RESEARCH REPORT

Air pollution and cardiovascular admissions association in Spain: results within the EMECAS project

F Ballester, P Rodríguez, C Iñiguez, M Saez, A Daponte, I Galán, M Taracido, F Arribas, J Bellido, F B Cirarda, A Cañada, J J Guillén, F Guillén-Grima, E López, S Pérez-Hoyos, A Lertxundi, S Toro, for the EMECAS group

J Epidemiol Community Health 2006;**60**:328–336. doi: 10.1136/jech.2005.037978

See end of article for authors' affiliations

Correspondence to: Dr F Ballester, Epidemiology and Statistics Unit, Escola Valenciana d'Estudis en Salut-EVES (Valencian School of Health Studies), c/Joaquín de Garay 21, 46017 Valencia, Spain; ballester_fer@gva.es

Accepted for publication 11 November 2005

Objective: To evaluate the short term effect of air pollution on cardiovascular admissions in 14 Spanish cities

Methods: The period under study was from 1995 to 1999. Daily emergency admissions for all cardiovascular diseases (CVD) and heart diseases (HD) were obtained from hospital records, and the corresponding daily levels of particulates, SO₂, NO₂, CO, and ozone were recorded. The magnitude of association was estimated using Poisson generalised additive models controlling for confounding and overdispersion. For each cause, lagged effects, up to three days, of each pollutant were examined and combined estimates were obtained. For ozone the analyses were restricted to the warm period. One and two pollutant models were performed.

Results: Associations were more consistent in lag 0 (concurrent day) and 1 (lag 0–1), except in the case of ozone where there was a more delayed relation (lag 2–3). For combined estimates an increase of 10 µg/m³ in the PM₁₀ levels in lag 0–1 was associated with an increase of 0.9% (95% CI: 0.4 to 1.5%) in the number of hospital admissions for CVD, and 1.6% (0.8 to 2.3%) for HD. For ozone the corresponding estimates for lag 2–3 were 0.7% (0.3 to 1.0) for CVD, and 0.7% (0.1 to 1.2) for HD. An increase of 1 mg/m³ in CO levels was associated with an increase of 2.1% (0.7 to 3.5%) in CVD admissions, and 4.2% (1.3 to 7.1%) in HD admissions. SO₂ and NO₂ estimates were more sensitive in two pollutant models

Conclusions: A short term association between increases in daily levels of air pollutants and the number of daily admissions for cardiovascular diseases, with specificity for heart diseases, has been described in Spanish cities.

Air pollution is a serious problem in the world today. It has been studied for many years following a series of dramatic episodes that took place in industrial countries in the mid-20th century. Renewed interest in this phenomenon is reflected by the number of studies that have been published since the beginning of the past decade, showing that—even within the usual ranges of pollution in developed countries—it still poses a health risk.¹

During this time several multisite studies have been carried out in different regions of the world providing strong evidence of the impact of air pollution on health. The APHEA study in Europe,^{2,3} and the NMMAPS in the USA,⁴ are two of the most influential studies in recent years. In Europe some national projects as in France⁵ or Italy⁶ have also been developed providing useful evidence for research and policy strategies. Within this context, the EMECAS project (acronym for Spanish multicentric study on the relation between air pollution and mortality) has evaluated the short term association between the levels of air pollution and mortality in Spain, analysing series from the early 1990s in 13 Spanish cities.^{7–10}

Cardiovascular diseases are one of the most important causes of poor health and death in the developed world. An increasing amount of evidence shows that the role of air pollution in causing cardiovascular damage is not negligible.¹¹ Moreover, experimental studies provide information on the potential mechanisms involved in this link.^{12,13} However, whereas many studies have evaluated the impact of pollution on mortality, the relation with hospital admissions has been less investigated.

Our Spanish project now includes the study of the relation between air pollution and the number of daily hospital admissions for cardiovascular and respiratory diseases. Therefore, its name has been changed to EMECAS (S stands for “Salud”, health instead of mortality). In this phase of the project a total of 16 cities, accounting for more than 10 million inhabitants, are participating (fig 1). More complete and updated data, both for outcomes and covariates, have been collected, thus enabling us to adequately control for confounding and explore the potential causes of heterogeneity. In this paper we present the results for the association between air pollution and cardiovascular admissions within the EMECAS project.

