Short-Term Effects of Air Pollution on Hospital Admissions of Respiratory Diseases in Europe: A Quantitative Summary of APHEA Study Results

CLAUDIA SPIX
GSF Forschungszentrum für Umwelt und Gesundheit
Institut für Epidemiologie
Neuherberg, Germany
H. ROSS ANDERSON
Department of Public Health Sciences
St. George's Hospital Medical School
London, United Kingdom
JOEL SCHWARTZ
Harvard School of Public Health
Boston, Massachusetts
MARIA ANGELA VIGOTTI
Institute of Clinical Physiology
National Research Council
Pisa, Italy
ALAIN LETERTRE
Observatoire Regional de la Santé
Paris, France
JUDITH M. VONK
State University of Groningen
Faculty of Medicine
Department of Epidemiology and Statistics
Groningen, The Netherlands
GIOTA TOULOUMI
University Athens Medical School
Department of Hygiene and Epidemiology
Athens, Greece
FRANCK BALDUCCI
Université Joseph Fourier Medical School
Lyon, France
TOMASZ PIEKARSKI
National Institute of Hygiene
Department of Medical Statistics
Warsaw, Poland
LJUBA BACHAROVA
National Center for Health Promotion
Bratislava, Slovakia
AURELIO TOBIAS
Institut Municipal d'Investigacio Medica
Barcelona, Spain
ANTTI PÖNKÄ
Helsinki City Center of the Environment
Helsinki, Finland
KLEA KATSOUYANNI
University Athens Medical School
Department of Hygiene and Epidemiology
Athens, Greece

ABSTRACT. The Air Pollution and Health: a European Approach (APHEA) project is a coordinated study of the short-term effects of air pollution on mortality and hospital admissions. Five West European cities (i.e., London, Amsterdam, Rotterdam, Paris, Milano) contributed several years of hospital admissions data for all respiratory causes. In the current study, the authors describe the results obtained from the quantitative pooling (meta-analysis) of local analyses. The diagnostic group was defined by ICD 460–519. The age groups studied were 15–64 y (i.e., adults) and 65+ y (elderly). The air pollutants studied were sulfur dioxide; particles (i.e., Black Smoke or total suspended particles); ozone; and nitrogen dioxide. The pollutants were obtained from existing fixed-site monitors in a standardized manner. We used Poisson models and standardized confounder models to examine the associations between daily hospital admissions and air pollution. We conducted quantitative pooling by calculating the weighted means of local regression coefficients. We used a fixed-effects model when no heterogeneity could be detected; otherwise, we used a random-effects model. When possible, the authors investigated the factors correlated with heterogeneity. The most consistent and strong finding was a significant increase of daily admissions for respiratory diseases (adults and elderly) with elevated levels of ozone. This finding was stronger in the elderly, had a rather immediate effect (same or next day), and was homogeneous over cities. The elderly were affected more during the warm season. The Sulfur dioxide daily mean was available in all cities, and it was not associated consistently with an adverse effect. Effects were present in areas in which more than one station was used in the assessment of daily exposure. Some significant associations were observed, although no conclusion that related to an overall particle effect could be drawn. The effect of Black Smoke was significantly stronger with high nitrogen dioxide levels on the same day, but nitrogen dioxide itself was not associated with admissions. The ozone results were in good agreement with the results of similar U.S. studies. The coherence of the results of this study and other results gained under different conditions strengthens the argument for causality.

THERE IS INCREASING INTEREST in the use of hospital admission data in studies of short-term effects of air pollution on health. This reflects the improved availability of admission data from routine systems and the possibility that, as a health outcome, admissions may offer some advantages over mortality data. Advantages include the likelihood that the diagnosis will be more accurate, the possibility that admission may be a more sensitive indicator of pollution effects, and the availability (for respiratory disease) of information on children and young adults. On the other hand, this source of data may be influenced by access to the health-care system and behavioral patterns.

The respiratory disease group mainly comprises infections of the lung or obstructive airways disease, either in acute form (asthma) or chronic form (chronic obstructive pulmonary disease [COPD]). As age increases, there is more overlap between COPD and asthma clinically, and it has been demonstrated that European doctors differ substantially in their diagnoses of these two conditions.[1] In all groups, infection is one of the major reasons for an exacerbation of airways disease. From this it follows that in a European study it might be better to study time series of all respiratory diagnoses than individual diagnoses; also, higher numbers give more statistical power. A possible disadvantage is the biasing of effect sizes to the null, if a relevant fraction of the admissions were insensitive to air pollution.

From what is known about toxicity of the air pollutants studied in Europe, it is possible that ambient concentrations might affect the respiratory system.[2] Whereas healthy people are unlikely to experience anything more than minor effects on the airways that are not associated with symptoms, subjects with preexisting disease could experience a worsening of symptoms that might precipitate an admission to hospital—or even death.

To date, most studies of respiratory hospital admission have been done in North America, where associations have been reported for particles and ozone, and to a lesser degree for sulfur dioxide (SO_2).[4–10] Fewer studies have been reported from Europe, and with the exception of the study by Walters et al.,[11] most researchers have focused on specific respiratory causes.

The Air Pollution and Health: a European Approach (APHEA) study is a Europe-wide collaborative effort to investigate the short-term effects of air pollution and to standardize the methods for analyzing epidemiological time series of counts. The health endpoints were total mortality, selected cause specific mortality, and respiratory emergency hospital admissions; details are described elsewhere.[12] A unique feature is the use of standardized methods of data selection and analysis for each center (see Katsouyanni et al.[13] for details). In this article, we present a quantitative summary of the respiratory hospital admissions results from five APHEA cities (i.e., London, Amsterdam, Rotterdam, Paris, and Milano). Results of admission time series of specific respiratory subgroups (i.e., COPD, asthma) are presented elsewhere.[14,16]

Material and Method

Material. Selected respiratory causes were defined by International Classification of Diseases (ICD9)-460–519. Except for asthma, these causes apply mainly to adults. They were analyzed separately for adults (i.e., 15–64 y of age) and the elderly (i.e., 65 y and above).

