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Short-Term Effects of Air Pollution on Mortality in Nine French Cities: A Quantitative Summary

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ABSTRACT: Between 1990 and 1995, 9 French cities provided data on daily air pollution, total mortality, cardiovascular mortality, and respiratory mortality. Personnel in individual cities performed Poisson regressions, controlling for trends in seasons, calendar effects, influenza epidemics, temperature, and humidity, to assess the short-term effects of air pollution. The authors describe results obtained from the quantitative pooling of these local analyses. When no heterogeneity could be detected, a fixed-effect model was used; otherwise, a random-effect model was used. Significant and positive associations were found between total daily deaths in these cities and the 4 air pollution indicators studied: (1) Black Smoke, (2) sulfur dioxide, (3) nitrogen dioxide, and (4) ozone. A 50- $\mu\text{g}/\text{m}^3$ increase in Black Smoke (24 hr), sulfur dioxide (24 hr), nitrogen dioxide (24 hr), or ozone (8 hr) was associated with increases in total mortality of 2.9% (95% confidence interval [CI] = 1.3, 4.4), 3.6% (95% CI = 2.1, 5.2), 3.8% (95% CI = 2.0, 5.5), and 2.7% (95% CI = 1.3, 4.1), respectively. Similar results were obtained for cardiovascular mortality. Except for sulfur dioxide, positive—but not significant—associations were found with respiratory mortality. The internal consistency among the cities studied, as well as consistency with previously published results, favors a causal interpretation of these associations.

<Key words: air pollution, Black Smoke, cardiovascular mortality, nitrogen dioxide, ozone, respiratory mortality, short-term effects, sulfur dioxide, total mortality>

THE RESULTS OF RECENT EPIDEMIOLOGICAL STUDIES have shown that ambient air pollution can adversely affect human health, even at levels close to or lower than current national standards.¹ Particulate matter is the pollutant most consistently associated with mortality; however, the lack of such an association for other pollutants, especially sulfur dioxide (SO₂), has been questioned. In particular, the independent mortality effect of particulate matter has been shown in the United States² but not in Europe, where the effect of SO₂ has not been modified by particle levels.³ Ozone (O₃) has also been associated with both total and cause-specific mortality; respiratory and cardiovascular systems are mainly affected by O₃.⁴ In a few studies, investigators have examined the effects of nitrogen dioxide (NO₂) on mortality and have suggested the existence of an adverse effect; however, the independence of this effect remains unclear.⁵

The association between air pollution and daily mortality has been studied in Europe, largely within the Air Pollution and Health: A European Approach (APHEA) project. In this study, investigators found consistent results in large Western European cities.³⁻⁵ The effects of air pollution have been well established in European metropolitan areas; however, few European studies have been conducted in relatively small urban areas. The investigators of the French 9-cities project, conducted between 1990 and 1995, attempted to quantify the short-term effects of air pollution on mortality in medium-sized cities. The investigators chose 9 medium-sized cities in which air pollution measurements had been made during the past few years. In addition, the investigators' choices were influenced by (1) the daily number of health outcomes, which vary in accordance with the size of a city; and (2) their desire to select cities that contrasted with each other with respect to climate, air pollution sources, and socioeconomic status of the population.

Materials and Method

In Table 1 are shown population sizes for the cities studied (i.e., 8 medium-sized cities and the Paris region). Also shown are daily mean deaths for (1) total mortality (based on the International Classification of Diseases, 9th revision [ICD9]; < 800), (2) cardiovascular mortality (ICD9 390-459); and (3) respiratory mortality (ICD9 460-519). The cities have a combined population of nearly 11 million, including 6 million in the Paris metropolitan area. Mortality data were taken from national statistics. The daily number of deaths was lowest in Le Havre, the smallest city, and highest in Paris. Cardiovascular mortality ranged from 30% of total mortality in Rouen to 37% in Marseille. The daily number of deaths from respiratory causes was close to 1 in all cities, except Paris, and respiratory causes represent approximately 7% of the total deaths.

The daily means for meteorological variables for the study period are given in Table 2. The average yearly low temperature ranged from 6.6 °C in Rouen to 10.9 °C in Marseille. Marseille reported the lowest humidity level and Le Havre reported the highest. Air pollution monitoring network stations established in each city provided hourly or daily air pollutant measurements. The pollutants studied were those generally measured in France: SO₂ was measured by ultraviolet fluorescence (except in Bordeaux, where it was measured by strong acidity); NO₂ was measured by chemiluminescence; O₃ was measured by ultraviolet absorption; and Black Smoke was measured by reflectometry. Daily 24-hr means were used for all pollutants, except O₃, for which 8-hr maximum values were used.

