

## Short-term Effects of Ambient Oxidant Exposure on Mortality: A Combined Analysis within the APHEA Project

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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 using data from 15 European cities, with a wide range of geographic, sociodemographic, climatic, and air quality patterns. The objective of this paper is to summarize the results of the short-term effects of ambient oxidants on daily deaths from all causes (excluding accidents). Within the APHEA project, six cities spanning Central and Western Europe provided data on daily deaths and NO<sub>2</sub> and/or O<sub>3</sub> levels. The data were analyzed by each center separately following a standardized methodology to ensure comparability of results. Poisson autoregressive models allowing for overdispersion were fitted. Fixed effects models were used to pool the individual regression coefficients when there was no evidence of heterogeneity among the cities and random effects models otherwise. Factors possibly correlated with heterogeneity were also investigated. Significant positive associations were found between daily deaths and both NO<sub>2</sub> and O<sub>3</sub>. Increases of 50 µg/m<sup>3</sup> in NO<sub>2</sub> (1-hour maximum) or O<sub>3</sub> (1-hour maximum) were associated with a 1.3% (95% confidence interval 0.9–1.8) and 2.9% (95% confidence interval 1.0–4.9) increase in the daily number of deaths, respectively. Stratified analysis of NO<sub>2</sub> effects by low and high levels of black smoke or O<sub>3</sub> showed no significant evidence for an interaction within each city. However, there was a tendency for larger effects of NO<sub>2</sub> in cities with higher levels of black smoke. The pooled estimate for the O<sub>3</sub> effect was only slightly reduced, whereas the one for NO<sub>2</sub> was almost halved (although it remained significant) when two pollutant models including black smoke were applied. The internal validity (consistency across cities) as well as the external validity (similarities with other published studies) of our results on the O<sub>3</sub> effect support the hypothesis of a causal relation between O<sub>3</sub> and all cause daily mortality. However, the short-term effects of NO<sub>2</sub> on mortality may be confounded by other vehicle-derived pollutants. Thus, the issue of independent NO<sub>2</sub> effects requires additional investigation. *Am J Epidemiol* 1997;146:177–85.

air pollution; environmental exposure; environmental illness; environmental pollutants; mortality; nitrogen dioxide; ozone

It is generally accepted that severe air pollution episodes, such as those in Europe and North America before 1960, can cause important acute adverse effects on human health including mortality (1). Recent epidemiologic studies have indicated short-term effects of air pollution on health at relatively low levels of air pollution, even lower than current national or international air quality standards (2–11). The majority of

these studies were concerned with the effects of the “classical” air pollutants, i.e., black smoke and SO<sub>2</sub> related to combustion sources. However, due to changes in the emission sources toward road transport, the air pollution profile has gradually changed toward a more pronounced photochemical component.

O<sub>3</sub> is generally regarded as one of the most toxic components of the photochemical air pollution mix-

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Abbreviations: APHEA, Air Pollution and Health: a European Approach; CI, confidence interval; PM<sub>10</sub>, particulate matter with a median aerodynamic diameter ≤ 10 µm; PM<sub>13</sub>, particulate matter with a median aerodynamic diameter ≤ 13 µm; RR, relative risk.

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ture. Several chamber (12–16) as well as epidemiologic studies (17–23) have suggested significant effects of exposure to O<sub>3</sub> on morbidity and more specifically on lung function decrements, respiratory and nonrespiratory symptoms, exacerbation of asthma, and increased number of hospital admissions. Most of the epidemiologic studies of short-term effects of NO<sub>2</sub> on health were focused on annoyance and symptoms reported in diaries, on hospitalization for respiratory diseases, and on pulmonary function (24–34). However, the evidence from these studies is not consistent.

A few studies have been conducted on the effects of photochemical air pollution on mortality (35–39). They suggested adverse effects of NO<sub>2</sub> and/or O<sub>3</sub> on mortality, although the independence of their effects from those of other pollutants, such as particles, is still unclear. Although total (all cause) mortality is a relatively nonspecific end point, it has the advantage of being the most reliable one. Also, concerning the effects of “winter” type pollutants (SO<sub>2</sub>, black smoke) on health, total mortality tends to provide the most consistent results.

