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Abdelkrim Zeghnoun, Pierre Czernichow, Pascal Beaudeau, Alexis Hautemanière, Loétizia Froment, et al.. Short-Term Effects of Air Pollution on Mortality in the Cities of Rouen and Le Havre, France, 1990–1995. Archives of Environmental Health, 2017, 56 (4), pp.327 - 335. 10.1080/00039890109604464 . hal-04825023

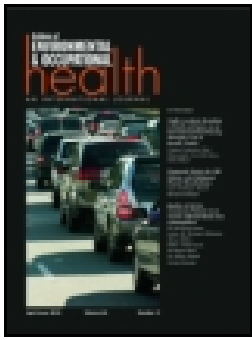
HAL Id: hal-04825023

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Archives of Environmental Health: An International Journal

ISSN: 0003-9896 (Print) (Online) Journal homepage: <http://www.tandfonline.com/loi/vzeh20>

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To cite this article: Abdelkrim Zeghnoun , Pierre Czernichow , Pascal Beaudeau , Alexis Hautemanière , LoÉTizia Froment , Alain Le Tertre & Philippe Quénel (2001) Short-Term Effects of Air Pollution on Mortality in the Cities of Rouen and Le Havre, France, 1990–1995, Archives of Environmental Health: An International Journal, 56:4, 327-335, DOI: [10.1080/00039890109604464](https://doi.org/10.1080/00039890109604464)

To link to this article: <https://doi.org/10.1080/00039890109604464>



Published online: 05 Apr 2010.



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Short-Term Effects of Air Pollution on Mortality in the Cities of Rouen and Le Havre, France, 1990–1995

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ABSTRACT. In this study, the authors examined the short-term effects of ambient air pollution on mortality across 2 French cities: Rouen and Le Havre. In Poisson regression models, which controlled for day-of-week effects, the authors used nonparametric smoothing to control for temporal trend, weather, and influenza epidemics. In Rouen, an interquartile range increase of 60.5–94.1 $\mu\text{g}/\text{m}^3$ of ozone was associated with an increase of 4.1% (95% confidence interval = 0.6, 7.8) of total mortality. Daily variations in sulfur dioxide (interquartile range increase = 17.6–36.4 $\mu\text{g}/\text{m}^3$) were also associated with an 8.2% increase (95% confidence interval = 0.4, 16.6) in respiratory mortality. An increase of 6.1% (95% confidence interval = 1.5, 10.9) of cardiovascular mortality was also observed with an interquartile range increase of nitrogen dioxide (i.e., 25.3–42.2 $\mu\text{g}/\text{m}^3$). With respect to Le Havre, an interquartile range increase in daily levels of sulfur dioxide (11.3–35.6 $\mu\text{g}/\text{m}^3$) was associated with an increase of approximately 3% (95% confidence interval = 0.8, 5) of cardiovascular mortality. For particulate matter less than or equal to 13 μm in diameter (interquartile increase = 21.5, 45.4 $\mu\text{g}/\text{m}^3$), an increase of 6.2% (95% confidence interval = 0.1, 12.8) was observed. The estimates of pollutant effects and their standard deviations were slightly affected by the degree of smoothing temporal variations in this study. When low collinearity was present, the 2-pollutant models provided acceptable estimates of pollutant effects. They suggested that the ozone effect was independent of the Black Smoke effect, and that the effects of sulfur dioxide and nitrogen dioxide were unlikely to be confounded by ozone concentrations. However, high collinearity leads to large estimates of the pollutant coefficient variances and, therefore, leads to inaccurate estimates of pollutant effects. The analysis of the contributory effects of different pollutant mixtures requires further investigation in those instances in which high collinearity between pollutants is present.

<Key words: air pollution, French cities, mortality, nitrogen dioxide, ozone, PM₁₃, short-term effects, sulfur dioxide>

HAUTE-NORMANDIE is one of the most industrialized areas in France, characterized by major and diversified industrial activities located mainly in the cities of Rouen and Le Havre along the Seine River. The inherent air pollution of these industrial activities can have harmful effects on the environment and on the health of

those who live in these cities. There have been important efforts by the industrial sector to reduce air pollution and development in the use of nuclear energy, the result of which has been a decrease in sulfur dioxide (SO₂) levels of more than 60% since 1980. Levels of nitric oxides (NO_x) have also been reduced. However, the

increase in road traffic has caused levels of photo-oxidants in air pollution to rise.