We encountered a problem in collecting data from the monitoring stations during the study period. For some cities, data were available for only 1 pollutant, and for other cities, data on pollutants were unavailable until recent years. Three cities (i.e., Le Havre, Paris, and

Table 1.—Population Size and Mortality Statistics for 9 Cities in France, 1990-1995

City	Population	Total mortality*		Cardiovascular mortality†		Respiratory mortality‡	
		Daily \bar{x}	SD	Daily \bar{x}	SD	Daily \bar{x}	SD
Bordeaux	557,670	12.3	3.7	4.5	2.2	0.9	0.9
Le Havre	259,965	6.3	2.6	1.9	1.4	0.4	0.7
Lille	1,067,563	22.4	5.2	7.6	2.9	1.8	1.5
Lyon	765,789	15.5	4.2	5.3	2.4	1.2	1.2
Marseille	855,411	21.7	5.2	8.0	3.0	1.7	1.3
Paris	6,178,359	125.0	15.8	39.0	7.5	9.0	3.7
Rouen	428,971	10.0	3.3	3.0	1.8	0.7	0.9
Strasbourg	422,642	8.5	3.0	3.1	1.8	0.6	0.8
Toulouse	606,706	10.2	3.3	3.7	1.9	0.7	0.9

Notes: \bar{x} = mean, and SD = standard deviation.

*International Classification of Diseases, 9th rev. (ICD9) < 800.

†ICD9 = 390-459.

‡ICD9 = 460-519.

Rouen) provided measurements for all 4 pollutants. Only SO₂ data were available for the city of Lille. Marseille had data for Black Smoke and SO₂ only, and Toulouse reported for NO₂ and O₃ only. Descriptive statistics for each pollutant, and the time period during which data were available, are provided in Table 3.

To ensure between-city comparability of pollutant exposure, only data from urban background stations were used, except for O₃ for which suburban station data were used. France has a nationally standardized classification system for air quality monitoring stations, and there are strict rules for station operation.⁶ The correlation between daily measurements at different stations in the same city ranged from 0.34 to 0.84 for SO₂, 0.55 to 0.84 for Black Smoke, 0.52 to 0.83 for NO₂, and > 0.95 for O₃. Six cities could provide measurements for O₃; however, 3 cities used only 1 station each, and 2 cities used 2 stations each. For the other pollutants, all cities collected information from at least 2 stations, except for Strasbourg, where only 1 station was available for each pollutant. The range of median pollutant levels did not differ greatly among cities, inasmuch as the maximum differential was only 42 µg/m³ for median levels of O₃ (Table 3).

We analyzed the daily data from the 9 cities by Poisson time-series regressions. We fit the data with autore-

gressive models that allowed for overdispersion. Adhering to APHEA methodology,⁷ we controlled for possible confounders, including long-term trends, seasons, days of the week, holidays, influenza epidemics, temperature, and humidity. Instead of using a parametric approach that controlled for confounders (as was done in APHEA), we used generalized additive models⁸ to ensure a nonlinear relationship between confounders and mortality. As part of the diagnostic testing of the models, we tested the residuals for autocorrelation, applied Akaike's information criteria, and plotted the residuals.

Statisticians from each monitoring station performed Poisson's time-series regression with their station's own data. To ensure comparability between the modeling processes, we subjected each model to quality control by the coordinating center, in collaboration with the statisticians from every center. Each center determined the best lag time for each pollutant (i.e., 1–5 days or cumulatively [i.e., the mean over several previous days]). Finally, for the meta-analysis, each center fitted a linear relationship between the average of lags 0–1 (day) of the pollutant and mortality. This approach avoided potential bias that could have resulted from use of the most significant lags in each city. We, therefore, based our choice of the linear form on the results from the local analyses.

To obtain a quantitative summary of the results across the centers, we applied meta-analysis methods to arrive at a pooled regression coefficient as a weighted mean of the city-specific regression coefficient. The weights are inversely proportional to the city variances. We then determined the weights, assuming a fixed-effect model when a chi-square test failed to detect heterogeneity at the sensitivity level of alpha = 20%. If the assumption of homogeneity was rejected, we adopted a random-effect model in which the between-cities variance was added to each estimated local variance, giving more similar weights—but also a larger variance. This variance inflation reflects greater uncertainty on the summary estimate when local results are heterogeneous. We used the moment method of Der Simonian and Laird⁹ to estimate the between-cities variance from the data. Given