METHOD

The cities participating in this study were: Barcelona, Bilbao, Cartagena, Castellón, Granada, Gijón, Huelva, Madrid, Oviedo, Pamplona, Seville, Valencia, Vigo, and Zaragoza, as complete data on hospital admissions were not available in the two cities in the Canary Islands (Las Palmas and Santa Cruz de Tenerife). In general, the study period was from 1995 or 1996 to 1999; although in Oviedo and Gijón it started in 1993. The number of daily emergency admissions with primary diagnosis for all cardiovascular diseases (9th International Classification of Diseases, ICD-9: 390–459) and heart diseases (ICD-9: 410–414, 427, 428) in each city and

Abbreviations: CVD, cardiovascular disease; HD, heart disease; O₃, ozone; TSP, total suspended particle; BS, black smoke; CO, carbon monoxide; SO₂, sulphur dioxide; NO₂, nitrogen dioxide

Figure 1 Cities participating in the EMECAS project.

among residents in the city was obtained from hospital records (table 1). Discharge diagnoses were used to classify each admission.

We collected data on air pollutants from the air pollution networks in each city and constructed variables for daily levels (24 hour average) of black smoke (BS), total suspended particles (TSP), particles smaller than $10\ \mu$ (PM_{10}), sulphur dioxide (SO_2), and nitrogen dioxide (NO_2); and the daily eight hour maximum moving average for carbon monoxide (CO) and ozone (O_3). A standardising data collection procedure was followed: (a) geographical location of the monitoring stations: only urban monitoring sites were considered; (b) completeness criteria for each pollutant: only those stations with data for more than 75% of the whole study period were considered, with a minimum of three sites for each pollutant, except ozone with two sites; (c) missing

values in one station were estimated by a regression model based on the values of the remaining stations, allowing also for seasonal variability. Despite the fact that every city had at least valid measurements for particulate matter, the different indicators used—that is, BS, TSP, or PM_{10} —did not allow for a common general indicator. To find out about potential differences in their impact on health we decided to maintain the original indicators separately.

Meteorological data (temperature, relative humidity, and barometric pressure) were obtained from the corresponding centres of the National Meteorological Institute. The variables used in the analysis were mean daily values of each meteorological condition. The weekly incidence of influenza was obtained from the surveillance systems of the regional health services and a daily indicator was obtained dividing it by 7.

Table 1 Summary of the outcomes, population, and study period

City	Study period	City population	Daily mean (and standard deviation) of hospital admissions	
			CVD*	HD†
Barcelona	1995–1999	1508805	35.7 (8.7)	20.7 (6.1)
Bilbao	1995–1998	647761	13.3 (4.6)	6.3 (2.9)
Cartagena	1997–1999	170483	4.8 (2.3)	2.8 (1.7)
Castellón‡	1996–1999	227709	4.6 (2.2)	2.3 (1.6)
Gijón	1993–1998	264381	6.7 (2.8)	3.5 (2.0)
Granada	1997–1999	245639	4.6 (2.4)	2.6 (1.8)
Huelva	1996–1999	140676	4.8 (2.5)	2.8 (1.8)
Madrid§	1997–1999	2866850	30.4 (8.2)	15.8 (5.1)
Oviedo	1993–1998	200049	4.4 (2.3)	2.3 (1.6)
Pamplona	1995–1999	243759	5.0 (2.5)	2.2 (1.6)
Seville	1997–1999	203787	16.6 (6.1)	10.0 (4.2)
Valencia	1996–1999	746682	12.3 (4.1)	6.9 (3.0)
Vigo	1996–1999	286772	5.4 (3.0)	2.8 (2.0)
Zaragoza	1995–1999	601658	14.5 (4.5)	7.4 (3.1)

*All cardiovascular diseases: ICD9 390–459. †Heart diseases: ICD9: 410–414, 427, 428. ‡Start date: 1 April 1996. §Area to study covers only 54% of the city population.

