

BRIEF REPORT

Particles, and not gases, are associated with the risk of death in patients with chronic obstructive pulmonary disease

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Objectives	We aim to assess the independent association of particles, after controlling for gaseous pollutants, with the risk of death among a cohort of patients with chronic obstructive pulmonary disease (COPD).
Methods	Residents of Barcelona, aged over 35 years, who attended emergency room services for COPD exacerbation from 1985 to 1989 and who died in the period 1990–1995 (n = 2305) were selected. The analysis followed a case-crossover procedure with ambidirectional controls. Air pollution exposure (particulate matter <10 µm (PM ₁₀), ozone, nitrogen dioxide and carbon monoxide) was measured at the city monitoring stations.
Results	Levels of PM ₁₀ (odds ratio for the interquartile difference = 1.11, 95% CI : 1.00–1.24), but not gaseous pollutants, were associated with mortality for all causes of death after adjusting for meteorological variables and influenza epidemics. In the two-pollutant models, the association of mortality with PM ₁₀ was not confounded by the inclusion of gases, while the association of gaseous pollutants was notably reduced after adjustment for particles. There was no interaction between particles and gaseous pollutants.
Conclusions	Findings reinforce the deleterious role of urban particles as a trigger of death in COPD patients, and suggest that they are the major culprit among the air pollutants. The role of other pollutants, if any, was additive and not multiplicative.
Keywords	Air pollution; lung diseases, obstructive; mortality; particles
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In a previous study, we found that particle levels (measured as black smoke) were associated with mortality in a cohort of chronic obstructive pulmonary disease (COPD) patients, using a case-crossover analysis.¹ This study provided individual estimates of risk in a cohort of patients suffering from COPD instead of the ecological associations reported by epidemiological studies using time-series in the general population.² However, we used black smoke, which was a poor indicator of fine particles and we did not assess other pollutants such as nitrogen dioxide (NO₂) or ozone (O₃), which have been found to play a synergistic role with particles in some studies.^{3,4} We aim to assess the independent association of particles after

controlling for gaseous pollutants, as well as the independent association of gases, in the risk of death among a cohort of patients with COPD. In addition, we have access to daily measures of small particles to improve the measurement of particles.

Materials and Methods

Characteristics of how cases were defined and recruited have been explained elsewhere.¹ Briefly, residents of Barcelona, aged over 35 years, who attended emergency room services for COPD exacerbation from 1985 to 1989, and who died during the period 1990–1995 (2305 individuals, 460 women and 1845 men) were included. Air pollution exposure was measured at the city monitoring stations, in a network including three samplers, which provided an average for the entire city. Details about the monitoring sites, the measurement methods, and the indicators can be found elsewhere.⁵ The 24-hour average levels of particulate matter (PM₁₀) were measured using the beta-radiation

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method, nitrogen dioxide (NO₂) and ozone (O₃) using a chemoluminescence method and carbon monoxide (CO) by infrared absorption. Results involving sulphur dioxide have already been reported¹ and were unrelated to mortality in this COPD population. The National Meteorological Institute collected daily information on average temperature and humidity from one station in the city and at the airport. Data on influenza epidemics were provided by the epidemiological surveillance services of the Barcelona city council.

The analysis followed a case-crossover procedure. Air pollution levels at the dates of death were compared with air pollution levels one week before and one week after death.¹ The association between mortality and particulate pollution was estimated by odds ratio (OR) using conditional logistic regression, which was run with the STATA statistical package (StataCorp, Texas). Odds ratios were calculated for the interquartile difference (between the 25th and the 75th percentile) of the distribution of each pollutant. Two-pollutant models were fit, including both pollutants in the same multivariate model, even though correlation between them could be strong. Interaction between the two pollutants was assessed by including the multiplicative term in the multivariate model. The lag structure was the cumulative lag over the two previous days (i.e. the average of the same and previous two days).

