those considered "hormonally dependent" in breast tumors (i.e., 10 fmol/mg). ER levels in two of the four men with ER-positive tumors were >7 fmol/mg and thus approached those considered hormonally dependent.

The findings from the present study suggest that preventive strategies developed for common chronic diseases may be effective also in preventing salivary gland cancer. Specifically, increasing consumption of fruits and vegetables, particularly those high in vitamin C, and limiting foods high in cholesterol may be effective in preventing such rare tumors.

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REFERENCES

1. Ries LAG, Miller BA, Hankey BF, et al, eds. SEER cancer statistics review, 1973–1991: tables and graphs. Bethesda, MD: National Cancer Institute, 1994. (NIH publication no. 94–2789).
2. Keller AZ. Residence, age, race, and related factors in the survival and associations with salivary tumors. Am J Epidemiol 1969;90:269–7.
3. Spitz MR, Tilley BC, Batsakis JG, et al. Risk factors for major salivary gland carcinoma: a case-comparison study. Cancer 1984;54:1854–9.
4. Preston-Martin S, Thomas DC, White SC, et al. Prior exposure to medical and dental x-rays related to tumors of the parotid gland. J Natl Cancer Inst 1988;80:943–9.
5. Spitz MR, Fueger JJ, Goepfert H, et al. Salivary gland cancer: a case-control investigation of risk factors. Arch Otolaryngol Head Neck Surg 1990;116:1163–6.
6. Belsky JL, Takeichi N, Yamamoto T, et al. Salivary gland neoplasms following atomic radiation: additional cases and reanalysis of combined data in a fixed population, 1957–1970. Cancer 1975;35:555–9.
7. Maxon HR, Saenger EL, Buncher CR, et al. Radiation-associated carcinoma of the salivary glands: a controlled study. Ann Otolaryngol 1981;90:107–8.
8. Modan B, Baidatz D, Mart H, et al. Radiation-induced head and neck tumors. Lancet 1974;1:277–9.
9. Ju DMC. Salivary gland tumors occurring after radiation of the head and neck area. Am J Surg 1968;116:518–23.
10. Palmer JA, Mustard RA, Simpson WJ. Irradiation as an etiologic factor in tumors of the thyroid, parathyroid, and salivary glands. Can J Surg 1980;23:39–42.
11. Block G. Vitamin C and cancer prevention: the epidemiologic evidence. Am J Clin Nutr 1991;53:270S-82S.
12. Steinmetz KA, Potter JD. Vegetables, fruit, and cancer. I: Epidemiology. Cancer Causes Control 1991;2:325–7.
13. Steinmetz KA, Potter JD. Vegetables, fruit, and cancer. II: Mechanisms. Cancer Causes Control 1991;2:427–42.
14. Rowe NH, Grammer FC, Watson FR, et al. A study of environmental influence upon salivary gland neoplasia in rats. Cancer 1970;26:436–44.
15. Alam BS, Alam SQ, Weir JC Jr, et al. Chemopreventive effects of β-carotene and 13-cis-retinoic acid on salivary gland tumors. Nutr Cancer 1984;6:4–12.
16. Block G, Hartman AM, Naughton D. A reduced dietary questionnaire: development and validation. Epidemiology 1990;1:58–64.
17. Kelsey JL, Thompson WD, Evans AS. Methods in observational epidemiology. New York, NY: Oxford University Press, 1986.
18. Willett W. Nutritional epidemiology. New York, NY: Oxford University Press, 1990:245–71.
19. Horn-Ross PL, Ljung B-M, Morrow M. Environmental factors and the risk of salivary gland cancer. Epidemiology (In press).
20. Block G. The data support a role for antioxidants in reducing cancer risk. Nutr Rev 1992;50:207–13.
21. Rose DP. Dietary fiber, phytoestrogens, and breast cancer. Nutrition 1992;8:47–51.
22. Adlercreutz H, Mousavi Y, Clark J, et al. Dietary phytoestrogens and cancer: in vitro and in vivo studies. J Steroid Biochem Molec Biol 1992;41:331–7.
23. Dimery IW, Jones LA, Verjan RP, et al. Estrogen receptors in normal salivary gland and salivary gland carcinoma. Arch Otolaryngol Head Neck Surg 1987;113:1082–5.