Although air pollution levels in most industrialized countries have declined, several epidemiological studies have shown short-term associations between relatively low levels of air pollution and mortality.¹⁻⁴ In Europe, the Air Pollution on Health: European Approach (APHEA) study^{5,6} examined the short-term effects of air pollution on mortality and hospital admissions in a multicity context and permitted a standardization of protocols. Fifteen European cities participated in this study, including the 2 French cities of Paris⁷ and Lyon.⁸ The combined analysis of this study^{9,10} confirmed a consistency in the associations between air pollution and daily mortality, despite the fact that there was a wide range of climates and environmental and population characteristics. In France, apart from the 2 earlier-mentioned studies (which followed the standardized APHEA approach), few studies were carried out, and those that were occurred mainly in Paris.¹¹⁻¹³ However, investigators used various methodological approaches that made comparison of their results with those provided by other studies difficult.

In the current study, we sought to evaluate the short-term associations between acid-particulate and photo-oxidant air pollution and daily mortality in the cities of Rouen and Le Havre. We used the same protocol of data collection and statistical analysis. The study was part of a national epidemiological surveillance system set up by the Institute de Veille Sanitaire subsequent to 1997 in 9 French cities.

Materials and Method

Study areas. Rouen is located 120 km to the northwest of Paris. It extends over a surface of 332.5 km² and, according to the 1990 census, it contained approximately 430,000 inhabitants. Sources of pollution are mainly industrial, particularly for SO₂ (93% of emissions result from industrial activities). Le Havre has a surface area of about 200 km², and in 1990 it was inhabited by approximately 260,000 individuals. It is located on the right bank of the estuary of the Seine River, 90 km downstream from Rouen and 220 km from Paris. Industrial activities are also responsible for more than 90% of SO₂ and NO emissions. The temperature is similar in the 2 cities; the mean temperature during the study period was approximately 12 °C (i.e., 8 °C in winter, 16 °C in summer). Relative humidity varied between 70% in summer and 81% in winter.

Environmental data. In each city, a permanent automated air-pollution network provided air-pollution data. SO₂ was measured by ultraviolet fluorescence techniques; particulate matter with an aerodynamic diameter of ≤ 13 μm (PM₁₃) was measured by radiometry; Black Smoke (BS) by reflectometric; nitrogen dioxide (NO₂) by chemiluminescence; and ozone (O₃) by ultraviolet absorption. We constructed exposure indicators by calculating the arithmetic mean of daily concentrations recorded by the ambient urban stations selected in each city (i.e., stations not directly influenced by industrial or

road traffic sources of pollution). For O₃, the 8-hr arithmetic mean (i.e., 9:00 A.M.–5:00 P.M.) in summer season was retained. If a pollutant was selected, the ambient urban stations must have been sufficiently correlated (i.e., correlation ≥ .70) and must have had sufficiently similar mean levels of pollution. The most ambient urban stations selected in this study complied with these two conditions. Indeed, among the stations selected in Rouen, 2 stations measured levels of SO₂, NO₂, and PM₁₃, and 3 measured levels of BS. The difference between the daily levels of pollutants recorded by these stations ranged from 1 μg/m³ for BS to 5 μg/m³ for PM₁₃. The correlation between these daily measurements ranged from 0.72 for BS to 0.85 for SO₂. In Le Havre, 2 stations were chosen for SO₂ and NO₂, and 3 were chosen for BS and PM₁₃. The difference between the daily levels of pollution recorded by these stations ranged from 4 μg/m³ for NO₂ to 12 μg/m³ for PM₁₃. The correlation ranged from 0.52 for NO₂ to 0.81 for SO₂. In both cities, 3 stations measured O₃ levels. However, only 1 station (i.e., 1 suburban station in Rouen and 1 urban station in Le Havre) was retained in each city because of its availability during the study period.

Following a missing value estimation procedure,⁵ the remaining percentage of missing values was lower than 2%. The period of exposure indicator availability varied from one pollutant to another and from one city to another between 1990 and 1995. Weather data, temperature, and relative humidity were obtained from METEO FRANCE during the period between 1990 and 1995.

Health data. Mortality data during the 1990–1995 period were provided by the National Institute of Health and Medical Research, which carries out the coding of the medical causes of death according to the International Classification of Diseases, ninth revision (ICD-9). We considered all deaths except those from accidental causes (ICD-9 codes < 800), nontumor respiratory causes (ICD-9 codes 460-519), and cardiovascular causes (ICD-9 codes 390-459) recorded according to the area of residence of the deceased. During the period between 1990 and 1995, 21,853 deaths were recorded in Rouen, including 6,630 (30.3%) cardiovascular deaths and 1,554 (7.1%) respiratory deaths. In Le Havre, 13,885 deaths were recorded for the same period, including 4,199 (30.2%) cardiovascular deaths and 959 (6.9%) respiratory causes of death. The percentage of deaths in the at-least-65-yr age group was approximately 70% in each city during the study period.

Influenza data were provided by the Teleprocessing National Network of monitoring and information on the Transmissible Diseases during the period 1990–1995.