Table 2.—Means for Meteorological Variables in the 9 Cities Studied, 1990–1995

City	Temperature (°C)		Relative humidity (%)
	Minimum	Maximum	
Bordeaux	9.3	18.5	56.1
Le Havre	8.9	14.0	71.4
Lille	7.1	14.6	60.3
Lyon	8.0	16.7	53.1
Marseilles	10.9	20.1	48.9
Paris	8.9	16.0	61.4
Rouen	6.6	14.4	63.8
Strasbourg	6.7	15.4	55.6
Toulouse	9.1	18.3	55.9

Table 3.—Medians of Pollutants (µg/m³) and Time Period of Data Availability in the 9 Cities Studied

City	BS (24 hr)	Time period	SO ₂ (24 hr)	Time period	NO ₂ (24 hr)	Time period	O ₃ (8 hr)	Time period
Bordeaux	13.2	01/90–12/95	9.2	01/90–12/95				
Le Havre	12.7	02/91–12/95	17.8	01/92–12/95	35.2	01/90–12/95	43.4	05/92–12/95
Lille			18.9	01/90–12/95				
Lyon			20.9	03/93–12/95	39.9	01/94–12/95	52.0	01/94–12/95
Marseille	16.0	01/90–12/95	16.0	01/90–12/95				
Paris	16.0	10/91–12/94	14.0	10/91–12/94	54.0	10/91–12/94	26.0	10/91–12/94
Rouen	14.1	10/90–12/95	25.6	11/91–12/95	32.9	07/91–12/95	57.9	04/91–12/95
Strasbourg			21.0	03/92–06/95	51.0	03/92–06/95	37.0	01/90–10/94
Toulouse					28.0	08/93–12/95	68.0	05/93–12/95

Notes: BS = Black Smoke, SO₂ = sulfur dioxide, NO₂ = nitrogen dioxide, and O₃ = ozone.

that Paris represented half of the population of all the cities, we conducted a sensitivity analysis to determine whether changes occurred in the fixed estimates when Paris data were excluded.

Results

Each city's relative risk (RR) of mortality associated with a 50- $\mu\text{g}/\text{m}^3$ increase in the average pollutant level for 0- and 1-day lags is shown in Tables 4–7.

SO₂. The average total mortality for each city, as well as pooled fixed-effect (with and without Paris included) and random-effect RRs (and their 95% confidence intervals [CIs]) associated with a 50- $\mu\text{g}/\text{m}^3$ increase in the average level of SO₂ after 0- and 1-day lags are shown in Figure 1. All local estimates were positive (i.e., RR > 1), although they reached a nominal significance level of 5% in the 4 cities of Bordeaux, Lille, Lyon, and Paris. The SO₂ results were heterogeneous across cities (*p* [for heterogeneity] = .13). In attempting to explain this heterogeneity, we found that separating the Bordeaux data from that of the other cities resulted in more homogeneous subgroups. A possible explanation is that Bordeaux was the only city that used strong acidity as a proxy for SO₂. All other cities presented a homogeneous estimated RR. The random joint effect (RR = 1.041) was greater than the fixed effect (RR = 1.036),

but its 95% CI was also wider for the random joint effect (95% CI = 1.018, 1.064 for random and 1.021, 1.052 for fixed). We also found heterogeneity in results for SO₂ relative to cardiovascular deaths in Bordeaux. Inasmuch as CIs were wide for SO₂ relative to respiratory mortality, no significant heterogeneity was found—even with the higher RR in Bordeaux. The exclusion of Paris gave a similar pooled RR as described above for total mortality, but there were a higher RR and wider CIs for cardiovascular and respiratory mortality (*p* = .05). A 50- $\mu\text{g}/\text{m}^3$ increase in SO₂ (Table 8) was associated with an increase of 3.6% in total mortality, 5.3% in cardiovascular mortality, and 5.6% in respiratory mortality.

Black Smoke. Figure 2 shows our findings for cardiovascular mortality for individual, as well as pooled fixed-effect, RRs (with and without Paris), and their 95% CIs, associated with a 50- $\mu\text{g}/\text{m}^3$ increase in the average level of Black Smoke after 0- and 1-day lags. The Black Smoke results were consistent across cities (*p* [for heterogeneity] = .75). All local estimates were positive, but none were significant. Under the fixed-effect model, a 50- $\mu\text{g}/\text{m}^3$ increase in the daily 0- to 1-day average Black Smoke levels was associated with an increase in total mortality equal to 2.9% (95% CI = 1.3, 4.4). The increase in daily cardiovascular deaths was 3.1% (95% CI = 0.5, 5.5). The pooled estimate (Table 8) was positive (RR = 1.027) for respiratory mortality, but it was not

Table 4.—Estimated Relative Risks (RRs) of Mortality and 95% Confidence Intervals (CIs) Associated with a 50- $\mu\text{g}/\text{m}^3$ Increase in Sulfur Dioxide Levels across 9 French Cities Studied