We obtained daily admission data from routine registers in all cities. The registration covered all hospitals in London, the Netherlands, and Milano, as well as hospitals selected for admitting short-stay patients in Paris. Registration was almost complete in the Netherlands, 92% in Milano, and 90% in Paris, and registration rose from 73% to 95% during the study period in London. The diagnosis by which the cases used here were selected was defined as the diagnosis at or after discharge (i.e., when all examination results were evaluated).

An overview of the data available for meta-analysis is provided in Table 1. When possible, we used daily counts of emergency admissions because this is likely to be a more sensitive indicator than general admissions. We were unable to differentiate between emergency and nonemergency admissions in Paris and Milano.

The pollutants studied were those generally available in European cities: sulfur dioxide (SO_2); nitrogen dioxide (NO_2); ozone (O_3); and indicators of particulate matter, Black Smoke (BS), and total suspended particulates (TSPs). The levels of SO_2 and NO_2 were obtained as a daily mean and a 1-h maximum, particles were obtained as a daily mean, and O_3 was obtained as a daily 8-h maximum (9 A.M.–5 P.M.) and a 1-h maximum. (Table 1).

Each center performed the Poisson time series regressions of their data individually. This approach was nec-

Table 1.—Summary Data: Admissions for Respiratory Causes (ICD 460–519) and Air Pollution Measurements

Country	City	Years	Mean daily admissions: Cold season	Mean daily admissions: Warm season	Comments
United Kingdom	London	1987–1991	36.3	30.7	Emergency admissions
The Netherlands	Amsterdam	1977–1989	2.2	2.1	Emergency admissions
	Rotterdam	1977–1989	1.7	1.5	Emergency admissions
France	Paris	1987–1992	36.2	29.2	Emergency and non-emergency admissions
Italy	Milano	1980–1989	11.8	9.0	Emergency and non-emergency admissions

			Pollutants (median of study period, in μg/m³)					
			SO_2		NO_2	O_3	Particulate matter	
Country	City	Inhabitants (× 1 000)	Daily mean	Daily maximum	Daily mean	daily 8–h average	BS daily mean	TSP daily mean
United Kingdom	London	7 200	29		35	14	13	
The Netherlands	Amsterdam	695	21	50	50	69	6	41
	Rotterdam	576	25	64	53	60	22	41
France	Paris	6 140	23	47	42	20	26	
Italy	Milano	1 500	66					120

Notes: NO_2 = nitrogen dioxide—daily mean and daily 1–h maximum; O_3 = ozone—daily 8–h average (9:00–17:00) and daily 1–h maximum; BS = black smoke—daily mean; and TSP = total suspended particulates—daily mean.

essary because the amount of data studied was too large to be studied at one place; it was also desirable because access patterns, weather patterns, and special events (e.g., strikes, holidays, epidemics) differ between places; therefore, we accounted for each city separately. The confounders included in each city were trend; seasonality; calendar effects (e.g., day of week, holidays); unusual events (strikes, reorganizations) as applicable; and meteorology (i.e., temperature and humidity). Where necessary, we included an autoregressive error term. For pollutants, each center determined a best-fitting 1-d result that allowed a delay of up to 3 d (5 d for O_3), as well as a best-fitting cumulative result that corresponded to the mean of the same day and from up to 3 d earlier (5 d for O_3). Each center established its own definition of warm season and cold season, depending on local climatic conditions, but in the main, April–September was considered warm. We used local medians for defining a pollutant as high or low for models testing effect modification of one pollutant by the level of another. Poisson regression coefficients can be expressed as relative risks per units of change.

Details about the principles of the time series analysis for this type of data are available elsewhere,[17] and information about the practical rules set by researchers to ensure maximum comparability—but allowing for the necessary flexibility within APHEA—is presented by Katsouyanni et al.[13] The individual center's results are published elsewhere.[15,18–24]

Method. The protocol required each center to fit the dose-response curve transformation that suited its data best. These were mostly nontransformed or log-transformed values—the latter describing a flattening of the dose-response curve with higher pollution levels. Given that these log-transformed curves tend to fit better when higher levels of air pollution are studied, we, in an effort to facilitate meta-analysis, refitted those models by using untransformed pollution values and by deleting all days from the series on which pollution levels exceeded 200 mg/m³. The relative risks given herein, therefore, apply best to relatively low levels of air pollution and should not be extrapolated, especially for the winter-type pollutants. Information about the conditions under which transformed curves are better fitted is available elsewhere.[15,18–24]

To provide a quantitative summary of results across the centers, we applied methods of meta-analysis by obtaining a pooled regression coefficient as a weighted mean of local regression coefficients—the weights being inversely proportional to the local variances. We performed calculations only for endpoint-pollutant combinations available from three or more countries, except for particulate matter, for which this restriction would have likely prohibited meta-analysis completely. Consequently, the particulate matter results were less stable.

We determined the weights, assuming a fixed-effects model, when a chi-square test failed to detect heterogeneity at the sensitive level of $\alpha = 20\%$ (see Appendix). When we had to reject the assumption of homogeneity, a random-effects model seemed more appropriate. In this model, the between-cities variance is added to each estimated local variance, thus giving more similar weights, but also a larger variance; this approach was an appropriate way of expressing that we were less sure of the pooled result in the case of heterogeneous local results. The local weights are expressed in the figures as "bubbles" of corresponding size around the parameter estimate. The between-cities variance can be estimated in several ways, we used an iterative ML-approach.[25]

In those instances in which heterogeneity was present and coefficients from at least five cities were available, we sought explanations for this in the form of weighted linear regressions of local coefficients on non-time-dependent properties of the cities in question. Candidates that might describe differences in sensitivity between populations or sources of bias were as follows: (a) indicators of the general population health status (e.g., age-standardized mortality rate, life expectancy, proportion of elderly, mortality rates from respiratory causes, smoking prevalence); (b) climate indicators (e.g., temperature, humidity—by season) during the study period and latitude; (c) an indicator of the outcome data quality differentiating between general and emergency admissions; (d) indicators of pollution data quality (e.g., number of stations, inhabitants represented per station, correlation between stations); and (e) indicators of the air pollution situation (e.g., number of inhabitants, pollution level, correlations between pollutants).