Statistical analysis by city

For each cause, a generalised additive model (GAM) of the Poisson regression family was fitted. This approach allows the possibility of incorporating variables in a non-parametric way using smooth functions such as loess or spline, therefore avoiding the need to presuppose the shape of the relation and later trying to reproduce it by means of an approximate functional expression. Data were analysed using the S-Plus GAM function with more stringent convergence criteria.¹⁴

The modelling process was as follows: In the first step, a "core" model was adjusted, including: (a) meteorological variables and influenza, by means of a spline smoothing function with four degrees of freedom (or three in the case of influenza), and (b) calendar variables (day of the week, holidays), and unusual events (medical strikes, for example). Next, the variable to control the seasonal variation and trend of the series (that is, the time variable) was introduced by means of a loess function. The window size was selected from among different values, taking the one minimising the sum of partial autocorrelation of squared residuals. After that, degrees of freedom for the splines of meteorological variables and influenza were tested. The values minimising Akaike's information criteria were selected. Finally, it was checked whether the variables for holidays and unusual events were maintained in the model. The decision was made according to a likelihood ratio test with a significance level of 0.20.

Secondly, for each pollutant, models were adjusted. The linearity of the relation was checked comparing the resulting models when the pollutant was added in a linear and in a non-linear way (with a spline smoothing function). This was done using a one way analysis of variance test. The linear model provided best results on 55% of the occasions, and the shape of the relation was compatible with a linear one in most cases. Therefore, to facilitate interpretation and comparability of the estimates, we added all pollutants linearly. The serial autocorrelation, when present, was corrected including the significant lags of response variable. Lagged effects, up to three days, of each pollutant were examined. Also averages for lag 0 and 1, and lags 2 and 3 were introduced as pollutant terms. For ozone the analyses were restricted to the warm period (May to October).

Finally, two pollutant models were estimated, including simultaneously all the possible pairs of pollutants, and examining the variations in the one pollutant models' coefficients when each of the other pollutants was included. For the role of the second pollutant in this analysis, particulates were considered as a whole, choosing PM₁₀ when available, then BS if there were no PM₁₀ data, and lastly TSP.

Combined estimates

The quantitative summary of city specific results was obtained by means of meta-analysis techniques, using both graphical and analytical methods. The combined estimates were obtained by weighted regression, in which the weights were the inverse of the local variances—that is, using the fixed effect model.¹⁵ Heterogeneity was checked by a χ^2 test under the fixed effect hypothesis and, if heterogeneity was detected, the random effect model was applied. In this case, the between cities variance was estimated using the moment method of Der-Simonian and Laird¹⁵ and added to the estimates of the local variance. When few studies are combined, the statistical power of the χ^2 test of heterogeneity may be too low. In these circumstances, some authors have suggested increasing the level of statistical significance above 0.05.¹⁶ In our study, heterogeneity was assumed to be present if $p < 0.20$.

For each cause and pollutant, the combined estimates were obtained for the same lag in all the cities. This was done to

Table 2 Descriptive data on the air pollutant variables (in $\mu\text{g}/\text{m}^3$, except CO in mg/m^3) and mean temperature (in $^{\circ}\text{C}$)

