

## A Combined Analysis of the Short-Term Effects of Photochemical Air Pollutants on Mortality within the EMECAM Project

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In recent years, some epidemiologic studies have attributed adverse effects of air pollutants on health not only to particles and sulfur dioxide but also to photochemical air pollutants (nitrogen dioxide and ozone). The effects are usually small, leading to some inconsistencies in the results of the studies. Furthermore, the different methodologic approaches of the studies used has made it difficult to derive generic conclusions. We provide here a quantitative summary of the short-term effects of photochemical air pollutants on mortality in seven Spanish cities involved in the EMECAM project, using generalized additive models from analyses of single and multiple pollutants. Nitrogen dioxide and ozone data were provided by seven EMECAM cities (Barcelona, Gijón, Huelva, Madrid, Oviedo, Seville, and Valencia). Mortality indicators included daily total mortality from all causes excluding external causes, daily cardiovascular mortality, and daily respiratory mortality. Individual estimates, obtained from city-specific generalized additive Poisson autoregressive models, were combined by means of fixed effects models and, if significant heterogeneity among local estimates was found, also by random effects models. Significant positive associations were found between daily mortality (all causes and cardiovascular) and NO<sub>2</sub>, once the rest of air pollutants were taken into account. A 10 µg/m<sup>3</sup> increase in the 24-hr average 1-day NO<sub>2</sub> level was associated with an increase in the daily number of deaths of 0.43% [95% confidence interval (CI), -0.003–0.86%] for all causes excluding external. In the case of significant relationships, relative risks for cause-specific mortality were nearly twice as much as that for total mortality for all the photochemical pollutants. Ozone was independently related only to cardiovascular daily mortality. No independent statistically significant relationship between photochemical air pollutants and respiratory mortality was found. The results in this study suggest that, given the present levels of photochemical pollutants, people living in Spanish cities are exposed to health risks derived from air pollution. *Key words:* combined analysis, EMECAM project, GAM autoregressive models, mortality, photochemical air pollutants. *Environ Health Perspect* 110:221–228 (2002). [Online 5 February 2002]

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In recent years, many epidemiologic studies have shown that increases in air pollution levels may adversely affect human health, even at levels close to or lower than current national and international standards [see Schwartz (1), Bascom et al. (2), and, more recently, Tenías et al. (3) for comprehensive surveys].

The health effect indicator for which most of the scientific evidence has been accumulated is mortality, both total (all causes) and cause-specific mortality, mainly deaths associated with cardiovascular and respiratory conditions (1,3–5). Mortality has the advantage of being the most reliable indicator and, moreover, tends to provide the most consistent results, at least with respect to the effects of airborne particles and sulfur dioxide (6). Road transport, however, is now more of a factor in emission sources, and thus the air pollution profile has gradually increased its photochemical component (nitrogen dioxide and ozone).

Although O<sub>3</sub> is generally regarded as one of the most toxic components of the photochemical air pollution mixture (6,7), not many studies have been conducted on the effects of photochemical air pollutants on mortality (5,8–10). Several chamber studies (11,12) as well as epidemiologic studies (13,14) have suggested some significant effects of exposure to O<sub>3</sub> on morbidity, specifically on lung function decrements, exacerbation of asthma, respiratory symptoms, and increased number of hospital admissions. O<sub>3</sub> has also been associated with daily deaths (7). NO<sub>2</sub> has been found to increase morbidity, at least for respiratory diseases (13,15–21).

In all of these studies, the adverse effects on health (specifically mortality), although important, are usually small. Presumably as a consequence of such moderate size, the results of these studies may present some inconsistencies. Some of the inconsistencies

found in these studies could be due to a different distribution of confounders and effect modifiers between the population analyzed (6). Furthermore, the different methodologic approaches involved and the varying techniques that the studies used make it difficult to draw clear conclusions from them. For all of these reasons, and in order to assess the short-term relationship between air pollution and health, several multicenter collaborative studies were launched over the last few years, such as the APHEA project (22), beginning in 1993, and, more recently, the NMMAPS (23), the most well known.

Using the APHEA approach, a collaborative study for Spain was launched in 1997. The EMECAM project (24), an acronym for

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“Spanish Multicentric Study of the Effects of Air Pollution on Mortality” (in Spanish), is a coordinated study, whose aim is to assess the short-term effects of air pollution on mortality, using data from 14 Spanish cities, Barcelona, Metropolitan Area of Bilbao, Cartagena, Castellón, Gijón, Huelva, Madrid, Oviedo, Pamplona, Seville, Valencia, Vigo, Vitoria, and Zaragoza, corresponding to the period 1990–1996 (Figure 1), involving nearly 9 million inhabitants and representing different sociodemographic, climatic, and environmental situations (24).

In this paper, we provide a quantitative summary of the short-term effects of the photochemical air pollutants NO<sub>2</sub> and O<sub>3</sub> on total mortality as well as cardiovascular and respiratory mortality in several Spanish cities



**Figure 1.** EMECAM cities.

\*Provided photochemical air pollutants data.

involved in the EMECAM project (24) using generalized additive models from single and multipollutant analyses.

## Materials and Methods

Data on NO<sub>2</sub> and O<sub>3</sub> were not available for all sites. Only 7 of the 14 EMECAM cities (Barcelona, Gijón, Huelva, Madrid, Oviedo, Seville, and Valencia; Figure 1) contributed data. In addition, data on carbon monoxide were not available for Gijón or Seville (24). Table 1 presents descriptive data for the seven cities. Mortality data were extracted from death records for the total population living within the boundaries of the cities. Only deaths occurring among residents were considered. Mortality indicators included daily total mortality from all causes excluding external causes [*International Classification of Diseases, 9th Revision (ICD-9)*, 001–799], daily cardiovascular mortality (ICD-9, 390–459) and daily respiratory mortality (ICD-9, 460–519).