Results

Daily counts of adult respiratory admissions were not associated consistently with daily mean SO_2. A random-effects model was necessary, and the pooled coefficient was close to 0. The heterogeneity between the cities was explained either by the number of stations measuring SO_2 or mean winter temperature or by the mean life expectancy. Amsterdam and Rotterdam had (a) only one measuring station, (b) the lowest mean winter temperature (2.5 °C) of all cities, and (c) the highest life expectancy (77 y), and no adverse effect of SO_2 could be detected. It should be noted, however, that differences in life expectancy were very small in the cities examined here (between 75 and 77 y), and the association could be explained by chance. Misclassification of exposure via use of just one station may have biased the measurable effect to the null. The SO_2 measurements in the other three cities were based on four stations in each of these cities, and effects (i.e., small, nonsignificant) were seen. In the elderly age group, results were homogeneous, and only in Paris were they mostly positive and significant. However, the joint parameter for the daily mean was significant, and we expected an overall increase of 2% (95% confidence interval [CI] = 1, 5) in elderly admissions with a concomitant increase in SO_2 of 50 μg/m³ (Table 2).

Although results within the Netherlands seemed unstable, most Black Smoke regression results for adult admissions tended to be positive. The joint effect was small, but it was positive and significant, and we expected a 3% increase (95% CI = 1, 5) in admissions with a concomitant increase in BS of 50 μg/m³. The 1-d effect was larger than the accumulated effect. No effect of TSP was visible. For the elderly—and for both TSP and BS—the effects were close to 0, without heterogeneity. The TSP effects were slightly larger, but still were not significant (Table 2, Fig. 1).

An inconsistent picture was displayed by the NO_2 regression results in both adults and elderly admissions. The Netherlands' results had large random variation, and random-effects models were needed. Only the pooled result for accumulated daily mean NO_2 was borderline significant, and we estimated an almost 2% increase (95% CI = 0, 3) with an NO_2 increase of 50 μg/m³. Associations with other NO_2 indicators and adult respiratory admissions were smaller. For the elderly, only Rotterdam reported a consistently positive, sig-

Table 2.—Summary Effects of Pollutants on Daily Respiratory Admissions as Relative Risk (RR) per 50-μg/m³ Increase in Pollutant

Pollutant	Cities	Age group (y)	RR	95% CI
SO_2 daily mean	L, A, R, P, M	15–64	1.009	0.992, 1.025
		65+	1.020*	1.005, 1.046
BS daily mean	L, A, R, P	15–64	1.028*	1.006, 1.051
		65+	1.020	0.996, 1.046
TSP daily mean	A, R, M	15–64	1.010	0.989, 1.031
		65+	1.016	0.994, 1.039
NO_2 daily mean	L, A, R, P	15–64	1.010	0.985, 1.036
		65+	1.019	0.982, 1.060
NO_2 daily maximum		15–64	1.004	0.996, 1.011
		65+	1.005	0.977, 1.033
O_3 8–h average	L, A, R, P	15–64	1.031*	1.013, 1.049
		65+	1.038*	1.018, 1.058
O_3 1–h maximum		15–64	1.019*	1.005, 1.033
		65+	1.031*	1.015, 1.047

Notes: SO_2 = sulfur dioxide, BS = black smoke, TSP = total suspended particulates, RR = relative risk, CI = confidence interval, A = Amsterdam, L = London, M = Milano, P = Paris, and R = Rotterdam.
*Significant at 5% level.

nificant association. Overall, there appeared to be no evidence of an NO_2 effect in either age group (Table 2).

The O_3 results in the adult group showed good agreement between cities. In London, a significantly positive association was seen with each type of O_3 indicator, and most results from the other cities also had a positive tendency. London and Paris results were very similar. Joint results were positive and significant and were even more so among the elderly. The strongest association was with the daily 8-h average. The most common lag was with the same or previous day; therefore, we may term the effect "almost immediate." An approximate 3% increase (95% CI = 1, 5) in adult admissions, and an approximate 4% (95% CI = 2, 6) in elderly admissions, were estimated with a concomitant increase of 50 µg/m³ daily 8-h average (Table 2, Fig. 2).

Results, by season. The by-season models were less stable than the all-year results and varied strongly among cities. Consequently, a random-effects model was almost always required. No seasonal differences were significant, except for one, but some trends became apparent.

The small effect of 1-d SO_2 in the elderly (2% all year) resulted from an effect in the warm season, although this difference was not significant (Table 3). The differences in BS effects between seasons were quite large, but not significant, and they were quite inconsistent between 1-d and cumulative effects. This points at instability—and at little else (Table 3). Though based on even fewer cities (n = 3), with respect to the adults, TSP indicates rather consistently—and, for cumulative effects even significantly—a stronger effect in the warm season (1-d TSP 3% [CI = 0, 6] per 50 µg/m³). This was not the case in the elderly (Table 3). Nitrogen dioxide had no effect on either age group during either season (Table 3). The effects of O_3 on adults were similar in both seasons, but in the elderly they were slightly larger in the warm season (Table 3, Fig. 3).

Results, by level of another pollutant. There was an indication that an SO_2 effect in adults might be observable only at higher levels of particles. Perhaps SO_2 acts as a proxy for particles instead of having an effect of its own, but in our study the difference was small, inconsistent, and was absent in the elderly. On the other hand, particle effect differences, by SO_2 levels, were either not detectable or inconsistent, and we conclude that the BS effect found was independent of SO_2. There was, however, a significant difference in the effect of BS, by level of NO_2 on the same day (i.e., it was much stronger or only detectable when NO_2 levels were high). This effect was stronger in the adults, whereas the BS effect was stronger overall. We expect up to 7% more adult respiratory admissions per 50 µg/m³ BS on high NO_2 days (95% CI = 0, 15). Whether BS effects depend on general local NO_2 levels, or whether the correlation between BS and NO_2 depends on a local level, could not be tested because of an insufficient number of data points (Fig. 4). Nitrogen dioxide, however, showed no consistent difference in effect size or showed no effect at all, by different same-day levels of BS or O_3.