City	Particulates Type†	Black smoke			SO ₂			NO ₂			CO-8h			O ₃ -8h*			Mean temperature		
		P10	P50	Mean	P10	P50	Mean	P10	P50	Mean	P10	P50	Mean	P10	P50	Mean	P10	P50	Mean
Barcelona	TSP	29.4	78.8	51.8	19.4	53.0	15.5	6.6	27.9	51.5	29.5	74.4	1.7	0.4	3.4	68.8	41.5	99.1	15.5
Bilbao	TSP	30.3	92.3	58.3	8.8	31.0	18.6	10.2	29.3	51.6	36.9	66.7	1.4	0.9	2.0	54.1	28.3	81.6	14.9
Cartagena	TSP	32.5	79.9	54.9				14.6	40.8								36.7	73.8	19.8
Castellón	TSP	32.0	92.1	60.4	7.7	29.4	7.7	3.8	12.7	23.4	11.4	39.2				88.5	66.6	110.3	18.2
Gijón	TSP	47.4	118.3	77.4				10.3	52.4	43.7	29.1	59.9	2.3	1.1	3.9	48.4	21.3	76.3	14.1
Granada	PM ₁₀	24.8	62.6	43.2				8.8	31.5	65.9	46.3	86.1	2.8	1.7	4.1	74.4	46.8	103.3	16.0
Huelva	PM ₁₀	23.1	57.3	38.6				4.5	22.6	30.7	17.6	46.1				80.2	47.2	118.9	18.3
Madrid	PM ₁₀	21.4	54.4	35.7				8.7	41.8	68.5	48.5	93.5	2.0	0.9	3.4	63.2	32.0	96.3	14.9
Oviedo	TSP	48.3	111.8	76.0				16.3	75.5	50.5	33.3	68.6	1.9	0.9	3.3				13.5
Pamplona					7.4	2.3	13.0	7.6	1.8	17.0									13.2
Seville	PM ₁₀	27.3	57.6	41.9				5.6	14.6	43.7	28.1	60.0	1.7	0.9	2.8	60.9	35.4	88.2	19.5
Valencia	TSP	44.1	80.7	61.0	20.3	66.4	16.6	9.4	24.4	76.2	55.9	99.6	2.6	1.6	3.8	46.0	30.8	59.1	18.8
Vigo					79.4	43.9	122.3	9.3	2.6	18.2									14.3
Zaragoza	PM ₁₀	17.3	50.3	32.8	23.8	61.3	9.3	2.0	19.9	47.8	25.6	75.0				45.9	26.2	73.7	15.6

*Hot season: May to October, both included. †Type of particulates indicator measured: TSP or PM₁₀. Average of mean daily concentrations (eight hours maximums moving average for CO and O₃) and 10th and 90th centiles.

Table 3 Summary of the correlation coefficients (ρ) between each pair of pollutants within cities

Pollutant	PM ₁₀	TSP	NO ₂	SO ₂	CO	O ₃
BS	$\rho=0.48$ n=1	m=0.16 M=0.69 P ₅₀ =0.43 n=3 NA	m=0.23 M=0.69 P ₅₀ =0.48 n=4	m=0.09 M=0.59 P ₅₀ =0.24 n=6	m=0.62 M=0.69 P ₅₀ =0.69 n=3	m=-0.43 M=-0.06 P ₅₀ =-0.16 n=4
PM ₁₀		n=0	m=0.13 M=0.62 P ₅₀ =0.40 n=5	m=0.20 M=0.51 P ₅₀ =0.46 n=5	m=0.34 M=0.45 P ₅₀ =0.37 n=3	m=-0.07 M=0.16 P ₅₀ =0.11 n=5
TSP			m=-0.13 M=0.65 P ₅₀ =0.48 n=6	m=0.06 M=0.69 P ₅₀ =0.31 n=7	m=0.06 M=0.59 P ₅₀ =0.47 n=5	m=-0.16 M=0.19 P ₅₀ =0.01 n=6
NO ₂				m=0.03 M=0.69 P ₅₀ =0.46 n=11	m=0.47 M=0.64 P ₅₀ =0.58 n=8	m=-0.27 M=0.07 P ₅₀ =-0.03 n=10
SO ₂					m=0.06 M=0.72 P ₅₀ =0.51 n=8	m=-0.37 M=0.33 P ₅₀ =-0.03 n=11
CO						m=-0.53 M=-0.10 P ₅₀ =-0.35 n=7

ρ , Pearson coefficient; m, minimum; M, maximum; P₅₀ median; n, number of cities with data for both pollutants, NA: not applied (n=0).

reduce the risk of bias through multiple comparisons by adjusting several lags of the pollutant and selecting the one with the greatest statistical significance. The magnitude of the association is expressed as the percentage change in the risk of death for a 10 $\mu\text{g}/\text{m}^3$ increase (1 mg/m^3 for CO).

