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


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 NO2 and/or O3 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 NO2 and O3. Increases of 50 μg/m³ in NO2 (1-hour maximum) or O3 (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 NO2 effects by low and high levels of black smoke or O3 showed no significant evidence for an interaction within each city. However, there was a tendency for larger effects of NO2 in cities with higher levels of black smoke. The pooled estimate for the O3 effect was only slightly reduced, whereas the one for NO2 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 O3 effect support the hypothesis of a causal relation between O3 and all cause daily mortality. However, the short-term effects of NO2 on mortality may be confounded by other vehicle-derived pollutants. Thus, the issue of independent NO2 effects requires additional investigation. Am J Epidemiol 1997;146:177–85.

Abbreviations: APHEA, Air Pollution and Health: a European Approach; CI, confidence interval; PM10, particulate matter with a median aerodynamic diameter ≤ 10 μm; PM2.5, 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$_3$ 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$_2$ 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$_2$ and/or O$_3$ 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$_2$, 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$_3$, are out of phase (i.e., mortality usually peaks in the winter whereas O$_3$ 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 using 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$_2$ and O$_3$ 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$_2$ and O$_3$ 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$_2$ is measured by the chemiluminescence method and O$_3$, 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$_2$ and the maxi-

<table>
<thead>
<tr>
<th>City</th>
<th>NO$_2$ (nm$^3$) (1-hour maximum)</th>
<th>O$_3$ (nm$^3$) (1-hour maximum)</th>
<th>BS (nm$^3$) (24-hour)</th>
<th>Daily mean temperature (°C)</th>
<th>Daily mean humidity (%)</th>
<th>Daily no. of deaths</th>
<th>Time period</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Athens</td>
<td>134.6 (50.1)</td>
<td>93.8 (42.8)</td>
<td>84.4 (48.0)</td>
<td>17.4 (7.1)</td>
<td>62.0 (12.4)</td>
<td>35 (6)</td>
<td>1987–1991</td>
<td>2,000,000</td>
</tr>
<tr>
<td>Barcelona</td>
<td>97.8 (40.2)</td>
<td>72.4 (34.9)</td>
<td>46.6 (25.3)</td>
<td>15.5 (6.3)</td>
<td>75.5 (9.4)</td>
<td>46 (9)</td>
<td>1986–1992</td>
<td>1,700,000</td>
</tr>
<tr>
<td>Köln</td>
<td>80.7 (33.8)</td>
<td>39.6 (24.1)</td>
<td>10.7 (6.8)</td>
<td>74.1 (11.0)</td>
<td>18 (5)†</td>
<td>1977–1989</td>
<td>740,000</td>
<td></td>
</tr>
<tr>
<td>London</td>
<td>109.4 (44.0)</td>
<td>41.2 (26.0)</td>
<td>14.8 (7.0)</td>
<td>12.3 (5.2)</td>
<td>72.1 (10.2)</td>
<td>175 (27)†</td>
<td>1987–1991</td>
<td>7,200,000</td>
</tr>
<tr>
<td>Lyon</td>
<td>132.7 (93.3)</td>
<td>15.2 (15.7)</td>
<td>36.1 (23.8)</td>
<td>11.7 (7.7)</td>
<td>74.9 (12.1)</td>
<td>8 (3)†</td>
<td>1985–1990</td>
<td>410,000</td>
</tr>
<tr>
<td>Paris</td>
<td>70.1 (31.8)</td>
<td>46.1 (32.9)</td>
<td>31.6 (21.1)</td>
<td>12.2 (6.5)</td>
<td>75.5 (12.8)</td>
<td>130 (17)†</td>
<td>1987–1990</td>
<td>8,140,000</td>
</tr>
</tbody>
</table>

* APHEA, Air Pollution and Health: a European Approach; BS, black smoke (for Köln, PM$_1$; for Lyon, PM$_{10}$); SD, standard deviation.
† The numbers refer to the populations covered by the data collection.
‡ Deaths from external causes were excluded.
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...
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-μg/m³ increase in the 1-day levels of NO₂ (1-hour maximum) and O₃ (1-hour maximum), respectively. The NO₂ results were consistent across cities (p for heterogeneity = 0.36). All the local estimates were positive (i.e., RR > 1), although they reached the nominal significance level (5 percent) in only three cities (Athens, Barcelona, and Paris). Significant adverse effects of O₃ 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 NO₂ and O₃ 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-μg/m³ increase in the hourly maximum 1-day pollutant levels is associated with an increase in the total daily number of deaths of 1.3 percent (95 percent CI 0.9–1.8) for NO₂ and 2.3 percent (95 percent CI 1.4–3.3) for O₃. However, there was significant heterogeneity (p = 0.019) among local estimates for O₃, due to the extreme estimate in London. The random effects joint estimate was greater (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 NO₂.