In most locations, mortality and pollution variables exhibit annual cycles that comprise a substantial fraction of their variability. Moreover, annual cycles of daily mortality and photochemical pollution, especially O<sub>3</sub>, are out of phase (i.e., mortality usually peaks in the winter whereas O<sub>3</sub> levels peak in the summer). Advanced time-series statistical analyses techniques, which only recently have been applied in air pollution epidemiology, are needed to deal with such problems (8, 11, 40–42).

In air pollution epidemiology, which deals with the effect of a complex mixture of air pollutants, a critical factor in assessing causality is the consistency of the results across studies conducted in populations with varying levels of potential confounders. The Air Pollution and Health: a European Approach (APHEA) study is an attempt to quantify the short-term effects of air pollution on mortality and hospital admissions us-

ing data from 15 European cities with a wide range of geographic, sociodemographic, climatic, and air quality patterns. In this paper, a combined analysis (meta-analysis) of data from several European countries concerning the short-term effects of NO<sub>2</sub> and O<sub>3</sub> on the total daily number of deaths is presented.

## MATERIALS AND METHODS

Within the framework of the APHEA project (43), six European cities contributed data for evaluating the short-term effects of photochemical air pollution on the total daily number of deaths, using NO<sub>2</sub> and O<sub>3</sub> as indicators of exposure. In table 1, the studied populations and time periods as well as the descriptive statistics of air pollutants, weather, and daily mortality series are shown for the participating cities. The cities span Central and Western Europe and comprise a population of more than 19 million. Mortality data were extracted from the national statistics records except in Athens, where the information was collected from the death certificates. In all cities except Athens and Barcelona, deaths from external causes were excluded from the total daily number of deaths. The inclusion of deaths from external causes adds random noise to the outcome variable; and its effect, if any, on the estimates should be toward the null. However, the number of deaths from external causes is only a small proportion of the total number of deaths (4–5 percent).

Daily air pollutant measurements were provided by the monitoring network established in each town. Although there was no quality control program within APHEA to ensure comparability of air pollution measurements, all European Union countries have their respective quality control program to conform with European Union requirements. NO<sub>2</sub> is measured by the chemiluminescence method and O<sub>3</sub>, by the ultraviolet absorption method (44, 45). The daily maximum 1-hour level for each pollutant was used, and the mean daily (24-hour) measurements of NO<sub>2</sub> and the maxi-

TABLE 1. Descriptive characteristics of the APHEA\* cities, contributing to the analysis of photochemical air pollution

City	NO <sub>2</sub> (µm/m <sup>3</sup> ) (1-hour maximum)	O <sub>3</sub> (µm/m <sup>3</sup> ) (1-hour maximum)	BS* (µm/m <sup>3</sup> ) (24-hour)	Daily mean temperature (°C)	Daily mean humidity (%)	Daily no. of deaths	Time period	Population†
	Mean (SD*)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)		
Athens	134.6 (50.1)	93.8 (42.8)	84.4 (48.0)	17.4 (7.1)	62.0 (12.4)	35 (6)	1987–1991	2,000,000
Barcelona	97.8 (40.2)	72.4 (34.9)	46.6 (25.3)	15.5 (6.3)	75.5 (9.4)	46 (9)	1986–1992	1,700,000
Köln	80.7 (33.8)		39.6 (24.1)	10.7 (6.8)	74.1 (11.0)	18 (5)‡	1977–1989	740,000
London	109.4 (44.0)	41.2 (26.0)	14.6 (7.0)	12.3 (5.2)	72.1 (10.2)	176 (27)‡	1987–1991	7,200,000
Lyon	132.7 (93.3)	15.2 (15.7)	38.1 (23.8)	11.7 (7.7)	74.9 (12.1)	8 (3)‡	1985–1990	410,000
Paris	70.1 (31.8)	46.1 (32.9)	31.6 (21.1)	12.2 (6.5)	75.5 (12.8)	130 (17)‡	1987–1990	6,140,000

\* APHEA, Air Pollution and Health: a European Approach; BS, black smoke (for Köln, PM<sub>10</sub>; for Lyon, PM<sub>10</sub>); SD, standard deviation.

† The numbers refer to the populations covered by the data collection.