RESULTS

Table 2 summarises the distributions of pollutant measurements and temperature for each city. The percentage of missing values was low. In only 4 of 63 (6%) of the pollutant series analysed was the percentage of missing values over 5%. For temperature the percentage of missing values was less than 0.2%.

Correlations between concurrent measurements at different stations in the same city were heterogeneous and in most cases were moderate to high (Pearson correlation (r): 0.3 to 0.7). However, in a few cities, correlation was poorer for some pollutant indicators, especially for SO₂. Regarding correlations between pollutants (table 3), BS, PM₁₀, SO₂, CO, and NO₂ were, on all occasions, positively correlated with each other. BS and CO correlated negatively with ozone that covaried positively with temperature (r : 0.29 to 0.74).

A total of 372 analyses for cause in one pollutant models were made—that is, the analyses for cause, lag, and pollutant in each city. Table 4 summarises the results of the analyses performed for each cause and pollutant. For all cardiovascular diseases (CVD), 66.6% of the analyses provided positive coefficients, and in the case of heart diseases (HD), the figure was 76%.

Regarding the time sequence of the association, greater local estimates were found for lag 0 in all cases but ozone. For

HD an effect in lag 1 was also seen in most cases. Ozone presented a more delayed effect—that is, lags 2 and 3 (fig 2). The mean of the concentrations of the concurrent day and the first lag has been used in a number of previous studies, thus allowing us to compare results. Therefore, we chose the average of lags 0 and 1 (except for ozone (lags 2 and 3)) as the pollutant indicator for estimating the combined effects. Among the indicators chosen 84% of the local estimates were positive for CVD and 89% for HD.

The combined estimates showed a positive association between each air pollutant indicator and the two groups of causes of cardiovascular admissions in all cases. The association with admissions for HD were always statistically significant.

When two pollutant models were used some changes in the estimates appeared, as shown in figure 3. In general, the coefficients for particulates were affected after the inclusion of CO or SO₂ in the models; however, PM₁₀ maintained its significant association. Control for CO or particulates diminished the SO₂ and NO₂ effects, leading, in some cases, to loss of statistical significance. The O₃ and CO coefficients were mostly unchanged after the inclusion of the other pollutants; only the introduction of particulates slightly diminished the estimates for CO.

DISCUSSION

In this study we found an association between the levels of air pollutants and hospital admissions for cardiovascular diseases for the group of participant cities, showing that, at current levels, air pollution represent a health risk for the Spanish population. Estimations of hospital admissions for

Table 4 Summary of the performed analysis

	BS n=36	PM ₁₀ n=30	TSP n=42	NO ₂ n=66	SO ₂ n=84	CO n=48	O ₃ n=66
All CVD*	p=20 s=6	p=25 s=1	p=21 s=6	p=41 s=6	p=58 s=8	p=32 s=5	p=51 s=13
HD†	p=25 s=3	p=23 s=10	p=28 s=7	p=53 s=22	p=67 s=21	p=39 s=15	p=47 s=12

n, number of performed analysis for each outcome; p, models with positive association; s, models with significant association ($\alpha=0.05$). *All cardiovascular diseases: ICD9 390–459. †Heart diseases: ICD9: 410–414, 427, 428.

Figure 2 Time sequence of the combined association between each air pollutant and hospital admissions for all cardiovascular diseases (A) and heart diseases (B). The results are shown as relative risk (and 95% confidence interval) of hospital admissions for cardiovascular diseases associated with an increase of $10 \mu\text{g}/\text{m}^3$ (1 mg for CO) in air pollutant level. BS, PM₁₀, SO₂, and NO₂ are expressed as 24 hour average levels. Ozone and CO are expressed as the maximum eight hour moving average levels.