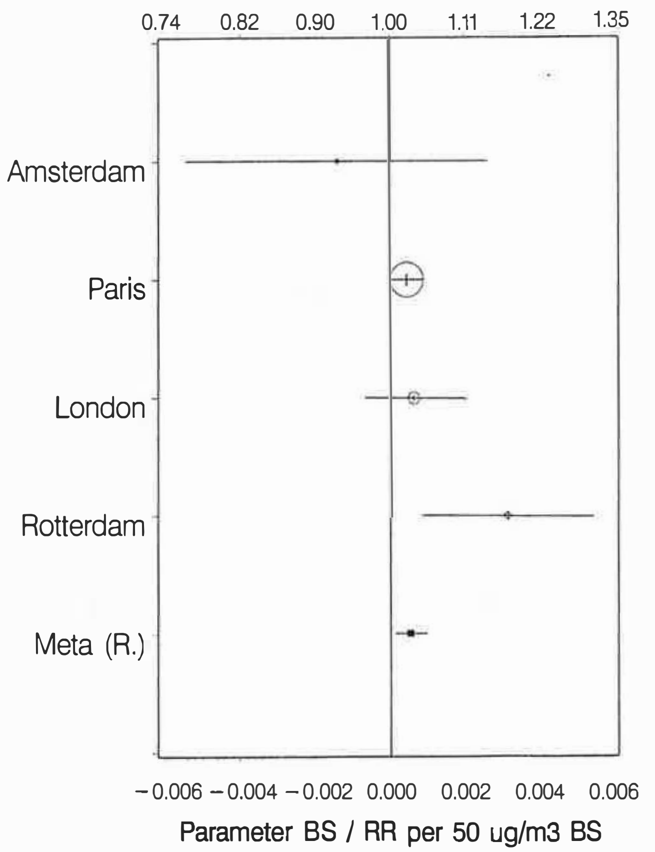

Fig. 1. Black Smoke (BS) effects on adult admissions in participating cities and pooled effect. The bubble size of the local results is proportional to the weight this city receives in the meta-analysis. (R) indicates that results were heterogeneous.

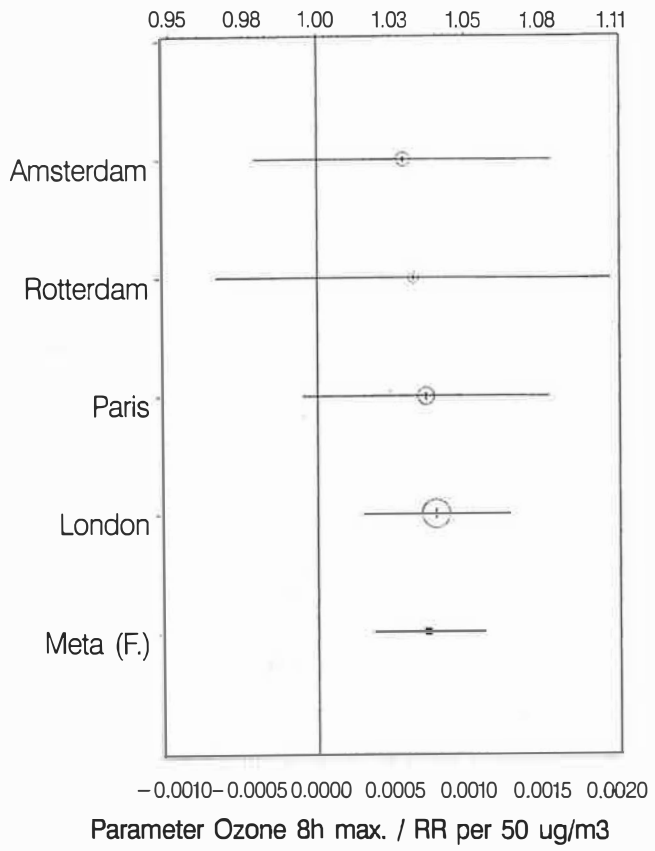

Fig. 2. Ozone (O_3) 8-h (9:00 A.M.–17:00 P.M.) average effects on elderly admissions in participating cities and pooled effect. The bubble size of the local results is proportional to the weight this city receives in the meta-analysis. The homogeneity of results is clearly visible. (F) indicates that results were homogeneous.

Table 3.—Summary Effects of Air Pollutants on Respiratory Admissions, by Season

Pollutant	Cities	Season*	15–64 y olds RR†	15–64 y olds 95% CI	65+ y olds RR†	65+ y olds 95% CI
SO_2 daily mean	L, A, R, P, M	Warm	1.01	0.98, 1.04	1.06‡	1.01, 1.11
		Cold	1.01	0.97, 1.07	1.02	0.99, 1.04
BS daily mean	L, A, R, P	Warm	0.99	0.90, 1.09	1.07‡	1.00, 1.15
		Cold	1.04‡	1.02, 1.07	1.00	0.95, 1.04
TSP daily mean	A, R, M	Warm	1.03§	1.00, 1.06	1.01	0.98, 1.04
		Cold	0.97	0.93, 1.02	1.02§	1.00, 1.05
NO_2 daily mean	L, A, R, P	Warm	1.00	0.96, 1.04	1.02	0.99, 1.06
		Cold	1.01	0.98, 1.04	1.00	0.98, 1.03
NO_2 daily maximum		Warm	1.00	0.99, 1.02	1.00	0.98, 1.02
		Cold	1.00	0.98, 1.01	1.00	0.98, 1.03
O_3 8-h average	L, A, R, P	Warm	1.02	0.99, 1.05	1.04‡	1.02, 1.07
		Cold	1.03	0.98, 1.08	1.02	0.99, 1.05
O_3 1-h maximum		Warm	1.01	0.99, 1.05	1.04‡	1.02, 1.05
		Cold	1.02	0.99, 1.05	1.03§	1.00, 1.06

Notes: RR = relative risk, CI = confidence interval, SO_2 = sulfur dioxide, BS = black smoke, TSP = total suspended particulates, O_3 = ozone, A = Amsterdam, L = London, M = Milano, P = Paris, and R = Rotterdam.
*Cold season mainly October–March; warm season mainly April–September.
†per 50-µg/m³ increase in pollutant.
‡Significant at 5% level.
§Significant at 10% level.