Daily air pollutants measurements were provided by the monitoring network established in each city. For NO<sub>2</sub> 1-hr maximum and 24-hr average values (measured by chemiluminescence) and for O<sub>3</sub> an 8-hr maximum value (measured by ultraviolet absorption) were the measurements considered. A standardizing data collection procedure was adopted. In the case of air pollutants, in particular, some criteria were followed (22,24):

admissibility (only urban air pollution stations, excluding those located in limited access highways, were considered); completeness (stations were included if they had data for at least 75% of the days and for 75% of the hourly values); number of air pollution monitoring stations (cities were included if they measured a particular air pollutant from at least three stations); and missing data imputation (the remaining missing data in one station were substituted by the mean daily level predicted from a regression of the measurements of the station on the values of the rest of the stations). Additional details on data and their sources can be found elsewhere (24).

The statistical analysis implemented by all study investigators followed a jointly standardized methodology using a common definition of variables, questions, and hypotheses for the individual studies (24–26). In the EMECAM project the pollution–mortality associations for each center (i.e., city) were investigated using generalized linear Poisson autoregression models (GLM) (27) where overdispersion was allowed for and adjusted for the potential confounding effects of observed confounders (weather factors such as temperature and humidity) as well as unobserved ones. Unobserved confounders were represented by sinusoidal terms (capturing long-term trends and seasonality from 6-week to annual cycles), dummy variables

**Table 1.** Descriptive characteristics of the EMECAM cities that contributed to the analysis of the relationship between mortality and photochemical air pollutants.

City	Daily mean temperature (°C), mean ± SD	Daily mean humidity (%), mean ± SD	Mortality counts, <sup>a</sup> mean ± SD			NO <sub>2</sub> (µg/m <sup>3</sup> ), 24-hr average, mean ± SD	O <sub>3</sub> (µg/m <sup>3</sup> ), 8-hr max value, mean ± SD	Population <sup>b</sup>	Period of analysis
			Total	Respiratory	Cardiovascular				
Barcelona									
All <sup>c</sup>	16.5 ± 5.8	71.5 ± 5.3	43.6 ± 8.6	3.8 ± 2.2	17.4 ± 5.1	53.6 ± 17.6	67.5 ± 32.2	1,643,545	1991–1995
Warm	21.0 ± 4.2	71.3 ± 5.7							
Cold	11.7 ± 2.7	71.8 ± 4.9							
Gijón									
All	13.8 ± 4.2	79.4 ± 9.3	6.3 ± 2.7	0.7 ± 0.9	2.2 ± 1.6	45.1 ± 17.9	—	261,724	1993–1996
Warm	17.4 ± 2.7	80.3 ± 8.1							
Cold	10.6 ± 2.6	78.6 ± 10.3							
Huelva									
All	18.3 ± 5.5	64.5 ± 20.6	2.5 ± 1.6	0.3 ± 0.5	1.0 ± 1.0	32.9 ± 10.9	—	142,547	1993–1996
Warm	22.7 ± 3.5	54.0 ± 22.0							
Cold	13.9 ± 3.2	75.2 ± 12.0							
Madrid									
All	14.4 ± 7.7	61.8 ± 16.7	60.8 ± 11.1	6.1 ± 3.1	22.0 ± 6.1	71.0 ± 20.0	42.1 ± 27.8	2,940,896	1992–1995
Warm	20.3 ± 5.4	53.8 ± 14.2							
Cold	8.4 ± 4.1	69.9 ± 15.0							
Oviedo									
All	13.2 ± 4.5	78.0 ± 11.2	4.5 ± 2.2	0.5 ± 0.7	1.5 ± 1.3	50.4 ± 13.1	—	198,050	1993–1996
Warm	16.4 ± 3.1	79.6 ± 9.7							
Cold	10.0 ± 3.2	76.3 ± 12.4							
Seville									
All	18.4 ± 6.1	64.4 ± 14.5	13.5 ± 4.2	1.2 ± 1.2	5.5 ± 2.6	58.9 ± 16.6	—	683,028	1992–1996
Warm	23.4 ± 4.3	57.9 ± 12.8							
Cold	14.1 ± 3.4	70.3 ± 13.3							
Valencia									
All	18.2 ± 5.5	64.8 ± 13.6	16.4 ± 4.8	1.5 ± 1.3	6.6 ± 2.9	66.8 ± 26.7	45.5 ± 19.7	749,796	1994–1996
Warm	22.9 ± 3.4	65.3 ± 12.8							
Cold	14.3 ± 3.0	61.0 ± 14.4							

<sup>a</sup>Total, all causes excluding external (ICD-9 < 800), respiratory (ICD-9 460–519), cardiovascular (ICD-9 390–459). <sup>b</sup>Population covered by the data collection. <sup>c</sup>All: all periods; warm: May–October; cold: November–April.

(representing day-of-week patterns, such as seasonality of shorter period, i.e., under 6 weeks), and the effect of influenza epidemics. In the EMECAM study, each center

determined the best-fitting 1-day effect for each pollutant (lags tested were from 0 to 3 days). In that project, modified effects were also examined by using a two-level indicator

variable for warm season (May–October) and cold season (November–April). Regression parameters for each season were thus derived, allowing an assessment of seasonal variation

**Table 2.** Relative risks of mortality and 95% confidence intervals associated with a 10  $\mu\text{g}/\text{m}^3$  increase in the level of pollutants across the EMECAM cities: all causes excluding external (ICD-9, 001–799).