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_2 and/or O_3 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_2 and O_3. Increases of 50 $\mu g/m^3$ in NO_2 (1-hour maximum) or O_3 (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_2 effects by low and high levels of black smoke or O_3 showed no significant evidence for an interaction within each city. However, there was a tendency for larger effects of NO_2 in cities with higher levels of black smoke. The pooled estimate for the O_3 effect was only slightly reduced, whereas the one for NO_2 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_3 effect support the hypothesis of a causal relation between O_3 and all cause 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. *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_2 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_3 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_{10}, particulate matter with a median aerodynamic diameter ≤ 10 μm; PM_{13}, 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 maximum 8-hour values for O_3 were also considered. Urban monitoring sites were used for NO_2; and for O_3, 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_2 and from 0.40 to 0.97 for O_3. 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 $\leq$ 10 μm (PM_{10}) 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_2 and O_3 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_3). 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 $\mu g/m^3$ 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_2 and 0–5 for O_3; and the best model for cumulative effects (average of up to 3 days for NO_2 and up to 5 days for O_3 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_2, O_3, 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_2 and O_3 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-$\mu g/m^3$ 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 logarith-

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

City	NO_2 ($\mu m/m^3$) (1-hour maximum)	O_3 ($\mu m/m^3$) (1-hour maximum)	BS* ($\mu m/m^3$) (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_7; for Lyon, PM_{13}); SD, standard deviation.
† The numbers refer to the populations covered by the data collection.
‡ Deaths from external causes were excluded.

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-$\mu g/m^3$ increase in the 1-day levels of NO_2 (1-hour maximum) and O_3 (1-hour maximum), respectively. The NO_2 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 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 NO_2 and 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-$\mu g/m^3$ increase in the hourly maximum 1-day pollutant levels is associated with an increase in the total daily number of deaths of

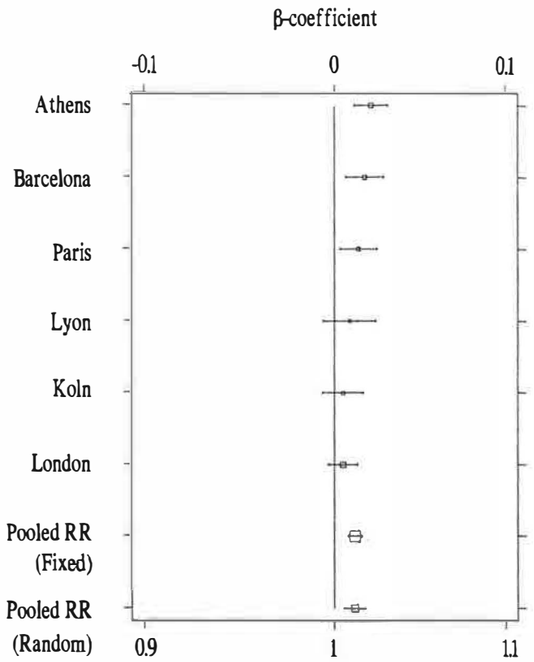

FIGURE 1. Estimated individual and pooled relative risks (RRs) of total daily number of deaths and their 95% confidence intervals associated with a 50-$\mu g/m^3$ increase in the levels of NO_2 (1-hour maximum).

1.3 percent (95 percent CI 0.9–1.8) for NO_2 and 2.3 percent (95 percent CI 1.4–3.3) for O_3. However, there was significant heterogeneity (p = 0.019) among local estimates for O_3, 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 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 NO_2 effects by high and low levels of black smoke or O_3 indicates no modification of 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-$\mu g/m^3$ increase in NO_2, 1-hour maximum) by median levels of black smoke (figure 3) revealed a tendency for larger effects of NO_2 in cities with higher levels of black smoke. This tendency was even clearer when city-specific RRs were plotted