Discussion

Problems with materials. One problem with data comparability was that Paris and Milano data were confined to all admissions, whether emergency or not. To explore the possible effect of this, we examined the available London data to examine the relationship between the two categories of admission. Some data on diagnosis categories were also available from Milano. The relationship varied with both diagnosis and age, and emergency admissions generally formed the vast majority of respiratory admissions among the elderly, but only approximately 50–70% of the admissions in adults were emergency admissions. From the point of view of the meta-analysis, admission patterns driven by nonemergency admissions were expected to bias the results downward. Results that include Paris and Milano coefficient estimates—especially for respiratory cases of adults—may, therefore, have been rather conservative. It is possible that some of the differences seen in effect between elderly and adults resulted from this phenomenon. We compared local results, however, and we did not find direct evidence of biased results.

The analysis of particle effects was hampered because different measurement methods were used. The methods used most frequently were the Black Smoke (smoke stain) method and TSP (gravimetric or β-attenuation). Size-fractionated particulate mass (PMx, particulate mass of particles below x µm in size) was rarely measured in Europe at the time of this study; within this data set, such measurements were available only from Paris (no meta-analysis possible). The average relationship between the different methods is not necessarily the same everywhere and would be affected by the local size distribution, the "blackness" of the particles, and perhaps by season. In the context of this study, results can be compared only qualitatively.

Methodology problems. It should be noted that certain frequently encountered problems of meta-analysis do not apply.[26] There was no selection bias. The participating cities were not selected by the results of the short-term analysis (results were unknown when the studies started), and no cities or results were excluded later. There were no important differences in health endpoints, exposure data, and analysis procedures used; we took great care to set rules for inclusion and to ensure comparability. Therefore, this meta-analysis was not an afterthought, but was planned from the onset of the study.

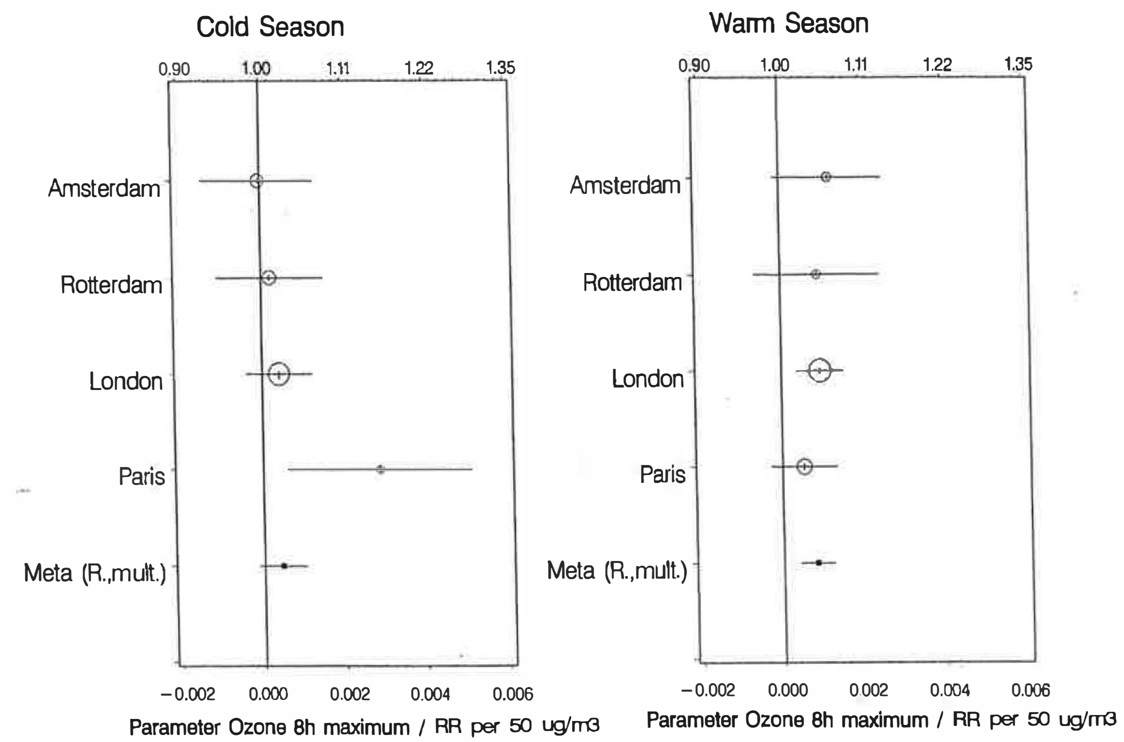

Fig. 3. Ozone (O_3) effects on elderly, by season. The effect was larger in the warm season. The bubble size of the local results is proportional to the inverse of the variance of the parameter, but actual weights were determined including covariance information. (Rmult.) indicates that multivariate results were heterogeneous.