	NO <sub>2</sub> or O <sub>3</sub>	NO <sub>2</sub> –O <sub>3</sub>	NO <sub>2</sub> –O <sub>3</sub> particles	NO <sub>2</sub> –O <sub>3</sub> SO <sub>2</sub>	NO <sub>2</sub> –O <sub>3</sub> CO	NO <sub>2</sub> –O <sub>3</sub> all pollutants
NO <sub>2</sub> 24-hr average	NO <sub>2</sub>					
Barcelona	1.00596 (1.00082–1.01114)	1.00617 (1.00092–1.01145)	1.00296 (0.99692–1.00903)	1.00620 (1.00057–1.01186)	1.00347 (0.99764–1.00933)	1.00166 (0.99516–1.00820)
Gijón	1.00532 (0.99153–1.01931)	—	1.00651 (0.99226–1.02097)	1.00497 (0.99086–1.01928)	—	1.00622 (0.99188–1.02076)
Huelva	1.03518 (0.99438–1.07766)	—	1.03049 (0.98793–1.07488)	1.01755 (0.97207–1.06516)	1.03709 (0.99407–1.08198)	1.01813 (0.96968–1.06900)
Madrid	1.00536 (1.00102–1.00971)	1.00529 (1.00095–1.00965)	1.00580 (0.99847–1.01317)	1.00543 (0.99880–1.01210)	1.00190 (0.99316–1.01072)	1.00253 (0.99339–1.01176)
Oviedo	1.02140 (0.99665–1.04677)	—	1.02881 (0.99965–1.05882)	1.03186 (1.00401–1.06050)	1.02261 (0.99234–1.05380)	1.03268 (1.00085–1.06553)
Seville	1.01112 (1.00043–1.02191)	—	1.01449 (1.00245–1.02667)	1.00954 (0.99871–1.02049)	—	1.01279 (1.00069–1.02504)
Valencia	1.00921 (0.99955–1.01897)	1.00709 (0.99742–1.01684)	1.00115 (0.99098–1.01143)	1.00758 (0.99780–1.01746)	1.00320 (0.99264–1.01388)	1.00210 (0.99124–1.01307)
All cities	1.00670 <sup>a</sup> (1.00415–1.00926)	1.00580 (1.00496–1.00664)	1.00555 <sup>a</sup> (1.00136–1.00976)	1.00693 <sup>a</sup> (1.00409–1.00977)	1.00378 <sup>a</sup> (0.99946–1.00812)	1.00430 <sup>a</sup> (1.00003–1.00859)
Q ( <i>p</i> -value) <sup>b</sup>	4.584 (0.001)	0.139 (0.449)	7.272 (<0.001)	3.842 (0.003)	3.949 (0.003)	6.224 (<0.001)
O <sub>3</sub> 8-hr maximum	O <sub>3</sub>					
Barcelona	1.00129 (0.99826–1.00433)	1.00016 (0.99695–1.00338)	1.00158 (0.99810–1.00507)	1.00058 (0.99720–1.00398)	1.00133 (0.99761–1.00505)	1.00130 (0.99738–1.00523)
Madrid	1.00292 (0.99941–1.00644)	1.00279 (0.99928–1.00631)	1.00250 (0.99896–1.00605)	1.00241 (0.99877–1.00606)	1.00292 (0.99927–1.00657)	1.00306 (0.99937–1.00677)
Valencia	1.02253 (1.00471–1.0467)	1.02024 (1.00243–1.03838)	1.01477 (0.99482–1.03512)	1.02065 (1.00279–1.03882)	1.01352 (0.99386–1.03357)	1.01407 (0.99337–1.03521)
All cities	1.00233 <sup>a</sup> (0.99855–1.00611)	1.00169 <sup>a</sup> (0.99783–1.00557)	1.00222 <sup>a</sup> (0.99998–1.00447)	1.00180 <sup>a</sup> (0.99796–1.00565)	1.00233 <sup>a</sup> (0.99979–1.00487)	1.00243 <sup>a</sup> (0.99979–1.00507)
Q ( <i>p</i> -value) <sup>b</sup>	5.509 (0.006)	5.418 (0.006)	1.662 (0.098)	4.886 (0.006)	1.613 (0.103)	1.634 (0.100)

<sup>a</sup>Random effects model; fixed effects model otherwise. <sup>b</sup>Chi-square of heterogeneity (*p*-value).

**Table 3.** Relative risks of mortality and 95% confidence intervals associated with a 10  $\mu\text{g}/\text{m}^3$  increase in the level of pollutants across the EMECAM cities: cardiovascular mortality (ICD-9, 390–459).