City	Total mortality		Cardiovascular mortality		Respiratory mortality	
	RR	95% CI	RR	95% CI	RR	95% CI
Bordeaux	1.198	1.054, 1.361	1.353	1.098, 1.666	1.270	0.799, 2.019
Le Havre	1.012	0.983, 1.041	1.049	0.996, 1.104	1.061	0.956, 1.178
Lille	1.045	1.010, 1.081	1.059	1.002, 1.120	1.061	0.947, 1.190
Lyon	1.097	1.023, 1.176	1.064	0.945, 1.199	1.092	0.859, 1.389
Marseille	1.058	0.996, 1.125	1.149	1.041, 1.268	1.084	0.879, 1.335
Paris	1.035	1.008, 1.063	1.026	0.980, 1.075	1.028	0.940, 1.125
Rouen	1.015	0.948, 1.087	1.013	0.893, 1.148	1.157	0.904, 1.482
Strasbourg	1.040	0.948, 1.141	1.008	0.864, 1.176	0.944	0.670, 1.329
Toulouse						

Table 5.—Estimated Relative Risks (RRs) of Mortality and 95% Confidence Intervals (CIs) Associated with a 50- $\mu\text{g}/\text{m}^3$ Increase in Black Smoke Levels across 9 French Cities Studied

City	Total mortality		Cardiovascular mortality		Respiratory mortality	
	RR	95% CI	RR	95% CI	RR	95% CI
Bordeaux	1.079	1.000, 1.165	1.091	0.964, 1.235	1.104	0.831, 1.466
Le Havre	1.012	0.929, 1.102	1.072	0.922, 1.247	1.135	0.845, 1.526
Lille						
Lyon						
Marseille	1.060	1.023, 1.098	1.047	0.988, 1.110	1.139	1.009, 1.285
Paris	1.020	1.002, 1.039	1.020	0.988, 1.052	0.989	0.927, 1.054
Rouen	1.007	0.951, 1.067	1.050	0.948, 1.163	1.034	0.848, 1.262
Strasbourg						
Toulouse						

Table 6.—Estimated Relative Risks (RRs) of Mortality and 95% Confidence Intervals (CIs) Associated with a 50- $\mu\text{g}/\text{m}^3$ Increase in Nitrogen Dioxide Levels across 9 French Cities Studied

City	Total mortality		Cardiovascular mortality		Respiratory mortality	
	RR	95% CI	RR	95% CI	RR	95% CI
Bordeaux						
Le Havre	1.021	0.954, 1.093	1.078	0.955, 1.217	1.223	0.949, 1.575
Lille						
Lyon	1.005	0.922, 1.096	1.049	0.905, 1.215	0.996	0.743, 1.334
Marseille						
Paris	1.042	1.022, 1.062	1.046	1.010, 1.083	1.022	0.953, 1.096
Rouen	1.044	0.970, 1.123	1.159	1.019, 1.319	1.054	0.813, 1.367
Strasbourg	1.000	0.933, 1.072	0.934	0.828, 1.054	1.066	0.822, 1.383
Toulouse	1.076	0.957, 1.210	1.023	0.854, 1.226	1.286	0.821, 2.015

Table 7.—Estimated Relative Risks (RRs) of Mortality and 95% Confidence Intervals (CIs) Associated with a 50- $\mu\text{g}/\text{m}^3$ Increase in Ozone Levels across 9 French Cities Studied

City	Total mortality		Cardiovascular mortality		Respiratory mortality	
	RR	95% CI	RR	95% CI	RR	95% CI
Bordeaux						
Le Havre	1.035	0.977, 1.096	1.014	0.913, 1.127	0.903	0.713, 1.143
Lille						
Lyon	1.037	0.998, 1.079	1.019	0.923, 1.126	1.089	0.951, 1.247
Marseille						
Paris	1.021	1.002, 1.040	1.021	0.983, 1.060	0.981	0.910, 1.057
Rouen	1.053	0.999, 1.109	1.071	0.969, 1.184	1.108	0.901, 1.362
Strasbourg	1.029	0.996, 1.063	1.011	0.959, 1.065	1.001	0.885, 1.132
Toulouse	1.013	0.959, 1.070	1.051	0.958, 1.154	1.051	0.851, 1.299