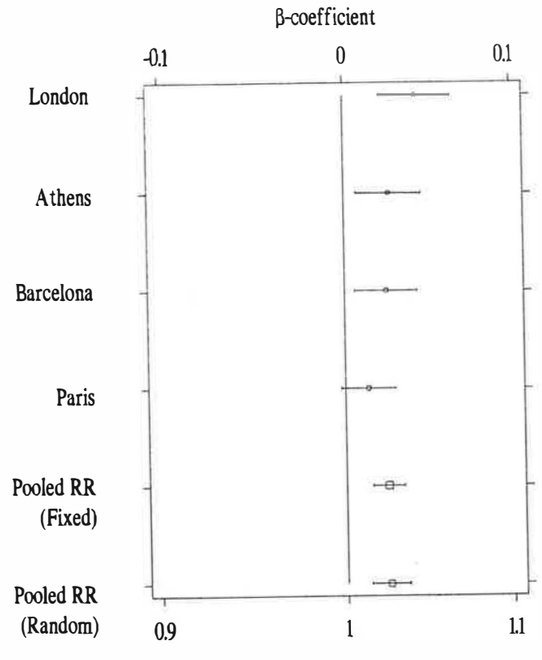

FIGURE 2. Estimated individual and pooled relative risks (RRs) of total daily number of deaths and their 95% confidence intervals associated with a 50-$\mu g/m^3$ increase in the levels of O_3 (1-hour maximum).

against median levels of black smoke during the cold season (data not shown). It should be noted that the correlation between daily mean PM_{10} and black smoke is stronger in winter than in summer (47). No similar pattern was observed for O_3 effects. In table 3 are shown the pooled estimates for NO_2 and O_3 obtained from two pollutant models that also included black smoke. The pooled estimates of the NO_2 and O_3 effects from these models remained significant for both pollutants. However, the pooled point estimate of NO_2 effects was substantially less (48 percent in the pooled regression coefficient) whereas the pooled point estimate of 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 (NO_2 and 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 NO_2 (1-hour maximum) and O_3 (1-hour maximum) after including estimates from four other cities not participating in the APHEA project. Estimates of the effects of NO_2 were available from Basel, Geneva, and Zurich and for the effects of 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 NO_2 and O_3. Cumulative (table 2) or daily 24-hour average values (data not shown) of 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 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.

O_3 is known to have acute pulmonary effects at ambient levels. Lippmann (53) found that exposure to O_3 levels in the range 240–400 $\mu g/m^3$ 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 $\mu g/m^3$ increase in levels of O_3 in children without respiratory complaints. Hoek et al. (54), studying 533 schoolchildren in the Netherlands, found that an increase of 100 $\mu g/m^3$ in O_3 levels is associated with a decrease of 21 ml of forced expiratory volume in 1 second. Other studies also found associations between 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 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 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 O_3 and/or 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-μg/m³ increase in the levels of pollutants, across the APHEA* cities

Pollutant (μg/m³)	No. of cities	RR	95% CI	p_{HET}†
NO_2 (1-hour maximum)	6			
Fixed effects model		1.013	1.009–1.018	0.357
Random effects model				
NO_2 (cumulative‡)	5			
Fixed effects model		1.020	1.017–1.026	<10^{-3}
Random effects model		1.021	1.007–1.034	
O_3 (1-hour maximum)	4			
Fixed effects model		1.023	1.014–1.033	0.019
Random effects model		1.029	1.010–1.049	
O_3 (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 χ^2 heterogeneity.
‡ Average of 2–5 successive days.

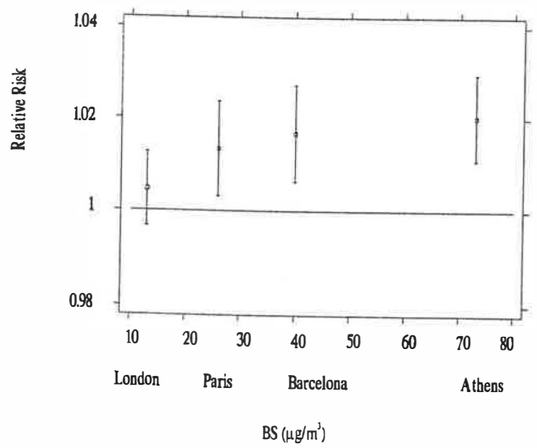

FIGURE 3. Estimated individual relative risks of total daily number of deaths and their 95% confidence intervals associated with a 50-μg/m³ increase in the levels of NO_2 (1-hour maximum) by median levels of black smoke (BS).