	NO <sub>2</sub> or O <sub>3</sub>	NO <sub>2</sub> –O <sub>3</sub>	NO <sub>2</sub> –O <sub>3</sub> particles	NO <sub>2</sub> –O <sub>3</sub> SO <sub>2</sub>	NO <sub>2</sub> –O <sub>3</sub> CO	NO <sub>2</sub> –O <sub>3</sub> all pollutants
NO <sub>2</sub> 24-hr average	NO <sub>2</sub>					
Barcelona	1.01026 (1.00105–1.01955)	1.00985 (1.00058–1.01920)	1.01432 (1.00383–1.02492)	1.01072 (1.00121–1.02032)	1.00442 (0.99405–1.01490)	1.00858 (0.99771–1.01957)
Gijón	1.01763 (0.99449–1.0431)	—	1.01772 (0.99378–1.04224)	1.01782 (0.99432–1.04188)	—	1.01743 (0.99342–1.04202)
Huelva	1.02036 (0.95457–1.09069)	—	1.03438 (0.96437–1.10947)	1.01283 (0.93819–1.09342)	1.00873 (0.93967–1.08287)	1.00975 (0.92926–1.09721)
Madrid	1.00911 (1.0196–1.01630)	1.00973 (1.00259–1.01693)	1.00791 (0.99557–1.02040)	1.00766 (0.99638–1.01908)	1.00072 (0.98579–1.01588)	1.00150 (0.98580–1.01745)
Oviedo	1.03366 (0.99010–1.07914)	—	1.04031 (0.98935–1.09390)	1.05174 (1.00307–1.10278)	1.03929 (0.98634–1.09509)	1.05550 (0.99960–1.11452)
Seville	1.02429 (1.00820–1.04063)	—	1.02833 (1.01037–1.04660)	1.02318 (1.00680–1.03982)	—	1.02697 (1.00887–1.04540)
Valencia	1.00617 (0.99115–1.02141)	1.00315 (0.98813–1.01839)	1.00001 (0.98417–1.01609)	1.00312 (0.98792–1.01856)	1.00453 (0.98802–1.02132)	1.00249 (0.98551–1.01976)
All cities	1.01127 <sup>a</sup> (0.99940–1.2314)	1.00896 (1.00595–1.01199)	1.01298 <sup>a</sup> (1.00586–1.02016)	1.01146 <sup>a</sup> (1.00540–1.01755)	1.00428 <sup>a</sup> (0.99914–1.00943)	1.01043 <sup>a</sup> (1.00240–1.01851)
Q ( <i>p</i> -value) <sup>b</sup>	4.686 (0.001)	0.644 (0.283)	7.574 (<0.001)	6.424 (<0.001)	1.879 (0.059)	8.136 (<0.001)
O <sub>3</sub> 8-hr maximum	O <sub>3</sub>					
Barcelona	1.00554 (0.99971–1.01140)	1.00505 (0.99919–1.0194)	1.00367 (0.99773–1.00964)	1.00480 (0.99893–1.01071)	1.00572 (0.99966–1.01182)	1.00482 (0.99870–1.01099)
Madrid	1.00541 (0.99955–1.01129)	1.00643 (1.00059–1.01231)	1.00634 (1.00028–1.01243)	1.00592 (0.99962–1.01227)	1.00488 (0.99850–1.01129)	1.00543 (0.99896–1.01194)
Valencia	1.03137 (1.00352–1.0600)	1.03045 (1.00255–1.05913)	1.02736 (0.99593–1.05980)	1.03023 (1.00229–1.05894)	1.03153 (1.00046–1.06358)	1.03034 (0.99762–1.06413)
All cities	1.00604 <sup>a</sup> (1.00084–1.01127)	1.00628 <sup>a</sup> (1.00123–1.01136)	1.00538 <sup>a</sup> (1.00090–1.00989)	1.00591 <sup>a</sup> (1.00067–1.01117)	1.00484 <sup>a</sup> (1.00078–1.01093)	1.00557 <sup>a</sup> (1.0007–1.01127)
Q ( <i>p</i> -value) <sup>b</sup>	3.242 (0.024)	3.046 (0.028)	2.273 (0.054)	3.035 (0.028)	2.700 (0.037)	2.243 (0.055)

<sup>a</sup>Random effects model; fixed effects model otherwise. <sup>b</sup>Chi-square of heterogeneity (*p*-value).

of the associations. Further details of the site-specific analyses have been presented elsewhere (24–26).

The relations between mortality and explanatory variables were mostly nonlinear (28). This nonlinearity could have limited the statistical methodology used due to its potential residual confounding and/or over-adjustment. In the absence of any hypothesis about the precise form of the relations, a flexible approach to covariate control is appropriate. We used generalized additive models (GAM) (29). The use of GAM for time series of counts was first introduced in 1993 (30). Since then this approach has become standard in air pollution epidemiology (31). The GAM extends the standard GLM by fitting nonparametric smooth functions to estimate the relations between the response and the predictors. In the estimation of these functions, we distinguished between observed confounders (i.e., weather variables), which we believe are connected to deaths in a causative way, and other unobserved confounders. For the former we consider estimating those unknown, infinite-dimensional parameter functions by using smoothing splines (32) of the meteorologic variables (average of the current value and the first lag of temperature and humidity, and average of lags two to four of temperature and humidity). Unobserved confounders, but with a systematic variation in time, were controlled for in two ways. First, we used Loess smooth

functions (33) of time. Loess is a weighted moving regression with a window centered about each value of the explanatory variable (29,31). Using this strategy we tried to remove long wavelength patterns (i.e., trend and seasonality) (28). Other unobserved confounders such as short wavelengths, say, less than 2 months, were controlled for by means of weekday indicators. Furthermore, to control for the effect of influenza on mortality, we used smoothing splines of daily counts of influenza cases (28,31). Finally, indicator variables were used to fit local characteristics such as holidays and unusual events such as health care worker strikes, the Olympics in Barcelona, and the Universal Exhibition in Seville (both in 1992).

The principal issue in the use of nonparametric smoothers is the choice of the fraction of the data (smoothing parameter) that will be included in the running smooth. We distinguished between smoothing splines and Loess. For the splines, we chose the number of degrees of freedom that minimized the Akaike's Information Criterion (AIC) corrected for nonparametric models (34) within the range (2–4). Because the meteorologic variables varied across the cities, we allowed the number of degrees of freedom to vary between them (31). In the case of the window size for Loess of time, we chose the span that minimized partial autocorrelation in the residuals, with the restriction of not using a span of less than 2

months. Again, to allow for city-specific differences, the smoothing parameters were optimized separately in each location.

Once the city-specific baseline models were fitted, air pollutant variables were added to the model. In particular, for both pollutants we introduced the averages of the same-day concentration (on the day of death) and the first lag (previous day) and of lags two and three. In the case of O<sub>3</sub>, we also included the average of lags four and five. We maintained the averages of air pollutant concentrations in all the final models without regarding their statistical significance. Because simultaneous exposure to other pollutants, especially particles, could be a potentially important source of variation, not only single pollutant but also multipollutant models were considered. In this way, we estimated for each city a model containing both photochemical air pollutants (NO<sub>2</sub> and O<sub>3</sub>); both photochemical air pollutants and particles (either black smoke or PM<sub>10</sub>); both photochemical air pollutants and sulfur dioxide; both photochemical air pollutants and carbon monoxide; and both photochemical air pollutants and all other air pollutants.