‡ Deaths from external causes were excluded.

mum 8-hour values for O<sub>3</sub> were also considered. Urban monitoring sites were used for NO<sub>2</sub>; and for O<sub>3</sub>, suburban sites were also included. The correlation between the daily measurements at different stations in the same city ranged from 0.20 to 0.84 for NO<sub>2</sub> and from 0.40 to 0.97 for O<sub>3</sub>. For each pollutant, the average daily values over all those monitoring stations that had measurements for more than 75 percent of the whole study period were estimated in each city and used for the final individual city analysis. For days with missing values in one station, values were estimated by a regression model based on the remaining stations' values, allowing also for seasonal variability. The rules adopted in the APHEA protocol about the geographic location of the monitoring stations used, the completeness criteria, and the applied methods for filling in missing values are described in more detail elsewhere (43, 46).

Although the present study is concerned with photochemical pollution, mean levels of black smoke as an indicator of ambient particulate matter are also presented in table 1 to point out the substantial variability across cities not only in the levels but also in the mixture of air pollution. Black smoke is measured by the British black smoke filter method, which measures light reflectance from the surface of a filter. The measurements are converted to mass using a calibration curve (47). Particles with a diameter less than 4 μm are collected with high efficiency (47). In European urban areas, black smoke is well correlated with particulate matter with a median aerodynamic diameter ≤ 10 μm (PM<sub>10</sub>) with a reported range of correlations from 0.53 to 0.74, which is stronger in the winter in most areas (47). The highest levels of NO<sub>2</sub> and O<sub>3</sub> were observed in Athens and Barcelona, where there were also high levels of black smoke. London, in contrast, had relatively low levels of black smoke.

The statistical analysis in each city followed a standardized methodology to ensure comparability of results. The details of the procedure are described elsewhere (46, 48). In summary, Poisson autoregressive models allowing for overdispersion were fitted with special attention to removing seasonal (annual to 6 weeks) and long-term trends from the mortality series; allowing for short-term effects of weather factors such as temperature (°C) and humidity (percentage); removing day of the week patterns; and taking into account local characteristics such as holidays, influenza epidemics, and other unusual events such as strikes and heat waves. The appropriate functional form of temperature and humidity or their interaction was decided according to the local weather conditions after extensive explanatory and analytical examination of the data. Information about influenza epidemics

was obtained from routinely collected data where available; otherwise, influenza epidemics were identified from the periodograms of the raw outcome series.

The dose-response relation was found to be curvilinear, with flattened slopes at higher levels of air pollution, in most cities with high concentrations (e.g., Athens for O<sub>3</sub>). This is in accordance with other studies (11, 40, 49, 50). For the sake of meta-analysis, additional analyses restricted to days with concentrations less than 200 μg/m<sup>3</sup> were done using linear pollutant terms. Therefore, extrapolation of the results of the present study above this level should be avoided.

For each center, the best model for 1-day measurements (1-day model) was chosen from lags 0 (same day) to 3 for NO<sub>2</sub> and 0–5 for O<sub>3</sub>; and the best model for cumulative effects (average of up to 3 days for NO<sub>2</sub> and up to 5 days for O<sub>3</sub> concentrations) was chosen on the basis of model fit as evaluated by the deviance. Modified effects were also examined by using a two-level indicator variable for warm (April to September) and cold (October to March) season. Urban air pollution invariably represents a complex mixture, which makes it difficult to determine the independent effects of single pollutants as well as their possible synergetic effects. In an attempt to address these issues, two methods were applied: 1) two-pollutant models, including all three combinations of NO<sub>2</sub>, O<sub>3</sub>, and black smoke; and 2) interactions between those three pollutants, examined by comparing the effects of one pollutant above or below the median levels of the other.

For the meta-analysis of the main effects of NO<sub>2</sub> and O<sub>3</sub> on total daily mortality, four additional cities from Northern Europe (Amsterdam (37), Basel, Geneva, and Zurich (38)) contributed data. The reported regression coefficients were based on comparable statistical analysis.