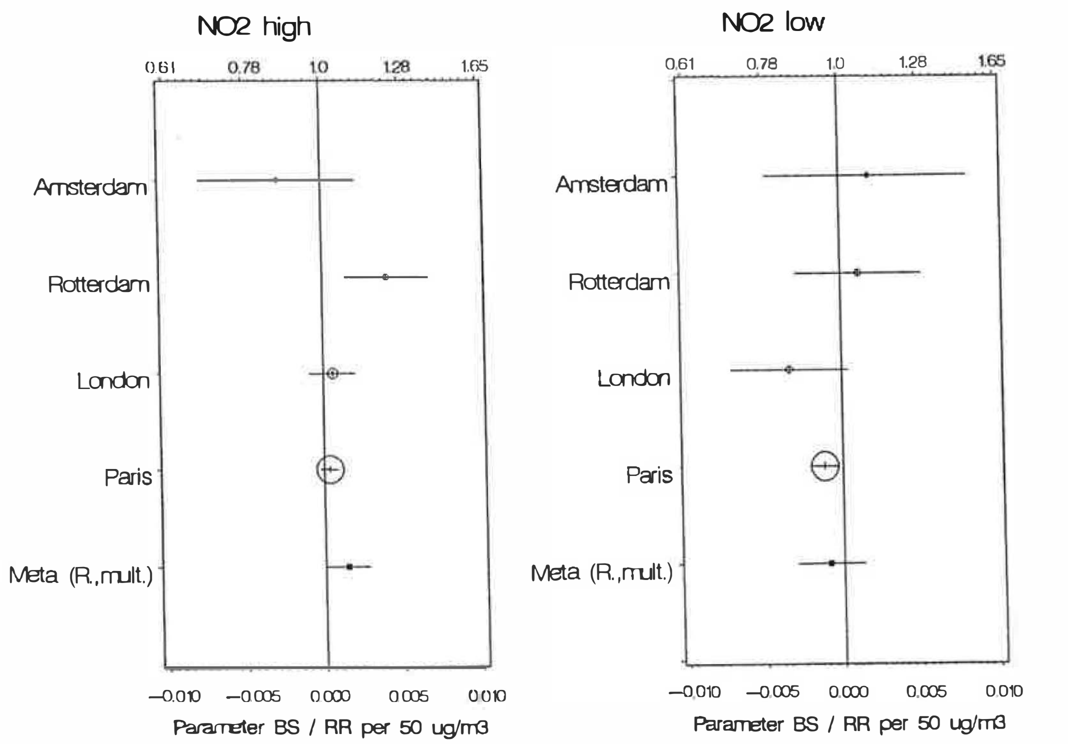

Fig. 4. Black Smoke (BS) effects on adults, by level of nitrogen dioxide (NO_2). Random variation between cities is visible, but clearly the pooled result during high levels of NO_2 was larger. The bubble size of the local results is proportional to the inverse of the variance of the parameter, but actual weights were determined including covariance information. (Rmult.) indicates that multivariate results were heterogeneous.

The interpretation of the by-season or by-level-of-another pollutant results is not completely straightforward. For example, if a threshold exists, and if the values of a pollutant lie mostly below this threshold in one season, then the differences in effect would reflect this threshold, rather than an effect modification by weather conditions. There was no pollutant in this analysis, however, that had no effect in its respective lower season and a strong effect in the other. If one looks at effects by level of another pollutant, differences may also be caused by thresholds if the two pollutants in question are strongly correlated. In this data set the correlation between NO_2 and BS was positive—but to a different degree in different cities. However, if this were the main explanation for the effect difference observed, a similar pattern would have arisen for SO_2, which was similarly correlated with particles (data not shown). Inasmuch as this was not the case, there must be another (at least partial) explanation. The dependence of the BS effect on NO_2 levels might point at a synergy between the adverse effects of various components of automobile exhausts, which produce both particles and NO_2, but are less responsible for SO_2 levels in the air. It might point at different effects of particles, by source of emission or composition of the particles. Given that NO_2 itself shows no effect, high NO_2 days could also be associated with another component of air pollution that causes this effect modification.

Overview of Results

Ozone. Associations of respiratory admissions with O_3 were large, significant, homogeneous, and immediate. They were stronger in the elderly than in adults and were stronger with the 8-h daytime average than with the daily maximum. The elderly group was also more affected than the adults in the warm season.

Suspended particles. There was a tendency toward an association of respiratory admissions with Black Smoke, but the very limited number of cities prevented final conclusions. Total suspended particles may show some effect on adults in the warm season. The BS effect appeared quite independent of the concurrent SO_2 level; it was, however, very dependent on the NO_2 level, and significantly larger effects were seen when NO_2 on the same day was above the local median.

Sulfur dioxide. No consistent evidence of an influence on respiratory admissions was found. The heterogeneity between cities was best explained by number of stations providing data (i.e., effects were larger when three or more stations provided data). Perhaps the elderly form a more sensitive subgroup.

Nitrogen dioxide. Although there were some positive associations with respiratory admissions, an NO_2 effect could not be confirmed for either age group.

Comparison with respiratory mortality in APHEA cities. Cause-specific mortality was available for nine APHEA cities (i.e., London, Paris, Lyon, Barcelona, Milano, Lodz, Poznan, Cracow, and Wroclaw). We saw evidence of an association between respiratory mortality and SO_2, BS, and O_3 in Western European cities, with relative risks of 1.05 for SO_2 daily mean (95% CI = 1.01, 1.04), 1.04 for BS (95% CI = 1.02, 1.07), and 1.05 (95% CI = 1.02, 1.08) for O_3 daily 8-h averages per 50-$\mu g/m^3$ increase in pollution. This association did not hold in the four Polish cities (no O_3 data available), whose pollution mixtures, with relatively high levels of particles and SO_2, might be different from those of Western European cities.[27]

Other studies. In most published studies, except those published or co-authored by Schwartz and Dockery, investigators used methods that are not quite comparable with those described here. Comparisons should be made cautiously. In many of the U.S. studies, sulfates were used as a pollutant. It is known that SO_4^{2-} forms very fine particles; in fact, Schwartz et al.[17] converted them to particulate matter with an aerodynamic diameter less than or equal to 10 µm (PM_{10}) (with locally different factors) for comparison purposes.

Bates and Sizto[3] analyzed the effects of O_3, NO_2, SO_2 (all 1-h maxima), coefficient of haze (COH), and sulfates (daily means) on respiratory admissions during January/February and July/August in Southern Ontario. The method of analysis was very different from the one we used. They found no associations in winter (except with temperature). In summer, respiratory admissions were correlated with SO_2 (2-d lag), O_3 (1–2-d lag), NO_2 (2-d lag), and SO_4^{2-} (1-d lag), but they were not correlated with COH. Bates and Sizto observed the largest correlations between SO_4^{2-} and all respiratory causes, followed by O_3 (1-d lag).

Thurston et al.[6] investigated summer data (July/August) gleaned during a 3-y period in Toronto (Canada) with respect to particle strong acidity (PSA) (H+), sulfates (daytime 1-h maximum), O_3 (daily 1-h maximum), TSP, PM_{10}, an $PM_{2.5}$ (daily means). Their method of analysis was different from the one we used. Ozone (same day) had the strongest influence on all admissions and particles had a moderate influence, whereas SO_2 and NO_2 had none. No comparable relative risks can be given, but qualitatively this is consistent with our findings.

During a 3-y period, Walters et al.[11] examined respiratory admissions in Birmingham (United Kingdom) relative to SO_2 and BS. Their method of analysis was different from the one we used. Both pollutants had an effect, but BS tended to show up more often in their study than in ours.

Dockery and Pope[9] reviewed and meta-analyzed studies (some of which were hospital-admission studies) for short-term effects of particulate air pollution with respect to daily mean PM_{10}; they converted other particle measurements to this standard, particularly TSP = PM_{10}/0.55 and BS ≈ PM_{10}. They calculated an approximate 4% increase in all respiratory admissions per 50 $\mu g/m^3$ PM_{10} (i.e., three studies). This increase is consistent with the approximate 3% we found for BS in our study.