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_2 and O_3 with total daily number of deaths in Athens. A study by Ostro et al. (39) in Santiago, Chile, suggested that O_3 may have an independent effect on mortality during summer since it had a stronger association with mortality than did PM_{10}. In that study, a significant association between total mortality and NO_2 was also found when the pollutant was considered alone; however, the association was diminished when PM_{10} was added into the model.

In the APHEA project, significant short-term adverse effects of O_3 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 O_3 (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_3 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_{10} were not available in most APHEA cities. However, in Paris the correlation between O_3 and particulate matter with a median aerodynamic diameter ≤ 13 μm (PM_{13}) 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_3 only slightly reduced the magnitude of the estimated O_3 effects. In addition, studies from the United Kingdom have shown that the correlation of PM_{10} with O_3 ranges from −0.11 to 0.25 in different cites (47). The effects of O_3 and NO_2 are independent of each other as indicated by the results of the two pollutant models. Thus, it is unlikely for O_3 to be a surrogate marker of other measured substances. The mechanism linking O_3 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_3 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-μg/m³ increase in the levels of the pollutant

Pollutant (μg/m³)	Model including black smoke			Model including both NO_2 and O_3		
	RR	95% CI	p_{HET}†	RR	95% CI	p_{HET}†
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						
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 χ^2 heterogeneity.

TABLE 4. 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 after adding estimates from four non-APHEA* cities (Amsterdam, Basel, Geneva, and Zurich)

Pollutant (μg/m³)	No. of cities	RR	95% CI	p_{HET}†
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	
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 χ^2 heterogeneity.

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-μg/m³ 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