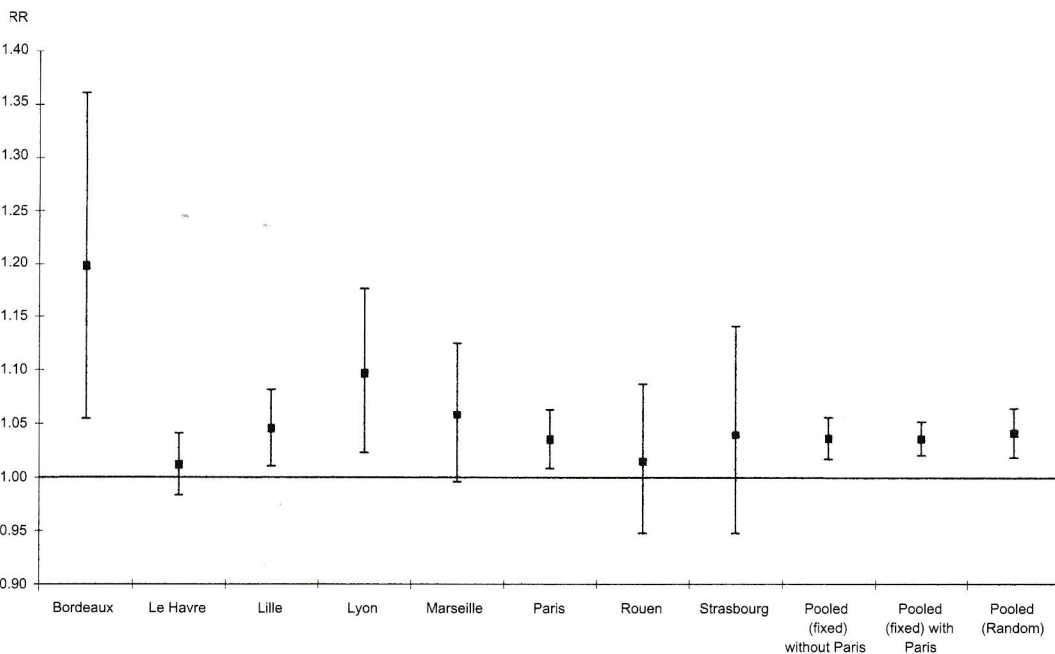


Fig. 1. Estimated individual and pooled relative risks (RRs) of total daily number of deaths and 95% confidence intervals associated with a 50- $\mu\text{g}/\text{m}^3$ daily increase (i.e., 24 hr) in levels of sulfur dioxide.

Table 8.—Estimated Pooled Relative Risks (RRs), with and without Paris, of Mortality and 95% Confidence Intervals (CIs) Associated with a 50- $\mu\text{g}/\text{m}^3$ Increase in Levels of Pollutants across 9 French Cities Studied

Pollutant	Total mortality		Cardiovascular mortality		Respiratory mortality	
	RR	95% CI	RR	95% CI	RR	95% CI
Black Smoke (24 hr)	1.029*	1.013, 1.044	1.031	1.005, 1.055	1.027	0.974, 1.083
	1.046†	1.019, 1.074	1.055	1.009, 1.104	1.111	1.013, 1.219
SO ₂ (24 hr)	1.036	1.021, 1.052	1.053	1.026, 1.080	1.056	1.002, 1.113
	1.036	1.017, 1.055	1.065	1.032, 1.098	1.071	1.004, 1.143
NO ₂ (24 hr)	1.038	1.020, 1.055	1.046	1.015, 1.078	1.040	0.978, 1.106
	1.023	0.988, 1.060	1.046	0.984, 1.111	1.103	0.971, 1.253
O ₃ (8 hr)	1.027	1.013, 1.041	1.024	0.997, 1.051	1.008	0.952, 1.062
	1.033	1.013, 1.053	1.026	0.990, 1.064	1.035	0.962, 1.114

Notes: SO₂ = sulfur dioxide, NO₂ = nitrogen dioxide, and O₃ = ozone.

*RR calculated under a fixed-effects model, with Paris.

†RR calculated under a fixed-effects model, without Paris.