The meta-analysis presented in this paper is an attempt to give a quantitative summary of all individual results. The present meta-analysis avoids many of the problems met in usual meta-analyses of independently published results (51), such as selection bias, comparability of health outcomes and exposure variables, statistical analysis and lack of information on confounding factors. Graphical and analytic methods have been used in the meta-analysis. Graphically, the individual as well as the pooled relative risks (RRs) associated with a 50-μg/m<sup>3</sup> increase in the pollutant levels and their 95 percent confidence intervals (CIs) are plotted, ordered by decreasing magnitude of RR. In the presentation of the RRs, weights inversely proportional to their variances have been applied. Because the confidence intervals are symmetric on the logarithm-

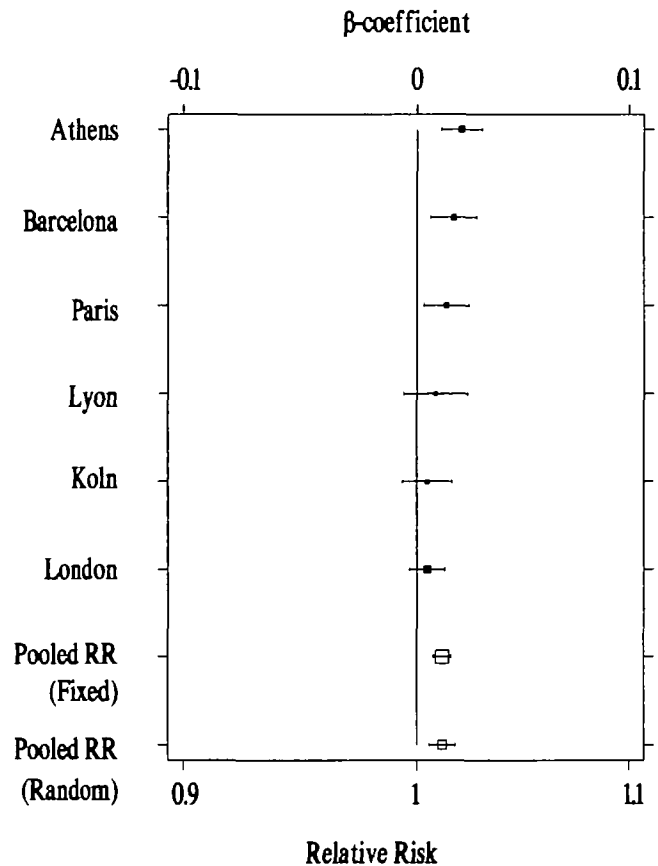
mic scale and the RR and its inverse have the same distance from 1 (the "null"), this scale was used in the graphical presentation.

The pooled regression coefficients were estimated as the weighted average of the individual ones, with the weights being the reciprocal of the local variances. The method, also called the "fixed effects model," is described in more detail elsewhere (51, 52). If significant heterogeneity among local estimates was found, random effects models were also applied. In the random effects models, we assume that the individual regression coefficients are a sample of independent observations from the normal distribution with the mean equal to the random effects pooled estimate and the variance equal to the between-cities variance. The between-cities variance is estimated from the data using the moment method of DerSimonian and Laird (51) and is added to the estimates of the local variance. This method gives more equal weights to individual estimates but also leads to larger variance for the pooled estimate. The test for heterogeneity was the regular chi-square test under the fixed effects hypothesis (51). If and where there was an indication of heterogeneity, several constant-over-time factors representing differences among cities in population health status (standardized mortality ratio, percentage of elderly, smoking prevalence), air pollution mixture, and/or climatic conditions were investigated as potential explanatory variables using weighted linear regressions.

## RESULTS

In figures 1 and 2 are shown the individual as well as the pooled (fixed and random) RRs and their 95 percent CIs associated with a  $50\text{-}\mu\text{g}/\text{m}^3$  increase in the 1-day levels of  $\text{NO}_2$  (1-hour maximum) and  $\text{O}_3$  (1-hour maximum), respectively. The  $\text{NO}_2$  results were consistent across cities ( $p$  for heterogeneity = 0.36). All the local estimates were positive (i.e.,  $\text{RR} > 1$ ), although they reached the nominal significance level (5 percent) in only three cities (Athens, Barcelona, and Paris). Significant adverse effects of  $\text{O}_3$  on total daily number of deaths were observed in all four cities for which data were available. In terms of magnitude of the effects, London, which has predominantly photochemical air pollution, was an outlier with the largest estimated effects.