Method

The principle of the generalized additive models (GAM) has been described previously in the literature.^{14,15} These models extend the generalized linear models (GLM), which were defined by McCullagh and Nelder,¹⁶ who used nonparametric smoothing functions to relate the response variable to the predictors. A GLM model primarily comprises a systematic component,

which relates the mean of the response variable $\mu = E[Y]$ to the sum of linear predictors via a link function g and a random component where it is supposed that response Y has a probability distribution from an exponential family. This approach implies that the variance of Y depends on the mean through a variance function V :

$$g(E[Y]) = g(\mu) = \beta_0 + \beta_1 x_1 + \dots + \beta_p x_p \quad \text{var}(Y) = \phi V(\mu), \quad (1)$$

where ϕ is a constant known as a dispersion parameter.

In a GAM model, the linear terms are replaced by a nonparametric smoothing function, f_i :

$$g(E[Y]) = g(\mu) = \beta_0 + \beta_1 f_1(x_1) + \dots + \beta_p f_p(x_p). \quad (2)$$

The primary smoothing functions used are Kernel smoothing functions, Spline smoothing functions, and moving regression smoothers (LOESS). In this study, we used LOESS.¹⁷

The GAM models have aroused considerable interest in air pollution epidemiology. They provide important information about the shape of the dependence between health outcome (i.e., mortality) and environmental covariates (i.e., temperature, relative humidity, and air pollution). They have made it possible for us to adequately control the influence of weather covariates and their interaction, to test the existence of a threshold effect of the studied pollutant, and to optimally adjust temporal variations.¹⁸

Mortality data used in this study were count data. The mean number of deaths per day in cities of average size, like Rouen and Le Havre, ranged from 0.4 for respiratory mortality to 10 for total mortality. The use of the Poisson distribution ($g[\mu] = \log[\mu]$, $\text{var}[Y] = \mu$) appears reasonable in our context. Count data often exhibit an overdispersion, compared with a Poisson assumption ($f = 1$). A simple way for us to model this situation is to allow the variance function to have a multiplicative dispersion parameter. Regression parameters are estimated, as described earlier; however, their standard deviations are corrected according to this dispersion parameter. Such a correction can be estimated by Pearson's χ^2 , divided by its number of degrees of freedom.¹⁶

When we took these parameters into consideration, the final model resulted in a Poisson regression model in which nonparametric smoothing functions were used and overdispersion control was used. It included LOESS function, with a reasonable degree of smoothing (span) that was based on graphical output for the following: time to control temporal trends and seasonal variations; influenza covariate to control the influence of influenza epidemic; and temperature and relative humidity, or possibly their interaction, to control their short-term effect on mortality. Binary variables for day of the week and holidays were also introduced. Finally, LOESS function for air pollutant(s) was introduced, therefore affording us the opportunity to test whether the relationship with mortality showed a threshold and to graphically visualize the shape of this relationship. For each covariate, various lags were evaluated. The choice of the best lag was based on statistical criteria (t test) and on the coherence of the results between these various lags. To

examine the effect of smoothing temporal variations on the estimates of air pollutant effects, we tested different spans. The preferred span provided a small Akaike Information Criterion (AIC),¹⁹ and there was little evidence of over- or underfitting in the residual autocorrelation function.

Plot of the residuals over time, as well as both autocorrelation and partial autocorrelation function plots, provided suitable tools for the examination of any remaining patterns in the residuals, and they also provided mechanisms with which to check large residual autocorrelations that may indicate discrepancies with the model fit. To test the influence of the remaining serial correlation on pollutant effects, we introduced autoregressive terms (i.e., inclusion of lagged working residuals of the final model as covariates) in the final model.

Results

Air pollution and mortality indicator statistics for each city are presented in Table 1. Seasonal values are also presented. With the exception of O_3 levels, levels of air pollution were higher in winter than in summer. Mean levels of air pollution are relatively similar in the two cities, except for O_3 levels, which were greater in Rouen than in Le Havre. The daily mean numbers of deaths were approximately 10 for total mortality (maximum = 24), 3 for cardiovascular mortality (maximum = 14), and 0.71 for respiratory mortality (maximum = 6) in Rouen. In Le Havre, the respective values were 6.34 (maximum = 18), 1.92 (maximum = 8), and 0.44 (maximum = 6). The daily number of deaths was somewhat elevated, particularly for respiratory mortality, with 50% of zero-death days over the study period. Correlations among air pollutants were relatively high (Table 2). In Rouen, the weakest correlation was observed between O_3 and PM_{10} (-0.18), and the strongest correlation existed between BS and NO_2 (0.77). In the city of Le Havre, the respective values were -0.06 (O_3 and SO_2) and 0.70 (BS and PM_{10}). The correlations between air pollution and weather covariates were lower.