1. Ware JH, Tribodeau LA, Speizer FE, et al. Assessment of the health effects of atmospheric sulphur oxides and particulate matter: evidence from observational studies. Environ Health Perspect 1981;41:255–76.
2. Sunyer J, Antó JM, Murillo C, et al. Effects of urban air pollution on emergency room admissions for chronic obstructive pulmonary disease. Am J Epidemiol 1991;134:277–86.
3. Schwartz J, Dockery DW. Particulate air pollution and daily mortality in Steubenville, Ohio. Am J Epidemiol 1992;135: 12–19.
4. Derriennic F, Richardson S, Mollie A, et al. Short term effects of sulphur dioxide pollution on mortality in two French cities. Int J Epidemiol 1989;18:186–97.
5. Pope CA, Schwartz J, Ransom MR. Daily mortality and PM_{10} pollution in Utah Valley. Arch Env Health 1992;47:211–17.
6. Schwartz J, Dockery DW. Increased mortality in Philadelphia associated with daily air pollution concentrations. Am Rev Respir Dis 1992;145:600–4.
7. Dockery DW, Schwartz J, Spengler JD. Air pollution and daily mortality: association with particulates and acid aerosols. Env Res 1992;59:362–73.
8. Schwartz J. Air pollution and daily mortality in Birmingham, Alabama. Am J Epidemiol 1993;137:1136–47.
9. Wichmann HE, Mueller W, Allhoff P, et al. Health effects during a smog episode in West Germany in 1985. Environ Health Perspect 1989;79:89–99.
10. Ponka A. Asthma and low level air pollution in Helsinki. Arch Environ Health 1991;46:262–70.
11. Touloumi G, Pocock SJ, Katsouyanni K, et al. Short-term effects of air pollution on daily mortality in Athens: a time-series analysis. Int J Epidemiol 1994;23:957–67.
12. Adams WC, Savin WM, Christo AE. Detection of ozone toxicity during continuous exercise via the effective dose concept. J Appl Physiol 1981;51:415–22.
13. Folinsbee LJ, McDonnel WF, Horstmann DH. Pulmonary function and symptom response after 6.6-hour exposure to 0.12 ppm ozone with moderate exercise. J Air Pollut Control Assoc 1988;38:28–35.
14. Horstman DH, Folinsbee LJ, Iver PJ, et al. Ozone concentration and pulmonary response relationships for 6.6-hour exposures with five hours of moderate exercise to 0.08, 0.10 and 0.12 ppm. Am Rev Respir Dis 1990;142;1158–63.
15. Hazucha MJ, Folinsbee JJ, Seal E Jr. Effects of steady-state and variable ozone concentration profiles in pulmonary function. Am Rev Respir Dis 1992;146:1487–93.
16. McDonnell WF, Muller KE, Brombery PA, et al. Predictors of individual differences in acute response to ozone exposure. Am Rev Respir Dis 1993;147:818–25.
17. Kinney PL, Thurston GD, Raizenne M. A meta-analysis of repeated FEV_1 data from six summer camp studies: mean effect of ozone on response heterogeneity. (Abstract). Am Rev Respir Dis 1993;147:A636.
18. Kinney PL, Ware JH, Spengler JD. A critical evaluation of acute ozone epidemiology results. Arch Environ Health 1988; 43:168–73.
19. Thurston GD, Ito K, Kinney PL, et al. A multiyear study of air pollution and respiratory hospital admissions in three New York State metropolitan areas results for 1988 and 1989 summers. J Expos Anal Environ Epidemiol 1992;2:429–50.
20. US Environmental Protection Agency. Air quality criteria for ozone and related photochemical oxidants. Washington, DC: Office of Research and Development, 1993. (Environmental Protection Agency publication no. EPA/600/AP-93/004a-c).
21. Burnett RT, Dales RE, Raizenne ME, et al. Effects of low ambient levels of ozone and sulphates on the frequency of respiratory admissions to Ontario hospitals. Environ Res 1994;65:172–94.
22. Frischer TM, Kuehr J, Pullwitt A, et al. Ambient ozone causes upper airways inflammation in children. Am Rev Respir Dis 1993;148:961–4.
23. Romieu I, Cortes Lugo M, Ruiz Velasco S, et al. Air pollution and school absenteeism among children in Mexico City. Am J Epidemiol 1992;136:1524–31.
24. Melia RJW, Florey C du V, Morris RW, et al. Childhood respiratory illness and the home environment. II. Association between respiratory illness and nitrogen dioxide, temperature and relative humidity. Int J Epidemiol 1982;11:164–9.
25. Hoek G, Brunekreef B, Meijer R, et al. Indoor nitrogen dioxide pollution and respiratory symptoms of schoolchildren. Int Arch Occup Environ Health 1984;55:79–86.
26. Neas LM, Dockery DW, Ware JH, et al. Association of indoor nitrogen dioxide with respiratory symptoms and pulmonary function in children. Am J Epidemiol 1991;134:204–19.
27. Braun-Fahrlander C, Ackermann-Liebrich U, Schwartz J, et al. Air pollution and respiratory symptoms in preschool children. Am Rev Respir Dis 1992;145:42–7.
28. Samet JM, Lambert WE, Skipper BJ, et al. Nitrogen dioxide and respiratory illness in infants. Am Rev Respir Dis 1993; 148;1258–65.
29. Pershagen G, Rylander E, Norberg S, et al. Air pollution involving NO_2 exposure and wheezing bronchitis in children. Int J Epidemiol 1995;24:1147–53.
30. Hackney JD, Linn WS, Avol EL, et al. Exposure of older adults with chronic respiratory illness to nitrogen dioxide. Am Rev Respir Dis 1992;146:1480–6.
31. Pantazopoulou A, Katsouyanni K, Kourea-Kremastinou J, et al. Short-term effects of air pollution on hospital emergency out patient visits and admissions in the Greater Athens, Greece area. Environ Res 1995;69:139–44.
32. Schwartz J, Zeger S. Passive smoking, air pollution and acute respiratory symptoms in a diary study of student nurses. Am Rev Respir Dis 1990;141:62–7.
33. Ponka A, Virtanen M. Chronic bronchitis, emphysema, and low-level air pollution in Helsinki, 1987–1989. Environ Res 1994;65:207–17.