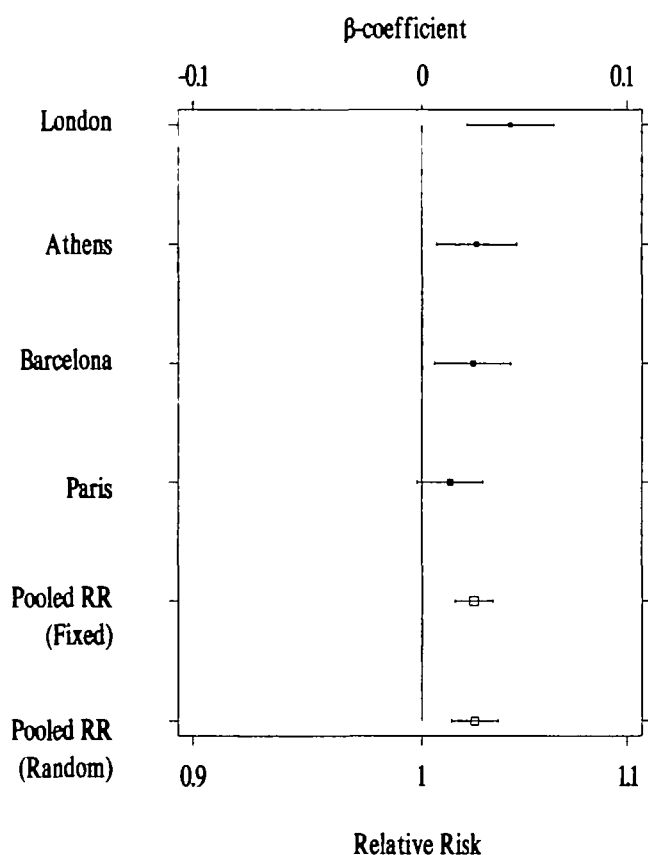
In table 2, the corresponding pooled RRs and their 95 percent CIs for  $\text{NO}_2$  and  $\text{O}_3$  are shown for 1-day and cumulative effects. The joint estimates were positive and highly significant for both pollutants. Under the fixed effects model, a  $50\text{-}\mu\text{g}/\text{m}^3$  increase in the hourly maximum 1-day pollutant levels is associated with an increase in the total daily number of deaths of



**FIGURE 1.** Estimated individual and pooled relative risks (RRs) of total daily number of deaths and their 95% confidence intervals associated with a  $50\text{-}\mu\text{g}/\text{m}^3$  increase in the levels of  $\text{NO}_2$  (1-hour maximum).

1.3 percent (95 percent CI 0.9–1.8) for  $\text{NO}_2$  and 2.3 percent (95 percent CI 1.4–3.3) for  $\text{O}_3$ . However, there was significant heterogeneity ( $p = 0.019$ ) among local estimates for  $\text{O}_3$ , due to the extreme estimate in London. The random effects joint estimate was greater ( $\text{RR} = 1.029$ ), but its 95 percent CI was also wider (95 percent CI 1.010–1.049). The cumulative effects were consistent with the 1-day estimates but somewhat greater, especially for  $\text{NO}_2$ .

Analysis by season showed that for both pollutants, the estimated RRs were slightly higher during the warm season. However, none of the differences between seasons was significant. Stratified analysis of  $\text{NO}_2$  effects by high and low levels of black smoke or  $\text{O}_3$  indicates no modification of  $\text{NO}_2$  effects by the levels of either pollutant within each city. However, the plot of the estimated individual RRs and their 95 percent CIs (for a  $50\text{-}\mu\text{g}/\text{m}^3$  increase in  $\text{NO}_2$ , 1-hour maximum) by median levels of black smoke (figure 3) revealed a tendency for larger effects of  $\text{NO}_2$  in cities with higher levels of black smoke. This tendency was even clearer when city-specific RRs were plotted



**FIGURE 2.** Estimated individual and pooled relative risks (RRs) of total daily number of deaths and their 95% confidence intervals associated with a 50- $\mu\text{g}/\text{m}^3$  increase in the levels of  $\text{O}_3$  (1-hour maximum).

against median levels of black smoke during the cold season (data not shown). It should be noted that the correlation between daily mean  $\text{PM}_{10}$  and black smoke is stronger in winter than in summer (47). No similar pattern was observed for  $\text{O}_3$  effects. In table 3 are shown the pooled estimates for  $\text{NO}_2$  and  $\text{O}_3$  obtained from two pollutant models that also included black smoke. The pooled estimates of the  $\text{NO}_2$  and  $\text{O}_3$  effects from these models remained significant for both pollutants. However, the pooled point estimate of  $\text{NO}_2$  effects was substantially less (48 percent in the pooled regression coefficient) whereas the pooled point estimate of  $\text{O}_3$  effects was affected to a much lesser extent (21 and 6 percent decreases in the fixed and random pooled regression coefficients, respectively). Including both pollutants ( $\text{NO}_2$  and  $\text{O}_3$ ) in the same model did not significantly change their estimated effect parameters (table 3).