The nonparametric smooth plot of relative risk for cardiovascular mortality and 95% confidence intervals versus NO_2 (left box) and minimum temperature (right box), after we controlled for covariates in Rouen, are shown in Figure 1. In Figure 1, there is no indication that a threshold in the relationship between NO_2 and cardiovascular mortality exists, and that the shape of this relationship is approximately logarithmic. On the basis of the same graphical dose-response relationship plot, some associations were strengthened by a logarithmic transformation of the pollutant covariate. With respect to minimum temperature, the nonparametric smooth plot indicated a high risk of cardiovascular mortality at both low and high temperatures.

The percentage increase in mortality and 95% confidence limits for an interquartile range (IQR) increase of daily levels of air pollutants in Rouen and in Le Havre are shown in Table 3. The lags between exposure to air pollutants and excess mortality are also presented in Table 3. In Rouen, significant associations were ob-

Table 1.—Statistical Summary of Air Pollutant and Mortality Indicators in the Cities of Rouen and Le Havre

Pollutant or mortality indicator	Rouen			Le Havre		
	Summer	Winter	Total	Summer	Winter	Total
	<i>07/91–12/95</i>			<i>01/90–12/95</i>		
Nitrogen dioxide*						
P25	22.94	29.20	25.26	23.35	29.08	25.88
P75	37.28	47.15	42.17	41.36	49.74	46.03
Mean	30.73	38.94	34.82	34.01	40.63	37.27
	<i>11/91–12/95</i>			<i>01/92–12/95</i>		
Sulfur dioxide*						
P25	14.68	20.75	17.61	9.32	13.68	11.25
P75	30.52	43.92	36.39	29.75	39.75	35.62
Mean	23.83	35.36	29.70	27.83	39.66	33.72
	<i>10/90–12/95</i>			<i>02/91–12/95</i>		
Black Smoke*						
P25	8.03	11.33	8.79	7.78	9.17	8.33
P75	16.67	30.28	23.00	16.00	25.96	19.84
Mean	13.04	23.75	18.65	12.59	20.22	16.32
	<i>01/90–07/94</i>			<i>01/90–4/93</i>		
PM ₁₃ *						
P25	18.91	19.88	19.21	21.08	22.00	21.54
P75	35.63	46.65	39.76	44.26	46.58	45.42
Mean	28.92	36.91	32.87	35.10	37.51	36.37
	<i>04/91–12/95</i>			<i>05/92–12/95</i>		
Ozonet						
P25	60.50	22.81	38.75	44.76	16.25	27.88
P75	94.13	55.00	77.13	73.63	41.65	61.13
Mean	79.62	39.67	60.57	62.63	29.78	46.85
	<i>Mean of:</i>					
Total mortality	9.58	10.37	9.97	6.00	6.67	6.34
Cardiovascular mortality	2.83	3.23	3.03	1.78	2.06	1.92
Respiratory mortality	0.60	0.81	0.71	0.36	0.51	0.44

Notes: PM₁₃ = particulate matter with an aerodynamic diameter ≤ 13 μm; P25 = 25th percentile, and P75 = 75th percentile. Summer months: April–September; winter months: October–March.

*Mean: 24 hr (μg/m³).

Table 2.—Correlation Matrix between Environmental Indicators in Rouen and Le Havre

Environmental indicator	Pollutant indicators					Weather indicators	
	NO ₂	SO ₂	BS	PM ₁₃	O ₃	Relative humidity	Minimum temperature
NO ₂	1.00	0.54	0.77	0.70	-0.25	0.05	-0.48
SO ₂	0.57	1.00	0.54	0.47	-0.30	0.13	-0.37
BS	0.62	0.67	1.00	0.73	-0.36	0.15	-0.44
PM ₁₃	0.58	0.68	0.70	1.00	-0.18	-0.04	-0.43
O ₃	-0.19	-0.06	-0.23	0.11	1.00	-0.62	0.49
Relative humidity	-0.04	-0.14	-0.08	-0.21	-0.50	1.00	-0.10
Minimum temperature	-0.30	-0.26	-0.46	-0.30	0.45	-0.07	1.00

Notes: The upper triangular correlation matrix corresponds to the correlation between environmental indicators in Rouen, and the lower one corresponds to indicators in Le Havre. NO₂ = nitrogen dioxide, SO₂ = sulfur dioxide, BS = Black Smoke, PM₁₃ = particulate matter with an aerodynamic diameter of ≤ 13 μm, and O₃ = ozone.