Case-crossover is limited in the adjustment of seasonality. With the selection of an ambidirectional 7-day control period, effect of long-term trend and day of the week were controlled,^{6,7} this strategy having been used previously.^{1,8,9} However, there is the potential for bias if there is any correlation between the exposure in the case period and the control periods. To evaluate bias due to selection of the control period, we have used a spectral plot and the Partial Autocorrelation Function (PACF) plot to assess the autocorrelation function. In addition, we have estimated the association changing the control period, and including day of the week as a covariate if the control period was not the same day of the week as the case period.

Results

Levels of PM₁₀, but not gaseous pollutants, were associated with mortality from all causes of death after adjusting for

meteorological variables and influenza epidemics (Table 1). Differences between case and control days for all pollutants followed a normal distribution. In the two-pollutant models, the association of mortality with PM₁₀ was not confounded by the inclusion of gases. There was no interaction between particles and gaseous pollutants (all interaction terms had a *P*-value > 0.5).

There was almost no bias for the coefficient of PM₁₀ (around 5% variation) when control periods at different lags up to 15 days (when no autocorrelation was observed) were assessed. The OR when the control period was 15 days was 1.106 (95% CI: 1.001–1.231).

Discussion

Of all the air pollutants, particles seem to play the most important role in increasing the risk of death among patients with COPD due to the strongest association in the one-pollutant models among all the pollutants for a similar exposure range, and the stability of the association in the two-pollutant models. Stratified analysis by season provided the same findings (data not shown). A promoting role of the effect of particles by the gaseous pollutants was not observed.

Multipollutant models have the problem of collinearity (high correlation between pollutants) which increased the standard errors.¹⁰ Therefore, the statistical cut-off of significance has less value in the two-pollutant models. In our study, the lowest correlation occurred between particles and O₃. Therefore, a model including particles and O₃ (Model 2) showed the lowest increase in standard error, and the association for particles remains the largest and statistically significant. An alternative way to treat collinearity is the use of factor analysis.⁹ However, we were unable to obtain clusters of pollutants (i.e. factors) with a clean separation of each pollutant in a single factor.

Nitrogen dioxide, CO and O₃ had no significant effect on the relative risk of death. However, given that measurement error of exposure (and underestimation of the effect) was probably larger for gases than for particles (due to a more heterogeneous geographical distribution),¹¹ caution in interpretation is needed.

We have investigated the acute effects of air pollution in the exacerbation of COPD in one of the few epidemiological studies

Table 1 Adjusted association (odds ratio and 95% CI^a) with mortality in patients with chronic obstructive pulmonary disease, Barcelona, 1990–1995

Pollutants	Interquartile range (µg/m ³) ^b	One-pollutant model	Two-pollutant models		
			Model 1	Model 2	Model 3
PM ₁₀	27	1.114 (1.000–1.240) ^c	1.105 (0.987–1.238)	1.129 ^c (1.028–1.240)	1.108 (0.936–1.115)
NO ₂ (24-h)	17	1.034 (0.983–1.070)	1.017 (0.945–1.095)	–	–
O ₃ (1-h)	21	0.979 (0.919–1.065)	–	0.939 (0.857–1.027)	–
CO (8-h)	4.5	1.052 (0.990–1.117)	–	–	1.017 (0.947–1.091)

^a Odds ratio for the interquartile difference, adjusted for temperature, humidity, hot days and influenza days.

^b Of the difference values between case and control days. Units are mg/m³ for CO.

^c *P* < 0.05.

Correlation coefficients of difference values between case and control days between PM₁₀ and NO₂ (24-h), O₃ (1-h), CO (8-h) were 0.70, 0.14 and 0.50, respectively.

including COPD patients. The present findings suggest that particles are the major culprit in the adverse health effects of air pollution in COPD patients. Potential mechanisms involved in the development of adverse effects in patients with COPD at such low mass concentrations of particles have been discussed.¹² The role of other pollutants, if any, was additive and not multiplicative.

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