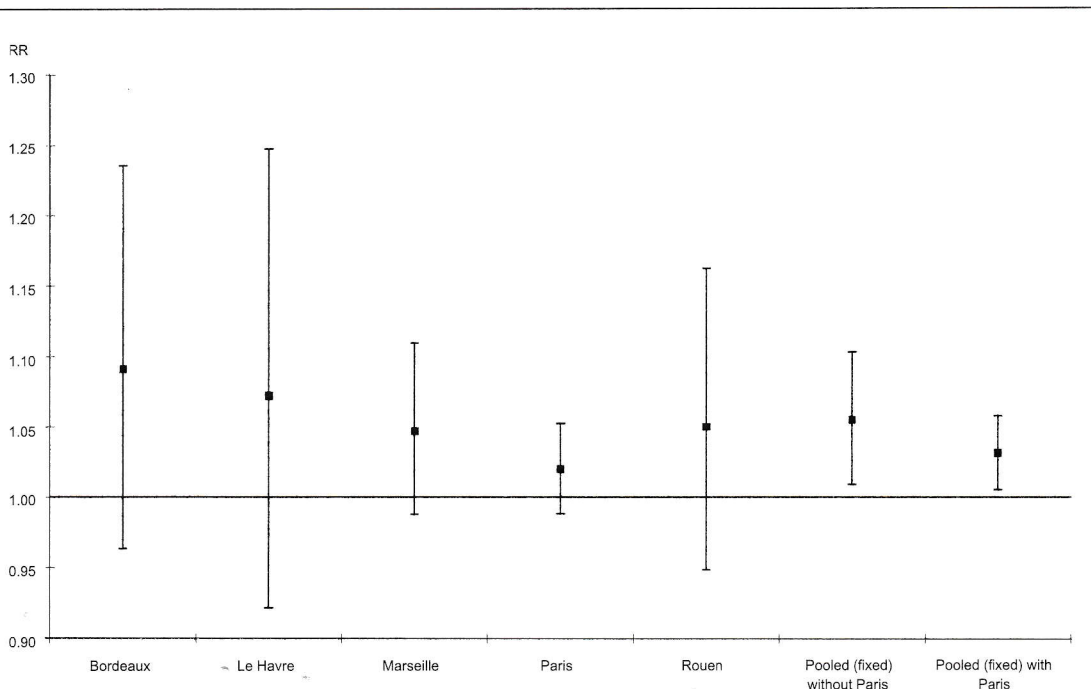


Fig. 2. Estimated individual and pooled relative risks (RRs) of cardiovascular daily number of deaths and 95% confidence intervals associated with a 50- $\mu\text{g}/\text{m}^3$ daily increase (i.e., 24 hr) in levels of Black Smoke.

significant (95% CI = 0.974, 1.083). Exclusion of Paris gave a higher and significant RR (= 1.111) in relation to respiratory deaths (95% CI = 1.013, 1.219).

NO₂. Figure 3 shows the statistics on respiratory mortality for individual and pooled fixed-effect RRs (with and without Paris), and their 95% CIs, associated with a 50- $\mu\text{g}/\text{m}^3$ increase in the average level of NO₂ after a 0- or 1-day lag. The NO₂ results were consistent across cities (p [for heterogeneity] = .73). All local estimates were positive, but none were significant. Under the fixed-effect model, a 50- $\mu\text{g}/\text{m}^3$ increase in the daily 0- to 1-day average NO₂ levels was associated with a 4.0% increase (95% CI = -2.2, 10.6) in daily respiratory

deaths. Effects on total mortality and cardiovascular mortality were 3.8% and 4.6%, respectively, and were significant at a nominal level of 5%. Exclusion of Paris gave systematically wider and nonsignificant CIs, a smaller RR for total mortality, a similar RR for cardiovascular mortality, and a higher RR for respiratory mortality (Table 8).

O₃. Pooled-effect estimates of O₃ were similar (in the 6 cities for which data were available) for total and cardiovascular mortality (Table 8). All local estimates were positive, although none were statistically significant, except total mortality for Paris. Pooled estimates were not sensitive to the inclusion of Paris. A 50- $\mu\text{g}/\text{m}^3$