served with the 3 mortality indicators. With respect to total mortality (all causes except accidental), the strongest association was observed in summer with O₃ for a 0–2-day lag (daily mean of current and the 2 previous days). An IQR increase (60.5–94.1 µg/m³) was associated with an increase of 4.1% (95% confidence interval [CI] = 0.6, 7.8%) in total mortality. Sulfur dioxide, with a 0–2-day lag (IQR increase = 17.6–36.4 µg/m³), was also associated with an increase of 8.2% (95% CI = 0.4, 16.6) in respiratory mortality. Finally, an increase of 6.1% (95% CI = 1.5, 10.9%) in cardiovascular mortality was observed with an IQR increase of NO₂ (25.3–42.2 µg/m³) for a 0–1-day lag. Positive associa-

tions were also observed with BS and PM₁₃ with the 3 mortality indicators, but they were not statistically significant at the 5% significance level. For Le Havre, significant associations were observed between cardiovascular mortality and daily levels of acid-particulate air pollution. An IQR increase in daily levels of SO₂ (11.3–35.6 µg/m³) was associated with an approximate increase of 3% (95% CI = 0.8, 5) in cardiovascular mortality. For PM₁₃ (IQR increase = 21.5–45.4 µg/m³), an increase of 6.2% (95% CI = 0.1, 12.8) was observed. We observed these associations for a 1-day lag. Although not statistically significant at the 5% significance level, positive associations were also observed with BS, NO₂,

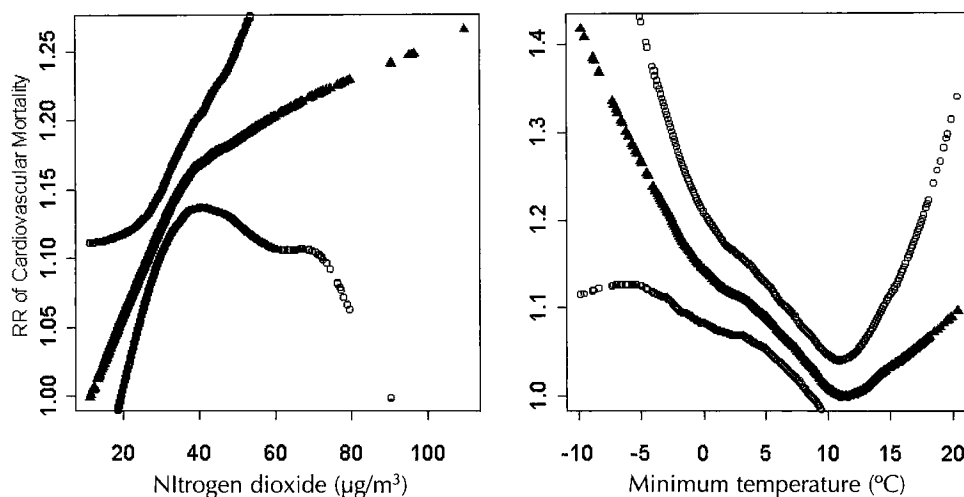


Fig. 1. Smoothed plot of relative risk and 95% confidence intervals of cardiovascular mortality related to nitrogen dioxide (0–1 lag [left box]) and minimum temperature (right box) in Rouen, France. The model contains an intercept term, LOESS smoother for temporal variations, indicators for day of week and holidays, and LOESS smoother for influenza and relative humidity.

Table 3.—Percentage Increase in Mortality and 95% Confidence Intervals (CIs) for an Interquartile Range Increase of Daily Levels of Air Pollutants in Rouen and Le Havre

Pollutant	Total mortality			Cardiovascular mortality			Respiratory mortality		
	% increase in mortality	95% CI	Lag (day[s])	% increase in mortality	95% CI	Lag (day[s])	% increase in mortality	95% CI	Lag (day[s])
<i>Rouen</i>									
BS	0.5	-1.8, 2.9	1	4.0	-0.4, 8.5	1	2.9	-5.6, 12.2	0–1
PM ₁₃	0.5	-1.1, 2.1	1	2.2	-0.6, 5.0	1	3.7	-1.2, 9.0	0–1
SO ₂	1.5	-0.7, 3.9	2	1.6	-2.2, 5.6	0	8.2	0.4, 16.6	2
NO ₂	2.3	0.0, 4.5	0–3	6.1	1.5, 10.9	0–1	1.7	-5.7, 9.7	1
O ₃	4.1	0.6, 7.8	0–2	5.3	-1.0, 12.0	0–2	7.2	-3.7, 19.3	1
<i>Le Havre</i>									
BS	0.3	-1.6, 2.2	0–1	1.9	-1.6, 5.6	0–3	2.9	-3.7, 9.9	0–1
PM ₁₃	1.9	-0.8, 7.4	1	6.2	0.1, 12.8	1	4.9	-4.3, 15.0	2
SO ₂	0.9	-0.3, 2.1	1	2.9	0.8, 5.0	1	8.7	-3.0, 21.9	0–1
NO ₂	1.0	-1.5, 3.5	1	2.9	-1.5, 7.6	1	7.8	-1.9, 18.5	0–1
O ₃	2.9	-0.4, 6.3	2	6.7	-0.9, 14.9	0–1	6.4	-7.2, 22.0	2

Notes: BS = Black Smoke, PM₁₃ = particulate matter with an aerodynamic diameter of ≤ 13 µm, SO₂ = sulfur dioxide, NO₂ = nitrogen dioxide, and O₃ = ozone.

and O₃. We adjusted these results for overdispersion; however, the daily counts of mortality did not exhibit a large degree of overdispersion in this study and, consequently, the correction was minor and did not affect the results substantially.