Burnett et al.[10] investigated data collected during 6 y in Ontario (Canada) with respect to O_3 and sulfates. Emergency admissions could have been selected from the database, but apparently the authors used all respiratory admissions. The method of analysis was very different from the one we used, especially because there was no meteorology correction. Their parameters can be expressed as approximate risk ratios. The study by Burnett et al.,[10] another by Thurston et al.,[5] and two by Schwartz[7,8] are summarized with the APHEA results in Tables 4–6.

In two cities in the United States, SO_2 effects were similar to those in the APHEA cities. Schwartz[7] interpreted them as being caused by the correlation between SO_2 and particles; however, among the APHEA cities, no association between the locally different SO_2-BS or TSP correlations and the locally different SO_2 effects was found (Table 4).

The effects of PM_{10} on elderly respiratory admissions in the U.S. studies were larger than those found for BS and TSP in the APHEA cities. Perhaps this difference occurred because PM_{10} is a more appropriate measure of the fraction of particles relevant for health effects. Also, the correlations between particulate mass and other pollutants tend to be different in the United States (Table 5).

With respect to O_3, only summer or warm season results (O_3 measurements are often discontinued during the cold season) are quoted in the literature, as are effects for daily maximum or daily mean; we found the 8-h daytime average to be the best predictor. Except for the very large effect found in Spokane (but with a 95% CI = 0, 54), the European and U.S. results for warm season and daily maximum appear quite similar in magnitude (i.e., all CIs overlap largely with the 2–5% effect size CI found for 50 μg/m³ daily 1-h maximum).

A review of the literature concerning, specifically, COPD admissions and asthma admissions is provided elsewhere.[14-16]

Comments and interpretation. In considering whether the associations observed are causal, one must examine the possibility of confounding by factors that could be associated with both pollution and health effects. Differences in diagnostic habits, treatment regimes, and health-care systems—as well as lifestyles—are unlikely confounders inasmuch as they may vary strongly between cities and countries, but not according to daily local pollution levels. More plausible confounders are weather and climate. In this study, the case for causality was strengthened by our finding of such consistent O_3 effects across the European cities, as well as in U.S. studies, in which different climates and weather patterns were noted. Similarly strong and consistent effects were found in APHEA in the subgroup of COPD admissions, for which additional data were available from Barcelona, which has a Mediterranean climate quite unlike that of London or the Netherlands.[14] Differences in actual effect size might be the result of differences in the pollution mix, differences in the spectrum of diseases admitted to hospital, or differences in the underlying susceptibility of people with those diseases to admission, based on national differences in primary care systems that affect the way exacerbations are handled. It must be noted, however, that from a statistical point of view, the strong O_3 effects were homogenous between cities.

The respiratory group mainly comprises infections of the lung or obstructive airways disease in either acute form (asthma) or chronic form (COPD); diagnoses are difficult to differentiate, especially in the elderly. A common exacerbating factor for all respiratory conditions, which may in turn be exacerbated or promoted by air pollution, is acute infection. Specifically, we may see an impairment of airway defenses against infections, an increase in airways hyperresponsiveness, toxic inflammation of the lung, modification of the response of asthmatics to inhaled allergens, airways obstruction, and impairment of gas exchange and ventilation/perfusion balance. Plausible mechanisms exist for respiratory disease to be affected by all four pollutants.[2]

The coherence of results across various cities and studies, especially for O_3, together with what is known about possible mechanisms, strengthens the argument that the associations found in this study were causal.

Table 4.—International Comparison of Effect of SO_2 Daily Mean on Respiratory Admissions of Cases 65 y or Older

Study	City	Lag	RR*	95% CI
APHEA	London	2	1.04	0.99, 1.08
	Amsterdam	2	1.02	0.98, 1.06
	Rotterdam	0–2*	1.02	0.98, 1.07
	Paris	0	1.03	1.00, 1.06
	Milano	0	1.00	0.97, 1.03
APHEA pooled result		**—**	**1.02**	**1.00, 1.05**
United States	New Haven (Schwartz 1995[7])	2	1.03	1.02, 1.05
	Tacoma (Schwartz 1995[8])	0	1.06	1.01, 1.12

*In Rotterdam, results were pooled from three different study periods.

Table 5.—Effects of Particulate Daily Means on Respiratory Admissions of Cases: An International Comparison of Relative Risk per 50-μm/m³ Increase in Pollutant

Study	City	Particulate type	Lag	RR*	95% CI
		Year-round results			
APHEA	London	BS	2	1.04	0.99, 1.10
	Amsterdam	BS	2	1.04	0.87, 1.24
	Rotterdam	BS	2	0.98	0.89, 1.09
	Paris	BS	0	1.02	0.99, 1.05
	Amsterdam	TSP	2	1.00	0.92, 1.10
	Rotterdam	TSP	1	1.02	0.93, 1.12
	Milano	TSP	1	1.02	0.99, 1.04
APHEA pooled result		**BS**	**—**	**1.03**	**1.01, 1.05**
		TSP	—	1.00	0.99, 1.03
United States	New Haven (Schwartz 1995[7])	PM_{10}	0	1.06	1.00, 1.13
	Tacoma (Schwartz 1995[7])	PM_{10}	0	1.10	1.03, 1.17
	Spokane (Schwartz 1995[8])	PM_{10}	0	1.09	1.04, 1.14

Study	Age group (y)	Particulate type	RR*	95% CI
	Warm season or summer only			
APHEA pooled result	15–64	BS	0.99	0.90, 1.09
	65+	BS	1.07	1.00, 1.15
	15–64	TSP	1.03	1.00, 1.06
	65+	TSP	1.01	0.98, 1.04
Buffalo (Thurston 1992[6])	All age groups	PM_{10}†	1.12	1.03, 1.22
New York (Thurston 1992[6])	All age groups	PM_{10}†	1.05	1.01, 1.10
Ontario (Burnett 1992[10])	All age groups	PM_{10}†	1.06	1.04, 1.08

Notes: BS = Black smoke, RR = relative risk, CI = Confidence Interval, TSP = total suspended particulates, and PM_{10} = particulate matter < 10 millimeters.
*Per 50-μm/m³ increase in pollutant.
†Converted from SO_4^{-2}, according to Schwartz (1996[8]).