One additional problem is the choice of the lags for the explanatory variables of the model. Too many lags could lead to identifying relations that actually occurred by chance. Because we were trying to analyze short-term relations, restrictions of a week or less seemed the most reasonable strategy

**Table 4.** Relative risks of mortality and 95% confidence intervals associated with a 10 µg/m<sup>3</sup> increase in the level of pollutants across the EMECAM cities: respiratory mortality (ICD-9, 460–519).

	NO <sub>2</sub> or O <sub>3</sub>	NO <sub>2</sub> -O <sub>3</sub>	NO <sub>2</sub> -O <sub>3</sub> particles	NO <sub>2</sub> -O <sub>3</sub> SO <sub>2</sub>	NO <sub>2</sub> -O <sub>3</sub> CO	NO <sub>2</sub> -O <sub>3</sub> all pollutants
NO <sub>2</sub> 24-hr average	NO <sub>2</sub>					
Barcelona	1.01426 (0.99738–1.03142)	1.01431 (0.99738–1.03153)	1.00198 (0.98355–1.02076)	1.01123 (0.99398–1.02878)	1.00452 (0.98679–1.02257)	1.00052 (0.98175–1.01964)
Gijón	1.04668 (0.99386–1.10231)		1.05328 (0.99964–1.10979)	1.04211 (0.98735–1.09991)		1.05068 (0.99615–1.10799)
Huelva	1.01550 (0.90606–1.13817)		1.03129 (0.91494–1.16243)	1.00344 (0.87903–1.14546)	1.01688 (0.90232–1.14598)	1.01636 (0.88340–1.16933)
Madrid	1.01750 (1.00483–1.03034)	1.01749 (1.00468–1.03046)	1.01931 (0.99724–1.04187)	1.01341 (0.99355–1.03367)	1.02054 (0.99415–1.04763)	1.02125 (0.99353–1.04975)
Oviedo	1.05344 (0.98132–1.13087)		1.05063 (0.96651–1.14206)	1.03534 (0.95418–1.12341)	1.02876 (0.94067–1.12509)	1.01189 (0.92082–1.11197)
Seville	1.01482 (0.97903–1.05191)		1.00508 (0.96578–1.04598)	1.00389 (0.96789–1.04123)		1.00290 (0.96332–1.04410)
Valencia	1.0226 (0.99092–1.05459)	1.02223 (0.99078–1.05468)	1.01361 (0.98058–1.04774)	1.02117 (0.98934–1.05403)	1.02547 (0.99100–1.06114)	1.01725 (0.98202–1.05374)
All cities	1.01822 <sup>a</sup> (0.91258–1.02389)	1.01690 (1.01378–1.02003)	1.01266 <sup>a</sup> (0.98203–1.02340)	1.01409 <sup>a</sup> (0.95792–1.02030)	1.01246 <sup>a</sup> (0.98355–1.02144)	1.01070 <sup>a</sup> (0.99520–1.02131)
Q (p-value) <sup>b</sup>	2.289 (0.028)	0.204 (0.426)	4.747 (0.002)	1.839 (0.054)	1.767 (0.068)	3.956 (0.003)
O <sub>3</sub> 8-hr maximum	O <sub>3</sub>					
Barcelona	1.00399 (0.99420–1.01388)	1.00408 (0.99426–1.01399)	1.00564 (0.99532–1.01606)	1.00456 (0.99473–1.01449)	1.00619 (0.99560–1.01690)	1.00649 (0.99572–1.01738)
Madrid	1.00104 (0.99022–1.01198)	1.00084 (0.99004–1.01175)	1.00071 (0.98981–1.01173)	1.00210 (0.99087–1.01346)	1.00095 (0.98974–1.01228)	1.00249 (0.99110–1.01402)
Valencia	1.01853 (0.96167–1.07875)	1.01827 (0.96143–1.07848)	1.01475 (0.95097–1.08281)	1.01996 (0.96287–1.08043)	1.00269 (0.94041–1.06909)	1.01098 (0.94490–1.08168)
All cities	1.00292 (0.99953–1.00631)	1.00286 (0.99938–1.00635)	1.00347 (0.99964–1.00731)	1.00376 (0.99445–1.00709)	1.00371 (0.97011–1.00732)	1.00470 (0.99177–1.00763)
Q (p-value) <sup>b</sup>	0.438 (0.345)	0.463 (0.338)	0.526 (0.318)	0.405 (0.356)	0.439 (0.344)	0.280 (0.399)

<sup>a</sup>Random effects model; fixed effects model otherwise. <sup>b</sup>Chi-square of heterogeneity (p-value).

(28). A week, furthermore, seems the more reasonable period of latency from a physiological point of view (22,24).

Finally, even controlling for unobserved confounders, for the temporal behavior of the relations and allowing flexible smoothing functions, it was possible that some residual autocorrelation remained after the estimation (28). This serial correlation was controlled for by introducing up to six lags of the response, leading to autoregressive Poisson GAMs (28,35).

The quantitative summary of all individual results (i.e., the results for each center), is given here using both graphical and analytic methods. The individual, as well as the combined relative risks (RR), associated with a  $10 \mu\text{g}/\text{m}^3$  increase in the pollutant levels and their 95% confidence intervals are plotted graphically. To standardize the results, weights inversely proportional to the variances of the RR were used in the graphical representation. Logarithmic scale was used because confidence intervals are symmetric on this scale. The combined estimates were weighted by means of city-specific regression coefficients, in which the weights were the inverse of the local variances. This method, also called the fixed-effects model, is described in more detail elsewhere (36,37). If significant heterogeneity among local estimates was found, random effects models were also applied. In this case, the between-cities variance was estimated using the moment method of DerSimonian and Laird (36) and was added to the estimates of the local variance. The test for heterogeneity was a chi-square test under the fixed-effect hypothesis (36). Because few observations were combined and, therefore, the statistical power of the test was small, the null hypothesis was rejected with  $p$ -values  $\leq 0.2$  (6). Where heterogeneity was present, and when it

was possible, the meta-analysis was repeated backward, taking out one city each time.