The effect of smoothing temporal variations on estimates of pollutant effects and their standard deviations are shown in Table 4. The AIC criterion decreased with increased smoothing (increased Span), until it reached a minimum. Additional smoothing slightly increased the AIC. Smoothing temporal variations, with span values below 0.15 (size of smooth window), caused over-

fitting, as reflected by more negative autocorrelations. Nevertheless, the estimates of pollutant effects and their standard deviations were affected slightly by the degree of smoothing in this study.

Graphical analysis of the residuals for the final models did not reveal apparent seasonal patterns. The autocorrelation check of residuals indicates a small amount of residual autocorrelation. The effect of adding autoregressive terms for some lags with greatest residual autocorrelation (< |0.07|) is presented in Table 5; the results were barely affected.

Table 6 shows the results of the 2-pollutant models

Table 4.—Influence of the Degree of Smoothing Temporal Variations on the Estimates of Air Pollutant Effects—Cardiovascular Mortality

City	Pollutant	Lag (day[s])	Span	Coefficient*	SE	t test	AIC
Rouen	NO ₂	0–1	0.10	0.125734	0.048442	2.60	1,854.64
			0.15	0.126917	0.048510	2.62	1,851.65
			0.20	0.128309	0.048532	2.64	1,849.95
			0.25	0.128235	0.048552	2.64	1,848.68
			0.40	0.119960	0.048624	2.47	1,849.26
Le Havre	SO ₂	1	0.10	0.001191	0.000431	2.77	1,642.13
			0.15	0.001160	0.000430	2.70	1,634.92
			0.20	0.001162	0.000430	2.70	1,630.27
			0.25	0.001167	0.000430	2.71	1,629.65
			0.40	0.001167	0.000431	2.71	1,630.39

Notes: NO₂ = nitrogen dioxide, SE = standard error, SO₂ = sulfur dioxide, and AIC = Akaike Information Criterion. NO₂—log transformation; SO₂—linear; and Span—size of the smooth window.

*Estimate of pollutant effects on cardiovascular mortality.

Table 5.—Influence of Adding Autoregressive Terms in the Models on the Estimates of Air Pollutant Effects

Mortality indicator	Pollutant	Lag (day[s])	Coefficient*	SE	t test
<i>Rouen</i>					
Cardiovascular	NO ₂	0–1	0.126917	0.048510	2.62
		Plus AR (4)	0.125560	0.048724	2.58
Total	O ₃	0–2	0.103322	0.045427	2.27
		Plus AR (1)	0.104234	0.045909	2.27
Respiratory	SO ₂	2	0.004454	0.002151	2.07
		Plus AR (5)	0.004351	0.002165	2.01
<i>Le Havre</i>					
Cardiovascular	SO ₂	1	0.001167	0.000430	2.71
		Plus AR (4)	0.001207	0.000429	2.82
	PM ₁₃	1	0.081100	0.040909	1.98
		Plus AR (2)	0.081154	0.041036	1.98

Notes: NO₂ = nitrogen dioxide, SO₂ = sulfur dioxide, O₃ = ozone, SE = standard error, PM₁₃ = particulate matter with an aerodynamic diameter of ≤ 13 μm, and AR = autoregressive term (lag appears within parentheses that follow this term). In Rouen: NO₂ = log transformation, O₃ = log transformation, and SO₂ = linear. In Le Havre: SO₂ = linear, and PM₁₃ = log transformation.

*Estimate of pollutant effects on mortality.

when air pollutant measurements were available simultaneously for the same period. Globally, these results suggest that the higher the correlation between the coefficient estimates (high collinearity), the higher the inflation of coefficient standard deviations. In Rouen, the 2-pollutant models—including O₃ and BS, O₃ and SO₂, or O₃ and NO₂—indicated a relatively low correlation between the coefficient estimates (low collinearity). The inflation of the coefficient standard deviations was relatively low in these models and ranged from 1.48 to 4.36%—results that reflected relatively stable coefficient estimates. In these models, the O₃ effect on total mortality was reduced slightly (–8.77%), but it remained significant when modeled simultaneously with BS. The effect of SO₂ on respiratory mortality was also reduced slightly (–2.76%) and remained significant when it was introduced in the same model with O₃. Similarly, modeling NO₂ and O₃ simultaneously indicated that NO₂ effects on cardiovascular mortality were relatively unchanged (+3.3%) and remained significant. In Le Havre, low collinearity was observed between O₃ and the 4 other measured pollutants (SO₂, NO₂, BS, and PM₁₀). However, the 2-pollutant models had not been tested because data were not available simultaneously for the same period. In both cities, a relatively high collinearity was observed between SO₂, BS, and NO₂, as well as between NO₂ and particulates (e.g., BS, PM₁₀). Although the percentage changes of the coefficient estimates were slight for some models, they remained unstable, as indicated by a large increase in their coefficient standard deviations.