Table 6.—Effects of Ozone Daily Maximum on Respiratory Admissions During the Warm Season/Summer Only: An International Comparison

Study	City	Age group (y)	Lag	RR*	95% CI
APHEA	London	65+	1	1.04	1.01, 1.06
	Amsterdam		1	1.05	0.99, 1.12
	Rotterdam		0–2†	1.05	0.97, 1.13
	Paris		0	1.02	0.99, 1.06
APHEA pooled result		**65+**	**—**	**1.04**	**1.02, 1.05**
United States	New Haven (Schwartz 1995[7])	65+	2	1.03	0.99, 1.07
	Tacoma (Schwartz 1995[7])		2	1.10	1.03, 1.15
	Spokane (Schwartz 1995[8])		2	1.24	1.00, 1.54
	Buffalo (Thurston 1992[5])	All	—	1.06	0.99, 1.12
	New York (Thurston 1992[5])		—	1.03	1.02, 1.04
	Ontario (Burnett 1992[10])		—	1.02	1.01, 1.03

*Per 50-μm/m³ increase in pollutant.
†In Rotterdam, results were pooled from three different study periods.

Appendix

χ^2 Test of Homogeneity

Given local estimates $\hat{\beta}_i$ (parameter or parameter vector) and $\hat{\Sigma}_i$ (variance or covariance matrix of $\hat{\beta}_i$), $i = 1, \ldots, N$, we obtain a fixed-effects model estimate of the joint parameter or parameter vector

$$\hat{\beta} = \sum_i w_i \hat{\beta}_i,$$

with weights or weight matrices

$$w_i = \hat{\Sigma}_i^{-1}\left(\sum_i \hat{\Sigma}_i^{-1}\right)^{-1}.$$

The test statistic

$$\sum_i (\hat{\beta}_i - \hat{\beta})' \hat{\Sigma}_i^{-1} (\hat{\beta}_i - \hat{\beta})$$

is χ^2-distributed with $(N - 1)$ p degrees of freedom, where N is the number of studies and p the dimension of β.

* * * * * * * * * *

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The APHEA collaborative group contains the following members: K. Katsouyanni, G. Touloumi, E. Samoli (Athens, Greece—Coordinating Center); H. E. Wichmann, C. Spix (Oberschleißheim, Germany); H. R. Anderson, A. Ponce de Leon, R. Atkinson, J. Bower, D. Strachan, M. Bland (London, United Kingdom); M. A. Vigotti, G. Rossi, L. Bisanti, F. Repetto, A. Zanobetti (Pisa, Italy); W. Dab, P. Quenel, S. Medina, A. LeTertre, B. Thelot, B. Festy, Y. LeMoullec, C. Monteil (Paris, France); J. P. Schouten, J. M. Vonk, A. C. M. deGraaf (Groningen, The Netherlands); D. Zmirou, P. Ritter, T. Barumandzadeh, F. Balducci, G. Laham (Lyon, France); B. Wojtyniak, T. Piekarski (Warsaw, Poland); L. Bacharova, F. Fandakova (Bratislava, Slovakia); J. Sunyer, J. Castellsague, M. Saez, A. Tobias (Barcelona, Spain); and A. Pönkä (Helsinki, Finland).

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Requests for reprints should be sent to Dr. C. Spix, Uni Mainz, IMSD, D55101 Mainz, Germany.

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Brain Cancer Mortality among French Farmers: The Vineyard Pesticide Hypothesis

JEAN-FRANCOIS VIEL
BRUNO CHALLIER
ALEXANDRE PITARD
DOMINIQUE POBEL
Department of Public Health
Biostatistics and Epidemiology Unit
Faculty of Medicine
Besancon, France

ABSTRACT. In this study, the authors assessed the contribution of vineyard pesticides to brain cancer mortality among agricultural workers. A pesticide exposure index (PEI) in vineyards was calculated for 89 French geographical units (départements). The authors estimated standardized mortality ratios among male farmers and farm laborers aged 35–74 y for the years 1984–1986. Poisson regression models, which were fitted to the ecological data, included random effects. Mortality from brain cancer among farmers was significantly higher than mortality for the overall population (standardized mortality ratio = 1.25, $p < .001$). Univariate analysis revealed a significant link with pesticide exposure in vineyards (relative risk = 1.10; 95% confidence interval = 1.03, 1.18), as did multivariate analysis (relative risk = 1.11; 95% confidence interval = 1.03, 1.19). These results corraborate the evidence that pesticides in vineyards contribute to mortality from brain cancer among farmers.

EVERY YEAR, 93 000 tons of pesticides (e.g., insecticides, herbicides, fungicides) are sprayed in France,[1] potentially exposing 700 000–1 000 000 workers (e.g., farm laborers, applicators, manufacturers, formulators, packers). Overall mortality and mortality from cancers have generally been lower among farmers than in the overall population,[2] although there is some evidence of a higher risk of certain cancer types in agriculture[3] potentially related to pesticide exposure. In this regard, we have recently highlighted a link between pesticides used in agriculture and bladder cancer within the French farmer population.[4]

In their review of all cancers among farmers, Blair et al.[3] classified brain cancer in the high-risk category. The influence of pesticide exposure on brain cancer occurrence is uncertain and is the focus of our study.

There seems to be no classical risk factor for this rare disease (French age-standardized mortality rate in 1990: 5.6/100 000 males).[5] It appears that no particular age range is at risk; brain cancer incidence rates increase slowly until 55–65 y of age, without a real peak.[5] This cancer takes many forms: glioma, glioblastoma, astrocytoma, medulloblastoma, oligodendroglioma, and ependymoma. To date, published studies have included either all of these types or only gliomas. Among 10 case-control studies in which agriculture was mentioned as an occupation,[6–15] a significantly higher risk was highlighted in 3.[7,9,13] The results in the remaining 7 studies were not significant statistically.[6,8,10–12,14,15] Among 13 agricultural mortality studies reported,[16–28] researchers reported significantly higher mortality ratios in only 3.[16,19,27] In 4 of 12 industrial studies (i.e., manufacturing or application processes),[29–40] investigators reported a significant relationship between pesticide exposure and