## Results

$\text{NO}_2$  had a positive and statistically significant relationship with mortality when combining the results of single pollutant models (Tables 2–4). However, these associations were unstable (note the large confidence intervals) and not consistent across cities (there was great evidence of heterogeneity as shown by the  $Q$ -statistic). With the exception of cardiovascular mortality (Table 3),  $\text{O}_3$  was not associated in a statistically significant way with mortality (although the sign of such relationships was always positive).

The picture changed in the case of multipollutant models (Figure 2). Carbon monoxide was confounding the relationship between  $\text{NO}_2$  and mortality. The confounding role of particles was not so clear. In the case of  $\text{O}_3$  other pollutants, except perhaps  $\text{NO}_2$ , did not confound the associations (although in general they were not statistically significant).

With respect to their statistical significance, results for 24-hr average  $\text{NO}_2$  (Tables 2–4, Figures 3–5) and 1-hr maximum  $\text{NO}_2$  were similar. Differences in RRs could be attributed simply to the different timing of the indicators. The RR for  $\text{O}_3$  (8-hr maximum) was statistically significant only for cardiovascular mortality (Table 3, Figure 4), although this was not the case when the 1-hr maximum value was the indicator used for  $\text{NO}_2$ .

Photochemical air pollutants were not associated with respiratory mortality once other pollutants were taken into account (Table 4, Figure 5). Finally, RRs for cause-specific mortality were higher (nearly double) than RRs for total mortality for all the photochemical pollutants (even when there

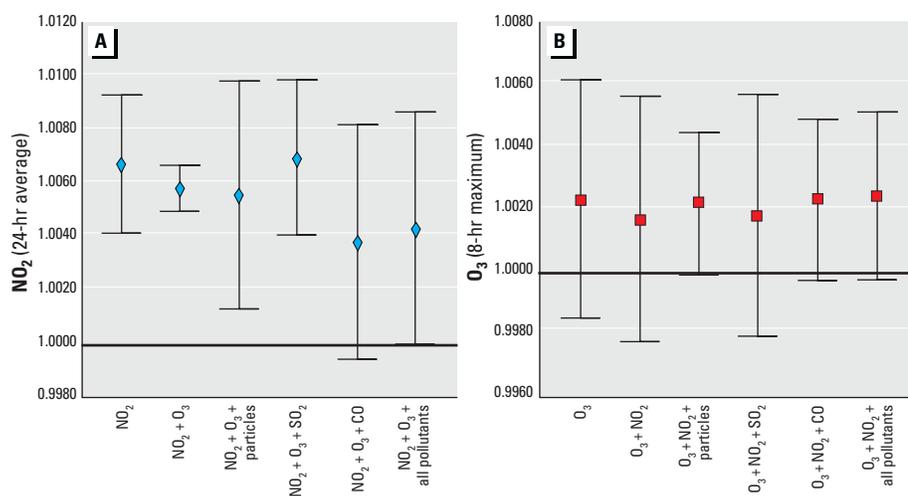
was not a statistically significant association, as in respiratory mortality).

Summing up the most significant results, a  $10 \mu\text{g}/\text{m}^3$  increase in the 24-hr average 1-day  $\text{NO}_2$  level was associated with an increase in the daily number of deaths of 0.43% (95% CI,  $-0.003$ – $0.86\%$ ) for all causes excluding external causes, once the rest of pollutants considered were taken into account and 1% (95% CI,  $0.24$ – $1.85\%$ ) for cardiovascular mortality, again, independently of the rest of considered pollutants. A  $10 \mu\text{g}/\text{m}^3$  increase in the 8-hr maximum 1-day  $\text{O}_3$  level augmented cardiovascular mortality by 0.56% (95% CI,  $0.07$ – $1.13\%$ ), once all the rest of pollutants were taken into account.

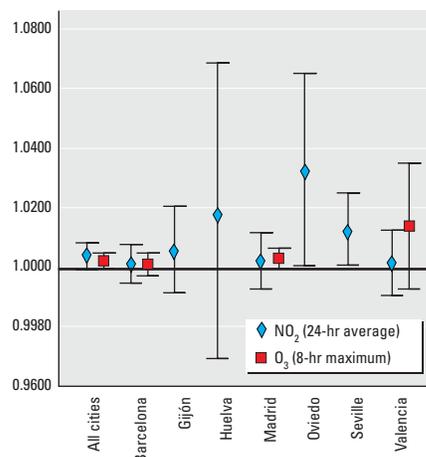
## Discussion

Significant positive associations were found between daily mortality (all causes and cardiovascular) and  $\text{NO}_2$ , once the rest of air pollutants ( $\text{O}_3$ , particles, sulfur dioxide, and carbon monoxide) were taken into account. In the case of significant relationships, RRs for cause-specific mortality were nearly twice as high as those for total mortality for all the photochemical pollutants.  $\text{O}_3$  was only related to cardiovascular daily mortality. No independent, statistically significant relationship between photochemical air pollutants and respiratory mortality was found.

These epidemiologic findings are supported by different, although not consistent, biological evidence. Experimental exposure to high levels of  $\text{NO}_2$  causes acute pulmonary toxic responses. Although  $\text{O}_3$  also has acute pulmonary effects at ambient levels, epidemiologic studies have yielded inconclusive results (38). Several studies have found significant adverse effects of  $\text{NO}_2$  mainly in respiratory symptoms among children or increased hospital admissions



**Figure 2.** Estimated combined RRs of total number of deaths and their 95% CIs associated with a  $10 \mu\text{g}/\text{m}^3$  increase in the levels of (A)  $\text{NO}_2$  (24-hr average) and (B)  $\text{O}_3$  (8-hr maximum value), controlling for other air pollutants.