Discussion

The existence of a permanent, automated, air-pollution network that has measured continuously over several years allowed the authors to investigate the associations between daily levels of air pollution and mortality data. First, the effects of various gaseous (SO₂, NO₂, and O₃) and particulate (BS, PM₁₀) pollutants were estimated in the 2 cities. Second, the effect of smoothing temporal variations and of the remaining serial correlation on the estimates of pollutant effects was examined. Third, we examined the 2-pollutant models to examine the specific pollutant effects.

Excess mortality was associated consistently with particulate pollutant levels and/or SO₂, as shown by the results of several earlier studies.^{8,9,20-23} In this study, although the associations of particulates and SO₂ with total mortality were not significant statistically, positive and significant associations were observed between SO₂ and respiratory mortality in Rouen, as well as between both pollutants and cardiovascular mortality in Le Havre. Several earlier time-series studies have produced similar associations between cardiovascular mortality and particulates.^{2,8,21,24}

Ozone was also associated with the daily number of all-cause mortality in Rouen. The few previous studies that have investigated the short-term effects of O₃ on mortality yielded results that varied. Significant effects have been reported for Los Angeles, New York, Philadelphia,^{25,26} and several European APHEA cities,¹⁰ but such effects have not been noted for several other

Table 6.—The 2 Pollutant Models of the Association between Mortality and Air Pollution in Rouen and Le Havre

Variable	Pollutant	Lag (day[s])	Coefficient*	SE	t test	Correlation coefficient†	Change in coefficient (%)	Change in SE (%)
<i>Rouen</i>								
Total mortality	O ₃ plus BS	0–2‡	0.103322	0.045427	2.27			
		0–2	0.094261	0.046245	2.04	–.15	–8.77	1.80
Cardiovascular mortality	NO ₂ plus BS plus O ₃	0–1	0.126917	0.048510	2.62			
		0–1	0.129540	0.077170	1.68	–.78	2.07	59.08
		0–1	0.131105	0.050625	2.59	.25	3.30	4.36
Respiratory mortality	SO ₂ plus BS plus NO ₂ plus O ₃	2	0.004454	0.002151	2.07			
		2	0.004545	0.002368	1.92	–.42	2.05	10.07
		2	0.004920	0.002367	2.08	–.42	10.46	10.05
		2	0.004331	0.002183	1.98	.15	–2.76	1.48
<i>Le Havre</i>								
Cardiovascular mortality	SO ₂ plus NO ₂ plus BS plus PM ₁₀ plus NO ₂	1	0.001167	0.000430	2.71			
		1	0.001266	0.000554	2.28	–.63	8.46	28.84
		1	0.001303	0.000564	2.31	–.65	11.62	31.12
		1	0.081100	0.040909	1.98			
		1	0.065420	0.047336	1.38	–.49	–19.33	15.71

Notes: SE = standard error, O₃ = ozone, NO₂ = nitrogen dioxide, BS = Black Smoke, SO₂ = sulfur dioxide, and PM₁₀ = particulate matter with an aerodynamic diameter of ≤ 13 μm. In Rouen: NO₂ = log transformation, O₃ = log transformation, and SO₂ = linear. In Le Havre: SO₂ = linear, and PM₁₀ = log transformation.

*Estimate of pollutant effects on mortality.

†Correlation between coefficients of pollutant effects in the 2-pollutant models.

cities.^{8,27,28} However, considerable evidence exists in support of the fact that O₃ is related with morbidity indicators for respiratory disease²⁷ (e.g., hospital admissions, reduction in lung function).

Nitrogen dioxide was also related to cardiovascular mortality in Rouen. A similar association was observed in Los Angeles.²⁹ A significant association was also reported with total mortality in Santiago, Chile.²¹ No significant associations, however, were found in 3 of 6 APHEA cities.¹⁰ Therefore, the results concerning the association between NO₂, as well as O₃, and mortality are inconsistent in the literature.

