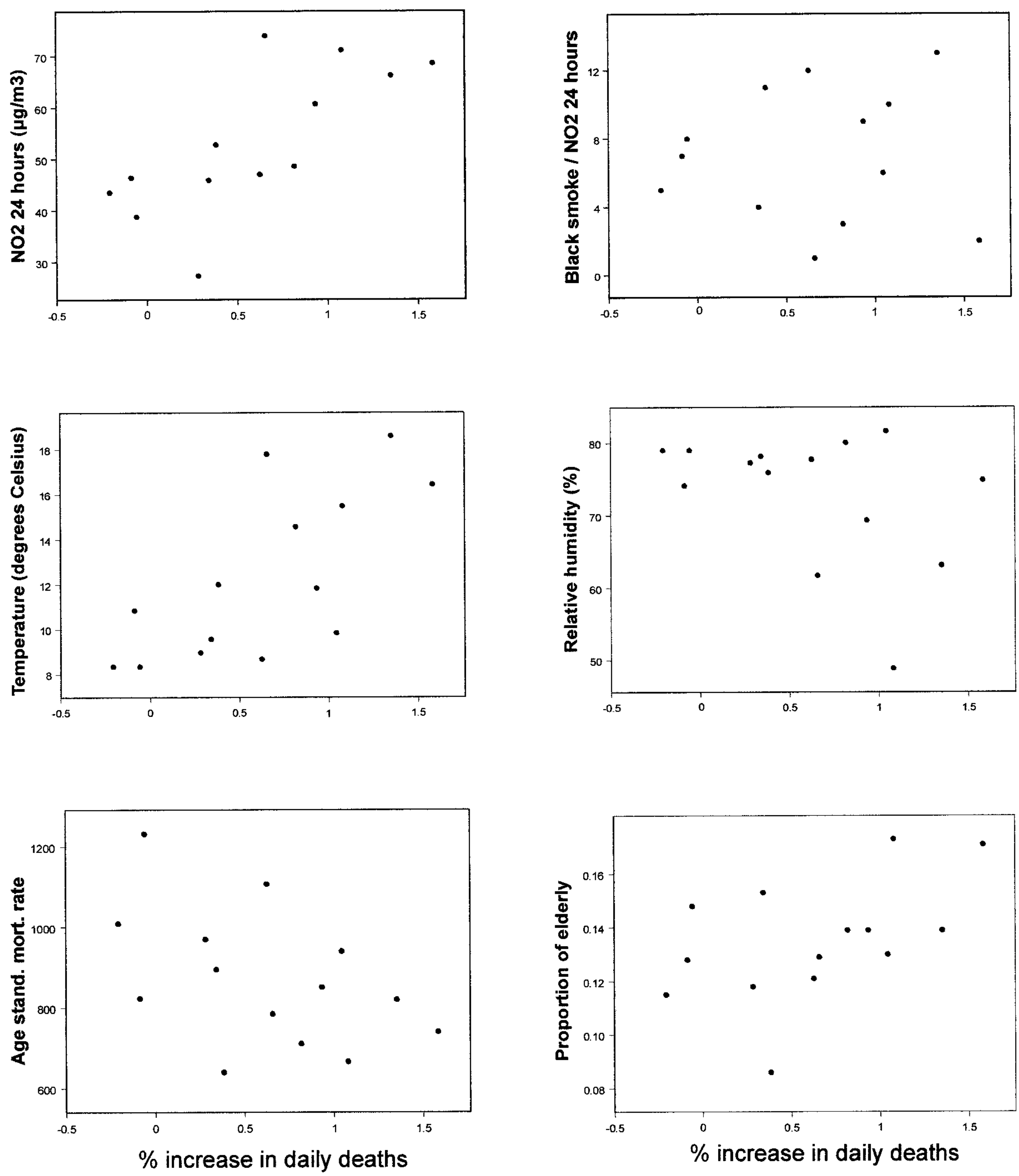

FIGURE 4. Percentage increase in the total daily number of deaths (excluding deaths from external causes) associated with an increase of 10 $\mu g/m^3$ in the levels of black smoke in each city, according to the levels of selected effect modifiers.