**Figure 3.** Estimated individual and combined RRs of total number of deaths and their 95% CIs associated with a  $10 \mu\text{g}/\text{m}^3$  increase in the levels of  $\text{NO}_2$  (24-hr average) and  $\text{O}_3$  (8-hr maximum value).

(13,17,21), whereas others failed to find any significant effects (19,39).

There are few studies relating photochemical air pollutants and mortality. This could be attributed to some of the inconsistencies found in those epidemiologic studies (6,13). Recent evidence on the effects on mortality (7,8), however, has weakened this line of argument. Likewise, when using daily data, mortality usually peaks in the winter, whereas O<sub>3</sub> levels peak in the summer (and daily NO<sub>2</sub> levels do not present peaks) (6,25). The unfamiliarity with advanced time-series statistical analysis techniques that deal with such problems (1,25,30,40) could also be a reason for the lack of studies. More controversial, however, is that the effects of photochemical air pollutants lack independence from the effects of other pollutants, such as particles, suggesting that photochemical pollutants could act as surrogates for particles (6,8,9,23,41).

Recently, and mainly due to a higher familiarity with advanced time-series statistical analysis techniques (1,7,25,30,40), a growing number of studies have investigated the short-term effects of photochemical air pollutants on mortality (2,3). In general, as in the present study, significant effects were found in single-pollutant models. Regarding daily total mortality, Kinney and Ozkaynak (8) found significant RRs associated for both NO<sub>2</sub> and O<sub>3</sub> (analyzed independently) in Los Angeles County, California. For Belgium, Sartor et al. (42) showed a significant association between daily mortality and ambient O<sub>3</sub> concentration (although only for the elderly and during the hot summer). Likewise, several studies in Australia (43,44) found significant associations between O<sub>3</sub> and total daily mortality. In the Netherlands, Hoek et al. (7) found that daily mortality was associated with concentrations of O<sub>3</sub> on the previous day (RR

= 1.06 for a change of 67 µg/m<sup>3</sup>). The relationship between O<sub>3</sub> and mortality could be stronger among the elderly (42–44).

With regard to cause-specific mortality, Kinney and Ozkaynak (8) found a significant relationship between photochemical air pollutants and cardiovascular mortality. Tobías et al. (45), in Barcelona, Spain, found that oxidant pollutants were related positively to cardiovascular mortality. They pointed out especially the role of O<sub>3</sub>, noting that a reduction in O<sub>3</sub> levels of about 50 µg/m<sup>3</sup> led to a 2.8% reduction in daily cardiovascular mortality. Simpson et al. (43), in Brisbane, and Morgan et al. (44) in Sydney, Australia, found statistically significant associations between O<sub>3</sub> and cardiovascular disease categories. Simpson et al. (43) pointed out that the coefficients, when significant, were higher for cardiovascular mortality than those for total mortality. Likewise, in the present study, RRs for cause-specific mortality were also higher than for total mortality.

However, as in our case, most of the studies found no statistically significant associations for respiratory mortality. Kinney and Ozkaynak (8) suggested that the small number of deaths from respiratory causes may have limited the ability to detect small pollution associations. Rather than the number of deaths, in absolute terms, we think that the failure in finding significant associations could be attributed to the low number of deaths from respiratory causes—that is, to the relation with its dispersion and, above all, to the limited number of cities in which air pollutant measurements were available.

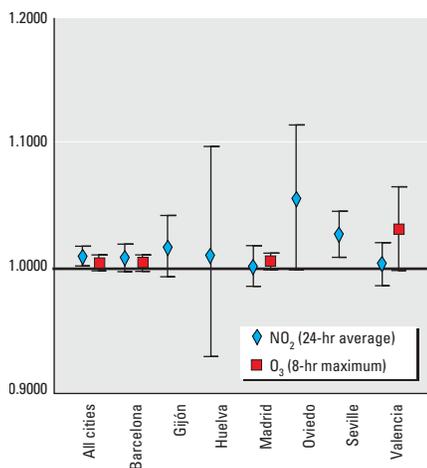
In the context of the multicenter collaborative studies, the APHEA project (6) found significant short-term adverse effects of O<sub>3</sub> on total daily number. The RRs associated

with a 50 µg/m<sup>3</sup> increase in O<sub>3</sub> (1-hr maximum) ranged from 1.3 to 8.6% with a pooled estimate of 2.9% (95% CI, 1.0–4.9%). Concerning the short-term effects of NO<sub>2</sub>, an overall significant increase in the total number of deaths by 1.3% (95% CI, 0.9–1.8%) for every 50 µg/m<sup>3</sup> NO<sub>2</sub> (1-hr maximum) levels was found, and the individual RRs ranged from 0.5 to 2.7%. Likewise, O<sub>3</sub> was a significant predictor of respiratory mortality (41) (RR of 1.05 associated with a 50 µg/m<sup>3</sup> increase) and cardiovascular mortality (RR = 1.02), and NO<sub>2</sub> was marginally significant for mortality due to cardiovascular causes (RR = 1.01).