Relative risks estimated in this study were robust in the sense that they were estimated (after controlling for potential sources of confounding [long-term and seasonal variations, influenza epidemics, weather conditions]), and statistical analysis accounted for the nature of mortality data. Moreover, we used nonparametric smoothers for day of study to adjust for temporal trends and variations in mortality, and we found that in both Rouen and Le Havre the estimates of pollutant effects were slightly affected by the degree of smoothing. Graphical analysis and autocorrelation check of the residuals for the adjusted final models did not indicate seasonal pattern or large residual autocorrelation. The addition of autoregressive terms for some lags with greatest residual autocorrelation barely affected our results, indicating that we may consider the residuals as white noise.

The mean levels of air pollution were relatively similar in the 2 cities. However, given that O₃ is cleaned by NO emitted by traffic, mean levels registered in the urban station in Le Havre were less than levels at the suburban station in Rouen. The main sources of SO₂ in both cities were petrochemical sites, thermal power stations, and chemical factories. Nitrogen dioxide, generally produced by road-traffic pollution, was mainly emitted by industrial sources in Le Havre (90%). NO₂ emissions, however, were divided between industrial and automobile sources in Rouen. Particles were emitted by vehicles and by some industrial processes (e.g., metallurgy, cement factory, combustion installation). As is the case in most industrial areas, the primary industrial origin of these pollutants resulted in a high correlation between them, which led to a collinearity problem when these pollutants were included simultaneously in the same regression model; therefore, estimates of regression coefficients and their standard deviations are sometimes inaccurate.³⁰ In Rouen, low collinearity of BS, NO₂, and SO₂ with O₃ was observed and, therefore, acceptable estimates of pollutant effects were provided by the 2-pollutant models. The estimate of the O₃ effect on total mortality from the model that included BS remained persistent and significant and suggested that the O₃ effect was independent from the BS effect. The estimate of the NO₂ effect on cardiovascular mortality, as well as the effect of SO₂ on respiratory mortality, also remained persistent and significant—despite being modeled with O₃. This fact suggests that the effects of both pollutants were most likely *not* confounded by O₃ concentrations. Similar results were observed in the Philadelphia²⁶ and European APHEA studies,¹⁰ but not in

the Mexico City study.³¹ In both Rouen and Le Havre, fitting a model with 2 (or more) highly correlated pollutants produced an inaccurate estimate of pollutant effects, as reflected by their large standard deviations.

Mortality data were available for a period of 4–6 yr in the 2 study locations. However, in view of the mid-sized populations studied, a small daily number of deaths were observed daily, particularly for respiratory mortality, which was associated with relatively large confidence intervals. We were also unable to study pollutant effects in population subgroups, such as elderly individuals, who may be at greater risk, as suggested by some studies.^{32,33}

The results observed in this study, as in all time-series studies, must be interpreted in terms of excess risk of premature deaths. Indeed, the toxic effects of inhaled air pollutants can be sufficient to cause premature deaths of people rendered vulnerable by preexisting diseases, such as advanced cardiorespiratory diseases, which principally characterize older people (i.e., as was the case in our study). This degree of premature death, called “harvesting effect,” cannot be determined by this type of study, but it has been discussed widely in the literature.^{34–37} Inasmuch as this type of study is observational, the absolute proof of individual pollutant-cause of death association is not attainable. However, the probability that our results, as well as results from other time-series studies, may have occurred by chance is small. The most persuasive argument is that in various studies, investigators have reported positive findings that have been reported in different studies for which various methods in the wide range of climates and environmental and population characteristics have been used. In addition, there has been a degree of coherence across various health indicators and various types of investigations.³⁸ Moreover, plausible biological mechanisms underlying these epidemiological observations were also postulated.^{39–43}

In conclusion, analysis of mortality among the populations of Rouen and Le Havre from 1990 to 1995 revealed an increase in deaths relative to air pollutant levels. In Rouen, the strongest association occurred between SO₂ and respiratory mortality, followed by NO₂ and cardiovascular mortality, and subsequently O₃ and total mortality. In Le Havre, the associations observed between both SO₂ and PM₁₀ and cardiovascular mortality were the most significant. These associations were robust in the sense that they were minimally affected by the degree of smoothing that we used to control for temporal trend and for seasonal variations, as well as by addition of autoregressive terms in the models. When low collinearity was present, the 2-pollutant models provided an acceptable estimate of pollutant effects. The models suggested that the O₃ effect was independent of the BS effect, and it was unlikely that the effects of SO₂ and NO₂ were confounded by O₃ concentrations. However, high collinearity leads to large estimates of the pollutant coefficient variances and, therefore, to an inaccurate estimate of pollutant effects. The analysis of the contributory effects of different pollutant mixtures requires further investigation if high collinearity between pollutants is present.

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This study benefitted from a grant from the 'Institut de Veille Sanitaire.'

The authors thank Air Normand for providing environmental data and Mr. Richard Medeiros for his valuable advice in editing the manuscript.

Submitted for publication October 18, 1999; revised; accepted for publication September 19, 2000.

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