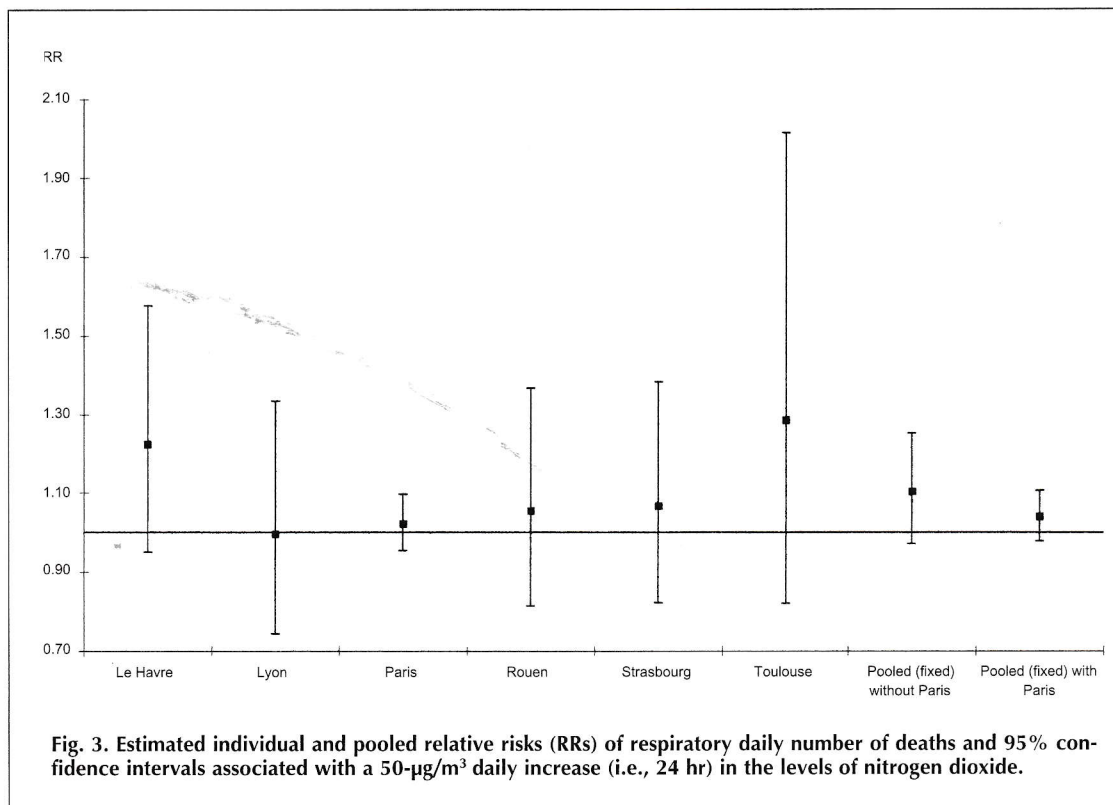


Fig. 3. Estimated individual and pooled relative risks (RRs) of respiratory daily number of deaths and 95% confidence intervals associated with a 50-µg/m³ daily increase (i.e., 24 hr) in the levels of nitrogen dioxide.

increase in O₃ was associated with a 2.7% increase in total mortality and a 2.4% increase in cardiovascular mortality. Results for respiratory mortality were less conclusive than for total mortality, as we found a negative effect in 2 cities, a null effect in 1, and a positive effect in 3 cities. The CIs were very large in all cities. The RR associated with a 50-µg/m³ increase in O₃ was 1.008 (95% CI = 0.952, 1.062). Exclusion of Paris gave a higher risk (RR = 1.035), but wider CIs also resulted.

Discussion

Our combined analysis summarizes the results from 9 French cities on the short-term effects on mortality of 4 indicators of air pollution. We found that all the pollutants studied had a clear and significant effect on total mortality, with a 50-µg/m³ increase in pollutants being associated with an increase of 2.7%–3.8% in total daily deaths. In the European meta-analysis (i.e., APHEA project), investigators estimated that an increase of 50 µg/m³ in air pollution levels was associated with an increase in total mortality of 1.3%–2.9%.^{3,5} Results for cardiovascular mortality showed a significant RR for Black Smoke, SO₂, and NO₂, ranging from 3.1% to 5.6%, with a 50-µg/m³ increase in these pollutants. Nonsignificant, but positive, associations were found with increases in O₃. Results for respiratory mortality were less conclusive, as we found no significant relationship between increased mortality and pollutants, except with SO₂. Moreover, coefficients were closer to 0 and very sensitive to the inclusion of Paris. Kinney and Hozkaynak¹⁰ also found no significant relationship

between increased O₃ and respiratory mortality. They suggested that the small number of deaths from respiratory causes might have limited their ability to detect minor pollution associations.

It should be noted that certain problems frequently encountered in meta-analysis do not apply to the present study. There was no selection bias because the participating cities were not selected on the basis of the results of short-term analyses, but, rather, on their ability to provide data. No cities or results were later excluded. No important differences were seen in health endpoints, exposure data, or the analysis procedures used. We set rules (see Method section) for exposures and confounding factor measurements. In each city, statisticians conducted sensitivity analyses by including different temperature lags, excluding daily extremes in temperature or pollutant levels, and by the use of robust regression.

The use of meta-analysis for the study of air pollution effects is commonly criticized because the combination of RRs, chosen at different lags, is considered, and the end result is that the impact of air pollution findings is maximized. We attempted to avoid this pitfall by choosing the cumulative 0- to 1-day lags a priori based on previous studies. However, defining a priori a fixed lag for each city can induce heterogeneity in the results, as the effect of air pollution may differ by time between cities, and may be affected by the overall (poor) health of a population or the extent of exposure to air pollution.