In table 4 are shown the pooled results of the 1-day effects of  $\text{NO}_2$  (1-hour maximum) and  $\text{O}_3$  (1-hour maximum) after including estimates from four other cities not participating in the APHEA project. Estimates of the effects of  $\text{NO}_2$  were available from Basel,

Geneva, and Zurich and for the effects of  $\text{O}_3$  from Basel, Amsterdam, and Zurich. The pooled estimates were of similar magnitude to those found in the APHEA cities only.

## DISCUSSION

This study summarizes the results from 10 cities (six of which participated in the APHEA project) spanning all of Central and Western Europe concerning the short-term effects of ambient oxidants exposure on total daily number of deaths. Significant positive associations were found between daily mortality and both  $\text{NO}_2$  and  $\text{O}_3$ . Cumulative (table 2) or daily 24-hour average values (data not shown) of  $\text{NO}_2$ , indicating prolonged exposure, were substantially better predictors of total daily mortality than 1-hour maximum values. The same was observed for cumulative or 8-hour maximum values of  $\text{O}_3$ , although to a much less extent. The effects of both pollutants were found slightly greater during the warm season, although the differences of the effects during the cold season were not significant for either pollutant.

$\text{O}_3$  is known to have acute pulmonary effects at ambient levels. Lippmann (53) found that exposure to  $\text{O}_3$  levels in the range 240–400  $\mu\text{g}/\text{m}^3$  resulted in increased lung permeability and reactivity, decreased forced respiratory values, and development of an inflammatory response. Kinney et al. (17) summarized the results of six studies and found an overall effect on forced expiratory volume in 1 second of 32 ml per 100  $\mu\text{g}/\text{m}^3$  increase in levels of  $\text{O}_3$  in children without respiratory complaints. Hoek et al. (54), studying 533 schoolchildren in the Netherlands, found that an increase of 100  $\mu\text{g}/\text{m}^3$  in  $\text{O}_3$  levels is associated with a decrease of 21 ml of forced expiratory volume in 1 second. Other studies also found associations between  $\text{O}_3$  exposure and increased frequency of respiratory illness in children (23), inflammatory response of the upper airways in normal children (22), or increased frequency of hospital admissions (19, 21, 55).

Experimental exposure to high levels of  $\text{NO}_2$  (higher than the ambient air concentrations) is known to cause acute pulmonary toxic responses. However, epidemiologic studies have given inconclusive results (56). Several studies have found significant adverse effects of  $\text{NO}_2$  mainly in respiratory symptoms among children or hospital admissions (27, 32, 33, 57, 58) whereas others failed to find any (30, 59).

Only a few studies have specifically investigated the short-term effects of  $\text{O}_3$  and/or  $\text{NO}_2$  on mortality. Kinney and Ozkaynak (35) found significant associations of both pollutants with total mortality as well as with the number of deaths due to cardiovascular causes in Los Angeles County. However, no signifi-

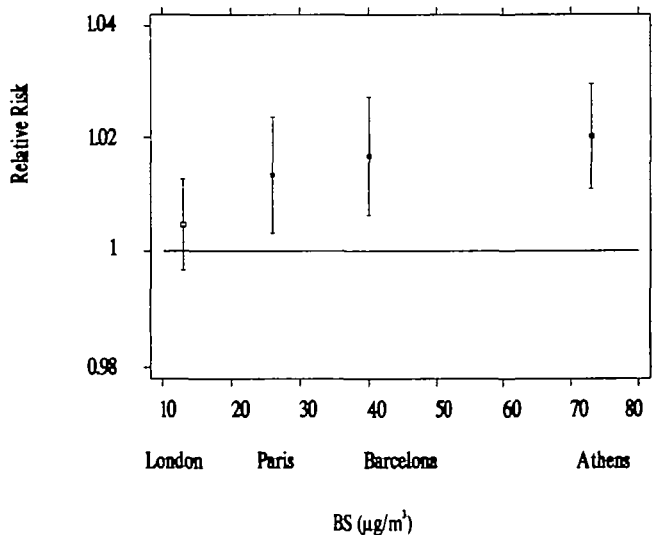
**TABLE 2. Estimated pooled relative risks (RRs) of total daily mortality and 95% confidence intervals (CIs) associated with a 50- $\mu\text{g}/\text{m}^3$  increase in the levels of pollutants, across the APHEA\* cities**