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 NO₂ effects by high and low levels of black smoke or O₃ indicates no modification of NO₂ 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-μg/m³ increase in NO₂, 1-hour maximum) by median levels of black smoke (figure 3) revealed a tendency for larger effects of NO₂ in cities with higher levels of black smoke. This tendency was even clearer when city-specific RRs were plotted.
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London -f Athens -f Barcelona -f Paris

Pooled RR (Fixed)

Pooled RR (Random)

Relative Risk

FIGURE 2. Estimated individual and pooled relative risks (RRs) of total daily number of deaths and their 95% confidence intervals associated with a 50-μg/m3 increase in the levels of O3 (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 PM10 and black smoke is stronger in winter than in summer (47). No similar pattern was observed for O3 effects. In table 3 are shown the pooled estimates for NO2 and O3 obtained from two pollutant models that also included black smoke. The pooled estimates of the NO2 and O3 effects from these models remained significant for both pollutants. However, the pooled point estimate of NO2 effects was substantially less (48 percent in the pooled regression coefficient) whereas the pooled point estimate of O3 effects was affected to a much lesser 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.

O3 is known to have acute pulmonary effects at ambient levels. Lippmann (53) found that exposure to O3 levels in the range 240–400 μg/m3 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 μg/m3 increase in levels of O3 in children without respiratory complaints. Hoek et al. (54), studying 533 schoolchildren in the Netherlands, found that an increase of 100 μg/m3 in O3 levels is associated with a decrease of 21 ml of forced expiratory volume in 1 second. Other studies also found associations between O3 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 NO2 (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 NO2 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 O3 and/or NO2 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-µg/m³ increase in the levels of pollutants, across the APHEA* cities

<table>
<thead>
<tr>
<th>Pollutant (µg/m³)</th>
<th>No. of cities</th>
<th>RR</th>
<th>95% CI</th>
<th>Phet†</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO₂ (1-hour maximum)</td>
<td>6</td>
<td></td>
<td>1.013</td>
<td>1.009–1.018</td>
</tr>
<tr>
<td></td>
<td>Fixed effects model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Random effects model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NO₂ (cumulative‡)</td>
<td>5</td>
<td></td>
<td>1.020</td>
<td>1.017–1.026</td>
</tr>
<tr>
<td></td>
<td>Fixed effects model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Random effects model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O₃ (1-hour maximum)</td>
<td>4</td>
<td></td>
<td>1.023</td>
<td>1.014–1.033</td>
</tr>
<tr>
<td></td>
<td>Fixed effects model</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Random effects model</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>O₃ (cumulative‡)</td>
<td>4</td>
<td></td>
<td>1.024</td>
<td>1.012–1.037</td>
</tr>
<tr>
<td></td>
<td>Fixed effects model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Random effects model</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* APHEA, Air Pollution and Health: a European Approach.
† p value for \( \chi^2 \) heterogeneity.
‡ Average of 2–5 successive days.

In the APHEA project, significant short-term adverse effects of O₃ 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-µg/m³ increase in O₃ (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 O₃ 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 PM₁₀ were not available in most APHEA cities. However, in Paris the correlation between O₃ and particulate matter with a median aerodynamic diameter \( \leq 13 \) µm (PM₁₃) 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 O₃ only slightly reduced the magnitude of the estimated O₃ effects. In addition, studies from the United Kingdom have shown that the correlation of PM₁₀ with O₃ ranges from —0.11 to 0.25 in different cites (47). The effects of O₃ and NO₂ are independent of each other as indicated by the results of the two pollutant models. Thus, it is unlikely for O₃ to be a surrogate marker of other measured substances. The mechanism linking O₃ 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 O₃ was a significant predictor of mortality from cardiovascular diseases.
and was marginally significant for mortality due to respiratory causes.

Concerning the short-term effects of 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-$\mu$g/m$^3$ increase in the 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 O$_3$ showed no significant modifications of the effects of NO$_2$ by the levels of either pollutant within each city. However, there was a trend for greater 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 NO$_2$ effects from models including black smoke, although still significant at the nominal level, was substantially reduced. These results imply that NO$_2$ may serve as a proxy variable of suspended particles or other vehicle-derived pollutants. Thus, the issue of independent effects of 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 $O_3$ effect support the hypothesis of a causal relation between $O_3$ and daily mortality. However, the short-term effects of $NO_2$ on mortality may be confounded by other vehicle-derived pollutants. Thus, the issue of independent $NO_2$ effects requires additional investigation.

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REFERENCES