No between-city heterogeneity was found in the results for total, cardiovascular, or respiratory mortality, except with SO₂. A plausible explanation is that Bordeaux was the only city that measured strong acidity as

proxy for SO₂. Coefficients from other cities gave homogeneous results, as did a pooled fixed estimate close to the random estimate, including Bordeaux. Moreover, an increase of 50 µg/m³ in strong acidity in Bordeaux represented the full range of this pollutant's distribution. There was no concurrent measurement of strong acidity and SO₂ in Bordeaux; however, the annual mean SO₂ in the years that followed the study period is one-third higher than the annual means for strong acidity. Applying this conversion factor in our study produced no noticeable change in the overall effect, and did lead to homogeneity in the results. On the other hand, perhaps strong acidity could better capture exposure to aerosol acidity. Gwynn et al.¹¹ reported a specific association of sulfates (SO₄²⁻) and hydrogen ions with total mortality or hospital admissions, and respiratory mortality or admissions, but no associations were found for circulatory mortality or admissions. Sulfates are associated with respiratory disease and mortality.¹² Factor analysis has revealed that both combustion-related pollutants and secondary aerosols (sulfates) are associated with cardiovascular mortality.¹³ When we compared cities that had a relative increase in interquartile range—rather than a fixed range—we obtained homogeneous results. Results from individual cities had wide CIs, as daily death counts were low, except in Paris. Detection of possible heterogeneity is related to the monitoring capabilities of the individual cities in the larger CIs in each city are more susceptible to overfitting. To compensate for this lack of capabilities, we performed graphical analyses by ordering local RRs in terms of different variable levels. These variables included medians of pollutants or other pollutants studied, duration of the series, number of stations used, city mean mortality level, and mean temperature. No clear relationship was found between any of the aforementioned variables.

Given that a few cities could provide data for all pollutants, and some provided data for only a brief period, we were unable to explore in detail possible effect modifiers, such as analyses of local results from a 2-pollutant model.

Air pollution data were not reliable in France at the beginning of the 1990s, the situation has now changed. A law passed in December 1996 requires that policies concerning the control of air pollution take into account their impact on public health. The law stipulates that an air quality program is to be set up in each region, on the basis of an assessment of emission sources, emission levels, and health impacts. This new policy climate could provide an opportunity for more complete pollution analysis in the future.

A sensitivity analysis was conducted on the potential effect of the inclusion of the Paris results. When the Paris results were included, RRs tended to be driven by the Paris results and CIs were wider. Yet, there was no great discrepancy between pooled fixed effects with and without Paris for total and daily cardiovascular deaths. Respiratory analyses were less conclusive than were cardiovascular analyses—results from city to city were more homogeneous and reflected wider CIs. The RRs for

respiratory mortality were more influenced by the inclusion of Paris data.

As is the case in all ecological studies, there is some misclassification of exposure, to a degree that could vary across cities. Personal exposure to outdoor pollutants is poorly estimated by the fixed monitoring stations because there is geographical heterogeneity, and there are indoor sources of pollution. Nevertheless, in time-series studies, days, rather than persons, are the units of observation. If this is an accurate approach, then personal exposure is poorly correlated to monitoring stations. Some investigators have shown that day-to-day variations in personal exposure are correlated strongly with daily variations in air pollution levels measured by monitoring stations.¹⁴⁻¹⁷

The biological mechanisms underlying the association between daily variation of exposure to pollutant levels and daily mortality are still debated. Particles seem to be the pollutant for which recent biological research indicates a possible causal effect. Recent findings tend to relate particulate pollution to increased plasma viscosity,¹⁸ increased risk of elevated heart rate,¹⁹ and electrocardiographic changes in dogs.²⁰

SO₂ is a respiratory irritant and bronchoconstrictor that can induce coughing and wheezing. Given that SO₂ is highly correlated with particles in some U.S. cities, Schwartz et al.²¹ postulated that this association could reflect the effect of particles. However, in the APHEA project, the effect of SO₂ was not modified by particle levels.³⁻⁵ Although the mechanism behind acidic aerosol health effect associations is not yet known, several have been suggested. Winchester²² argued that acid-coated particles could lead to the solubilization of metals in the lung. Seaton et al.²³ hypothesized that acidic, ultrafine aerosols provoke alveolar inflammation.

It is well documented that experimental exposure to high levels of NO₂ can alter pulmonary function.²⁴ In epidemiological studies, researchers found an association between current levels of NO₂ and mortality.^{5,25,26} However, this association was not as strong when particles were included in the model. These results imply that NO₂ may serve as a proxy variable for vehicle-derived pollutants.

At current levels, O₃ has had acute pulmonary effects on susceptible populations in the cities we studied.²⁷ Even at low levels, O₃ can induce inflammation. In epidemiological studies, findings on the adverse effects of O₃ have consistently shown an association with total mortality and with emergency hospitalizations for respiratory disease—mainly asthma.^{28,29}

In conclusion, the coherence of results across various cities and studies, especially for Black Smoke and O₃—along with what is known of possible mechanisms—reinforces our argument that the associations found in this study were most likely causal.

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