Pollutant ( $\mu\text{g}/\text{m}^3$ )	No. of cities	RR	95% CI	$p_{\text{HET}}^\dagger$	
NO <sub>2</sub> (1-hour maximum)	6	Fixed effects model	1.013	1.009–1.018	0.357
		Random effects model			
NO <sub>2</sub> (cumulative‡)	5	Fixed effects model	1.020	1.017–1.026	<10 <sup>-3</sup>
		Random effects model			
O <sub>3</sub> (1-hour maximum)	4	Fixed effects model	1.023	1.014–1.033	0.019
		Random effects model			
O <sub>3</sub> (cumulative‡)	4	Fixed effects model	1.024	1.012–1.037	0.537
		Random effects model			

\* APHEA, Air Pollution and Health: a European Approach.

†  $p$  value for  $\chi^2$  heterogeneity.

‡ Average of 2–5 successive days.



**FIGURE 3.** Estimated individual relative risks of total daily number of deaths and their 95% confidence intervals associated with a 50- $\mu\text{g}/\text{m}^3$  increase in the levels of NO<sub>2</sub> (1-hour maximum) by median levels of black smoke (BS).

cant association was observed for respiratory deaths. The authors suggested that the small number of deaths from respiratory causes may have limited the power to detect small pollution associations. Touloumi (36) also found significant positive relations between NO<sub>2</sub> and O<sub>3</sub> with total daily number of deaths in Athens. A study by Ostro et al. (39) in Santiago, Chile, suggested that O<sub>3</sub> may have an independent effect on mortality during summer since it had a stronger association with mortality than did PM<sub>10</sub>. In that study, a significant association between total mortality and NO<sub>2</sub> was also found when the pollutant was considered alone; how-

ever, the association was diminished when PM<sub>10</sub> was added into the model.

In the APHEA project, significant short-term adverse effects of O<sub>3</sub> on total daily number of deaths were found in all cities, although they differed substantially geographically, sociodemographically, and in terms of air quality (different levels and/or mixture of air pollutants). The RRs associated with a 50- $\mu\text{g}/\text{m}^3$  increase in O<sub>3</sub> (1-hour maximum) ranged from 1.3 to 8.6 percent with a pooled estimate of 2.9 percent (95 percent CI 1.0–4.9). In all APHEA cities, the correlation between daily O<sub>3</sub> and black smoke was relatively low and in most cases negative (range of the correlation across APHEA cities –0.33 to 0.13). Levels of PM<sub>10</sub> were not available in most APHEA cities. However, in Paris the correlation between O<sub>3</sub> and particulate matter with a median aerodynamic diameter  $\leq 13 \mu\text{m}$  (PM<sub>13</sub>) was as low as –0.081. Results from the two pollutant models indicated that inclusion of daily black smoke levels in the same model as O<sub>3</sub> only slightly reduced the magnitude of the estimated O<sub>3</sub> effects. In addition, studies from the United Kingdom have shown that the correlation of PM<sub>10</sub> with O<sub>3</sub> ranges from –0.11 to 0.25 in different cities (47). The effects of O<sub>3</sub> and NO<sub>2</sub> are independent of each other as indicated by the results of the two pollutant models. Thus, it is unlikely for O<sub>3</sub> to be a surrogate marker of other measured substances. The mechanism linking O<sub>3</sub> with mortality is not known. However, the full spectrum of acute reactions might lead to a life-threatening pulmonary compromise in persons with severe chronic lung disease (35). In the meta-analysis of the air pollution effects on cause-specific mortality within the APHEA project, it was found that O<sub>3</sub> was a significant predictor of mortality from cardiovascular diseases

**TABLE 3. Summary results from two pollutant models from the APHEA\* cities, including estimated pooled relative risks (RRs) of total daily mortality and 95% confidence intervals (CIs) associated with a 50- $\mu\text{g}/\text{m}^3$  increase in the levels of the pollutant**