Ambient particles are a mixture with different physical and chemical characteristics of which the particular health effects are not fully understood. There is growing evidence that particles with a smaller aerodynamic diameter (that is, 10 or even 2.5 μm[35] or perhaps smaller[36]) are more relevant for human health. In Europe, BS, a measure of black particles with aerodynamic diameter <4.5 μm has, historically, been the routine indicator of particles. BS, a photometric measure, is converted to mass using the same outdated calibration curve for all locations. As a result, the mass quantities calculated are unlikely to be accurate. PM_{10} measurements (used to set the PM standard since about 20 years ago in the United States but only recently in Europe) represent all particles with an aerodynamic diameter less than 10 μm, a mixture of primary and secondary particles from different sources with varying characteristics and levels of toxicity. In the European PEACE project, in which both BS and PM_{10} were measured in 28 European areas, the

PM_{10}/BS ratios ranged from 0.67 to 3.67.[37] $PM_{2.5}$ has not been routinely measured to any extent so far. Although it is generally accepted that ambient particles have important health effects, it is also recognized that there remain uncertainties concerning the nature of the exposure and the mechanisms of effect. The heterogeneity of single-city effect estimates supports the hypothesis that the composition of particles differs among locations in a way relevant to their health effects. An indirect way (given that, in this situation, it is very difficult to implement experimental designs) to investigate the toxicity of particles according to specific aspects of their particular characteristics is to evaluate the potential effect modification of factors influencing their composition across a number of environments. The extended database available to this study allowed us this possibility.

Among the potential effect modifiers identified, an important one is NO_2 concentration, an indicator of pollution originating from traffic. The higher the NO_2 concentrations (in absolute terms or relative to PM_{10}) the larger the effect observed on mortality. This relation suggests that particles originating from vehicle exhausts are more toxic than those from other sources. Unfortunately, it was not possible to investigate the BS-to-PM_{10} ratio as an effect modifier in our study, because only four cities provided complete and independent concurrent BS and PM_{10} measurements. Our conclusion is supported by other work. For example, Laden *et al*[38] have examined the elemental composition of all of the $PM_{2.5}$ filters from the Harvard Six Cities Study. Using estimates of the daily mass concentration of traffic particles, long-range traffic particles, crustal particles, and particles from local sources in each city simultaneously in a regression for daily mortality, they found associations with particle mass from traffic and from long-range transport. The slope (per $\mu g/m^3$) of the effect for the traffic particles was twice as great as that for the long-range transport particles.

We have also found important effect modification by other variables. The effect parameters estimated are larger in warmer and drier countries. Temperature is a much more important effect modifier than humidity. The results remain the same if latitude is used instead of temperature. A possible explanation for this finding may be that in warmer countries, outdoor fixed-site air pollution measurements may represent the average population exposure better than the measurements in colder climates, as people tend to keep their windows open and spend more time outdoors. This finding is consistent with the larger effect estimates found during the warm season in previous studies.[7,28,29] Other studies, however, have found little difference in effect size estimates by season.[34]

In previous reports,[7] we have hypothesized that the health status of a population may be an effect modifier in the PM-mortality association. This hypothesis was confirmed by our finding that the larger the age-standardized mortality rate is (that is, the shorter the life expectancy), the smaller are the estimated PM_{10} effects. A large age-standardized mortality rate was related to a smaller proportion of elderly persons (Spearman $r = -0.33$) in this study and, probably, to the presence of competing risks for the same disease entities. It was therefore related to a smaller proportion of individuals belonging to vulnerable groups (for example, those with chronic respiratory diseases) who are more susceptible to PM effects.