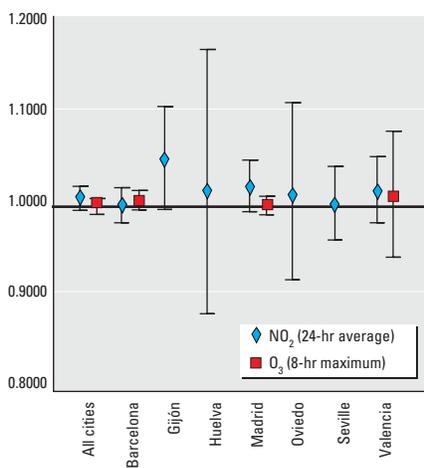
With the exception of O<sub>3</sub>, the results of the present study were more pronounced than those found by the APHEA project, with increases in daily mortality associated with a 50 µg/m<sup>3</sup> increase in NO<sub>2</sub> (24-hr average), equal to 2.15% for total mortality (compared to 1.3% in the APHEA case), 5% for cardiovascular mortality (compared to 1% in the APHEA case), and an RR associated with a 50 µg/m<sup>3</sup> increase in O<sub>3</sub> (8-hr maximum), equal to 2.8% for cardiovascular mortality (compared to 5% in the APHEA case). Our findings, however, are similar to those found by Quénel et al. (46), except for those related to respiratory mortality. The RRs associated with a 50 µg/m<sup>3</sup> increase in NO<sub>2</sub> were 1.038 for total mortality (1.0215 in our case), 1.046 for cardiovascular mortality (1.05 in our case), and the RR for cardiovascular mortality corresponding to O<sub>3</sub> was 1.024 (1.028 in our case).

As mentioned above, it is possible that photochemical air pollutants could be markers of exposure to other air pollutants, specifically particles, which could lead to a confounded association. Ostro et al. (10) in Santiago, Chile, found a significant association between O<sub>3</sub> and mortality when the pollutant was considered alone; however, the association was diminished when particulate matter < 10 µm in aerodynamic diameter was added to the model. Likewise, when analyzing multipollutant (photochemical and other air pollutants) models, Borja-Aburto and colleagues (47,48) in Mexico City, Lee et al. (49) in Seoul and Ulsan, Korea, and Bremner et al. (50) in London found no independent effects of either O<sub>3</sub> or NO<sub>2</sub>.

Some studies (6,44,51) found that photochemical air pollutants, even at low concentrations, were associated, independently, with mortality (all causes, cardiovascular and asthma mortality). As in the APHEA project (6), in all the EMECAM cities, the correlation between O<sub>3</sub> and black smoke was relatively low and in most cases negative (24). In the combined analysis of the ambient oxidant air pollution effects on total mortality, results from the models that included black



**Figure 4.** Estimated individual and combined RRs of cardiovascular deaths and their 95% CIs associated with a 10 µg/m<sup>3</sup> increase in the levels of NO<sub>2</sub> (24-hr average) and O<sub>3</sub> (8-hr maximum value).



**Figure 5.** Estimated individual and combined RRs of respiratory deaths and their 95% CIs associated with a 10 µg/m<sup>3</sup> increase in the levels of NO<sub>2</sub> (24-hr average) and O<sub>3</sub> (8-hr maximum value).

smoke and O<sub>3</sub> simultaneously only slightly reduced the magnitude of the estimated O<sub>3</sub> effects (6). In the case of NO<sub>2</sub>, however, although still significant at the nominal level, the effects were substantially reduced. 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 (14).

Some limitations could be present in our study. First, measurement error and nondifferential bias is a problem for pollutants. O<sub>3</sub>, for instance, has higher concentrations in nonurban areas, which were not considered in this study. This fact could contribute to the lack of statistical significance of such air pollutants. In addition, O<sub>3</sub> is highly correlated with maximum temperature, implying that the effects can be hardly separated. In an attempt to further investigate this point, we re-analyzed some of the cities (those in which we found statistically significant parameters either in single or in multipollutant models) using daily maximum temperature instead of 24-hr average O<sub>3</sub> concentrations. In all cases results were similar, even with respect to the statistical significance of the parameters. We hypothesize that daily variations in temperature were small, at least in the three Spanish cities considered (Barcelona, Madrid, and Valencia).

Second, in general, the associations between daily mortality and photochemical air pollutants were heterogeneous. We investigated, in a very exploratory way, the role of some variables as effect modifiers. Levels of particles and sulfur dioxide and average temperature were the main source of such heterogeneity. The differences arose generally from the biggest city, Madrid, where those variables presented the highest coefficients of variation. The analysis of the between-study variability is an important issue in combined results. However, the small number of cities analyzed precludes any deeper investigation into this issue.

Finally, photochemical air pollutants were treated as linear terms in our analysis. However, the dose–response relationship of such air pollutants, O<sub>3</sub> in particular, could be nonlinear (31). We had three reasons to use a linear approximation in this study. First, we could not reject the null hypothesis of linear fit in the approximate partial tests (29) for some of the photochemical air pollutant averages. For a single variable in the model, this would be equivalent to testing for a difference between a linear fit and a smooth fit that includes a linear term along with the smooth term. We therefore had both linear and smooth functions of averages of the same pollutant that were difficult to combine. The second problem is that, with smoothing terms, it is not easy to derive straightforward pointwise estimates nor their pointwise standard errors

of the RRs of death for a particular air pollutant change or for a specific level. Third, three studies have recently explored the possibility of the existence of a threshold in the dose–response curve for particulate air pollution, using multicity studies in the United States (52,53) and in Spain (31). In all cases, a linear, not threshold, relationship was seen, implying that, at least for particles, linear models provide an adequate estimation of the effect of air pollution on mortality at low to moderate concentrations. At any rate, this point deserves further research.

To conclude, the results presented here show an independent association between mortality and photochemical pollutants. NO<sub>2</sub>, the 24-hr average values in particular, has a greater impact on mortality. In the case of significant relationships, this association is greater for groups of specific causes, particularly cardiovascular mortality. However, results are not homogeneous among the cities. In some cities, there was no evidence of association, or else the association is negligible. Although the estimates provided in this study cannot be considered as definitive due to the above mentioned limitations, the results do suggest that, given the present levels of photochemical pollutants, people living in Spanish cities are exposed to health risks derived from air pollution.

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