Pollutant ( $\mu\text{g}/\text{m}^3$ )	Model including black smoke			Model including both $\text{NO}_2$ and $\text{O}_3$		
	RR	95% CI	$P_{\text{HET}}^\dagger$	RR	95% CI	$P_{\text{HET}}^\dagger$
$\text{NO}_2$ (1-hour maximum)						
Fixed effects model	1.006	1.000–1.012	0.41	1.015	1.009–1.020	0.43
Random effects model						
$\text{O}_3$ (1-hour maximum)						
Fixed effects model	1.018	1.009–1.027	<0.05	1.025	1.015–1.034	<0.05
Random effects model	1.028	1.005–1.050		1.032	0.997–1.068	

\* APHEA, Air Pollution and Health: a European Approach.

†  $p$  value for  $\chi^2$  heterogeneity.

**TABLE 4. Estimated pooled relative risks (RRs) of total daily mortality and 95% confidence intervals (CIs) associated with a 50- $\mu\text{g}/\text{m}^3$  increase in the levels of pollutants after adding estimates from four non-APHEA\* cities (Amsterdam, Basel, Geneva, and Zurich)**

Pollutant ( $\mu\text{g}/\text{m}^3$ )	No. of cities	RR	95% CI	$P_{\text{HET}}^\dagger$
$\text{NO}_2$ (1-hour maximum)	9			
Fixed effects model		1.015	1.009–1.017	0.001
Random effects model		1.018	1.010–1.019	
$\text{O}_3$ (1-hour maximum)	7			
Fixed effects model		1.023	1.014–1.033	0.057
Random effects model		1.029	1.010–1.049	

\* APHEA, Air Pollution and Health: a European Approach.

†  $p$  value for  $\chi^2$  heterogeneity.

and was marginally significant for mortality due to respiratory causes.

Concerning the short-term effects of  $\text{NO}_2$ , an overall significant increase in the total number of deaths by 1.3 percent (95 percent CI 0.9–1.8) for every 50- $\mu\text{g}/\text{m}^3$  increase in the  $\text{NO}_2$  (1-hour maximum) levels was found, and the individual RR ranged from 0.5 to 2.7 percent. However, the individual estimates were not significant in three of six APHEA cities. Stratified analysis by low and high levels of black smoke and  $\text{O}_3$  showed no significant modifications of the effects of  $\text{NO}_2$  by the levels of either pollutant within each city. However, there was a trend for greater  $\text{NO}_2$  effects in cities with higher average levels of black smoke. This pattern was even stronger when average levels of black smoke during winter were considered. The pooled estimate of  $\text{NO}_2$  effects from models including black smoke, although still significant at the nominal level, was substantially reduced. These results imply that  $\text{NO}_2$  may serve as a proxy variable of suspended particles or other vehicle-derived pollutants. Thus, the issue of independent effects of  $\text{NO}_2$  on total mortality needs additional examination.

In all the APHEA cities, an effort was made to derive citywide average levels of outdoor air pollution

to represent, as much as possible, the average population exposure. However, some degree of exposure misclassification, which is a problem in most air pollution studies, may be present. Although nondifferential misclassification is unlikely to bias the estimated effects of the air pollutants away from the null, the impact of differential exposure misclassification is difficult to assess. Differential exposure misclassification could be induced by, among other ways, a changing over time outdoor/indoor air pollution ratio and/or differential measurement error at different levels of air pollution. In the APHEA project, special attention was paid to control adequately for factors that change over time, and days with extreme pollution levels were excluded from the analyses.

In all studies included in the present overview, special attention was paid to control efficiently for several factors known to be associated with mortality. Autoregression models were used to adjust for autocorrelation (41, 42). Thus, the observed relations are unlikely to be attributed to confounding by climatic variables, seasonal trends, or autocorrelation. Although the effects of some unmeasured confounders cannot be excluded, the internal validity (consistency across cities) as well as the external validity (similarities with other

published studies) of our results on the O<sub>3</sub> effect support the hypothesis of a causal relation between O<sub>3</sub> and daily mortality. However, the short-term effects of NO<sub>2</sub> on mortality may be confounded by other vehicle-derived pollutants. Thus, the issue of independent NO<sub>2</sub> effects requires additional investigation.

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