The only clear effect modifier identified in the previous APHEA project[7] was a geographic separation between Central-Eastern and Western European countries, and the estimates for BS effects found here for these regions are close to the ones reported before.

Differences in the levels of the identified effect modifiers may explain the small difference found in the estimated effects between the APHEA2 and NMMAPS projects. In the NMMAPS project, regional differences were found in the effect estimates that were larger in the Northeast of the United States and smaller in the Southeast. The continuing pattern of regional differences in both studies suggests that further work on particle composition as an explanatory factor is warranted.

In the analysis by Levy *et al*,[33] effect modification has also been investigated. Larger increases in mortality were found in populations with a proportion of persons over 65 years of age greater than 13% (0.77%) than in those with a smaller proportion of elderly (0.64%). The most important positive predictor of the effect size was the ratio $PM_{2.5}/PM_{10}$. In univariate analysis, there was some effect modification by NO_2, but in a multivariate model, including ten effect modifiers among which was the ratio $PM_{2.5}/PM_{10}$, little effect modification by NO_2 was observed.

Comparing the results for BS and PM_{10}, we find the same effect sizes and modification patterns. The estimates for BS are more heterogeneous and greatly influenced by the effect parameters found in the four Polish cities where BS represents industrial and heating coal combustion as well as traffic. Previous studies have reported larger BS effects.[13,14] These results together with the indications that traffic particles are more toxic, noted above, suggest that continued monitoring of BS, or ethelometric monitoring of carbon, would be of considerable interest and importance for both future studies and assessment of potential health risks, and question the wisdom of abandoning the measure.

In conclusion, our results confirm those previously reported in Europe and the United States about the magnitude of the effects of ambient particles on the total daily number of deaths. They also indicate that the heterogeneity found in the PM effect parameters from different cities reflects real effect modification, which may be explained by factors characterizing the air pollution mix, climate, and the health of the population. This finding has important consequences for estimating the air pollution health effects in a specific population and can influence policy and decisions for environmental management.

The Air Pollution and Health: A European Approach (APHEA2) collaborative group consists of: K. Katsouyanni, G. Touloumi, E. Samoli, A. Gryparis, Y. Monopolis, E. Aga, and D. Panagiotakos (Greece; coordinating center); C. Spix, A. Zanobetti, and H. E. Wichmann (Germany); H. R. Anderson, R. Atkinson, and J. Ayres (United Kingdom); S. Medina, A. Le Tertre, P. Quenel, L. Pascale, and A. Boumghar (Paris, France); J. Sunyer, M. Saez, F. Ballester, S. Perez-Hoyos, J. M. Tenias, E. Alonso, K. Kambra, E. Aranguez, A. Gandarillas, I Galan, and J. M. Ordonez (Spain); M. A. Vigotti, G. Rossi, E. Cadum, G. Costa, L. Albano, D. Mirabelli, P. Natale, L. Bisanti, A. Bellini, M. Baccini, A. Biggeri, P. Michelozzi, V. Fano, A. Barca, and F. Forastiere (Italy); D. Zmirou and F. Balducci (Grenoble, France); J. Schouten and J. Vonk (The Netherlands); J. Pekkanen and P. Tittanen (Finland); L. Clancy and P. Goodman (Ireland); A. Goren and R. Braunstein (Israel); C. Schindler (Switzerland); B. Wojtyniak, D. Rabczenko, and K. Szafraniek (Poland); B. Kriz, A. M. Celko, and J. Danova (Prague, Czech Republic); A. Paldy, J. Bobvos, A. Vamos, G. Nador, I. Vincze, P. Rudnai, and A. Pinter (Hungary); E. Niciu, V. Frunza, and V. Bunda, (Romania); M. Macarol-Hitti and P. Otorepec (Slovenia); Z. Dörtbudak and F. Erkan (Turkey); B. Forsberg and B. Segerstedt, (Sweden); F. Kotesovec and J. Skorkovski (Teplice, Czech Republic); and M. Pavlovic and D. Simic (Croatia).

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