34. Forsberg B, Stjernberg N, Falk M, et al. Air pollution levels, meteorological conditions and asthma symptoms. Eur Respir J 1993;6:1109–15.
35. Kinney PL, Ozkaynak H. Associations of daily mortality and air pollution in Los Angles County. Environ Res 1991;54: 99–120.
36. Touloumi G. Health effects of air pollution and meteorologic variables: methodological considerations with reference to the Athens case. Unpublished doctoral thesis. University of Athens Medical School, Athens, Greece, 1994.
37. Wietlisbach V, Pope CA, Ackermann-Liebrich U. Air pollution and daily mortality in three Swiss urban areas. Soc Prev Med 1996;41:107–15.
38. Verhoeff AP, Hoek G, Schwartz J, et al. Air pollution and daily mortality in Amsterdam, the Netherlands. Epidemiology 1996;7:225–30.
39. Ostro B, Sanchez JM, Aranda C, et al. Air pollution and mortality: results from a study of Santiago, Chile. J Expos Anal Environ Epidemiol 1996;6:97–114.
40. Schwartz J, Marcus A. Mortality and air pollution in London: a time series analysis. Am J Epidemiol 1990;131:185–94.
41. Schwartz J, Spix C, Wichmann HE, et al. Air pollution and acute respiratory illness in five German communities. Environ Res 1991;56:1–14.
42. Schwartz J. Air pollution and daily mortality: a review and meta-analysis. Environ Res 1994;64:36–52.
43. Katsouyanni K, Zmirou D, Spix C, et al. Short-term effects of air pollution on health: a European approach using epidemiologic time series data. The APHEA project: background, objectives, design. Eur Res J 1995;8:1030–8.
44. European Commission. Council directive 85/203/EEC of March 1985 on air quality standards for nitrogen dioxide. In: European Community Environment Legislation, Vol. 2: Air. Luxemburg: Office for Official Publications of the European Community, 1992.
45. European Commission. Council directive 92/72/EEC on air quality pollution by ozone. Luxemburg: Office for Official Publications of the European Community, 1992.
46. Katsouyanni K, Schwartz J, Spix C, et al. Short-term effects of air pollution on health: a European approach using epidemiological time series data. The APHEA protocol. J Epidemiol Commun Health 1996;50(suppl):S12-S18.
47. Quality of Urban Air Review Group. Airborne particulate matter in the United Kingdom. London: Department of the Environment, 1996.
48. Schwartz J, Spix C, Touloumi G, et al. Methodological issues in studies of air pollution and daily counts of deaths and hospital admissions. J Epidemiol Commun Health 1996; 50(suppl):S3-S11.
49. Lippmann M, Ito K. Separating the effects of temperature and season on daily mortality from those of air pollution in London 1965–1972. Inhal Toxicol 1995;7:85–97.
50. Ostro B. A search for a threshold in the relationship of air pollution to mortality: a reanalysis of data on London winters. Environ Health Perspect 1984;58:397–9.
51. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88.
52. Whitehead A, Whitehead J. A general parametric approach to the meta-analysis of randomized clinical trials. Stat Med 1991; 10:1665–77.
53. Lippmann M. Health effects of ozone: a critical review. J Air Pollut Control Assoc 1989;39:672–95.
54. Hoek G, Fischer P, Brunekreef B, et al. Acute effects of ambient ozone on pulmonary function of children in the Netherlands. Am Rev Respir Dis 1993;147:111–17.
55. Cody RP, Weisel CP, Birnbaum G, et al. The effect of ozone associated with summertime photochemical smog on the frequency of asthma visits to hospital emergency departments. Environ Res 1992;58;184–94.
56. Berglund M, Bostrom CE, Bylin G, et al. Health risk evaluation of nitrogen oxides. Scand J Work Environ Health 1993; 19(suppl 2):7–72.
57. Ponka A. Absenteeism and respiratory disease among children and adults in Helsinki in relation to low-level air pollution and temperature. Environ Res 1990;52:34–46.
58. Koo LC, Ho JH-C, Yo E-Y, et al. Personal exposure to nitrogen dioxide and its association with respiratory illness in Hong Kong. Am Rev Respir Dis 1990;141:1119–26.
59. Schwartz J. Lung function and chronic exposure to air pollution: a cross-sectional analysis of NHANES. Environ Res 1989;50:309–21.