Table 5 Combined estimates of the association between cardiovascular hospital admissions and air pollutants. The effects are expressed as the percentage change in risk (and 95% confidence interval) for a 10 $\mu\text{g}/\text{m}^3$ (1 mg for CO) increase in air pollutant level*. One pollutant models

Cause	All cardiovascular diseases					Heart diseases				
Air pollutant	Lag*	Model†	% Change	LL	UL	Lag*	Model+	%Change	LL	UL
Black smoke-24h	0-1	r	0.24	-0.18	0.67	0-1	f	0.71	0.13	1.29
PM ₁₀ -24h	0-1	r	0.91	0.35	1.47	0-1	f	1.56	0.82	2.31
TSP-24h	0-1	f	0.07	-0.23	0.36	0-1	f	0.45	0.04	0.86
SO ₂ -24h	0-1	r	1.33	0.21	2.46	0-1	r	1.72	0.50	2.95
NO ₂ -24h	0-1	f	0.38	0.07	0.69	0-1	f	0.86	0.44	1.28
CO-8h	0-1	r	2.06	0.65	3.48	0-1	r	4.15	1.31	7.08
O ₃ -8h\$	2-3	f	0.69	0.34	1.03	2-3	r	0.66	0.10	1.21

*Average of lags 0 and 1 of each pollutant except average lags 2 and 3 for ozone for 24 and 8 hours indicators. †Type of procedure in combined analysis: f, fixed model; r, random model (p for heterogeneity <0.20). \$Results for ozone are for warm period (May to October). LL, lower limit and UL, upper limit of the 95% confidence interval for % change.

heart diseases presented a higher magnitude than for all cardiovascular diseases.

Our results for particulates are consistent with those of other studies. Figure 4 summarises the estimates from six multicity studies on the association between pollution from

PM₁₀ and cardiovascular admissions.^{3 6 17-19} In these studies the analytical approach was quite similar. Differences could be attributable to the fact that in the studies in the USA the hospital admissions refer only to people aged over 65 years—those included in the Medicare programme. This could

Figure 3 Combined estimates of the association between hospital admissions for heart diseases and air pollutants. The effects are expressed as relative risk (and 95% confidence interval) of hospital admissions for a 10 $\mu\text{g}/\text{m}^3$ (1 mg for CO) increase in air pollutant level. Two pollutant models. Note: on the left side of each box are the results from single pollutant models in all the cities with available data on the pollutant under study in each case (for instance SO₂). Moving to the right we have pairs of estimates for the same pollutant: the one on the left corresponds to the results for the pollutant under study (that is, SO₂) in the one pollutant model within cities having data on both pollutants—that is, SO₂ and the second one, for example, CO; and the line on the right shows the results for SO₂ in the model including both pollutants (SO₂ and CO). For particulates as the second pollutant, and to avoid splitting it into three different indicators, we create an indicator for particulates selecting PM₁₀ when available, BS when no PM₁₀ data are available, and finally TSP if no PM₁₀ or BS data are available.

Figure 4 Association between hospital admissions for cardiovascular diseases and PM10 in some multicentre time series studies. The results are expressed as the percentage increase in risk (and 95% confidence intervals) for a 10 µg/m³ increase in the concentration of PM10 (lag 0). *Studies among older than 65. †Cardiovascular diseases: ICD-9: 390–429 except in EMECAS: ICD-9: 390–459.

explain the slightly greater effect found in such studies. Following the debate on methodological approaches, data from 10 of the cities in the NMMAPS study were analysed using a hierarchical bivariate model. A 0.71% (0.35 to 0.99) increase in hospital admissions for cardiovascular causes was associated with a 10 µg/m³ increase in PM₁₀ levels.²⁰ On the other hand, as in our study, higher risks have been described for the association with heart diseases, thus showing a pattern of specificity in the effect.^{21–22}

Studies including SO₂ have obtained a variety of results. In some no significant association with cardiovascular morbidity was found,^{22–24} whereas others report a risk increase of about 2% associated with a 10 µg/m³ increase in SO₂ levels.^{6–25} In many studies the association between SO₂ and cardiovascular morbidity is visibly attenuated or disappears when other pollutants are included in the models.^{21–26–28}

The relation of NO₂ with hospital admissions for cardiovascular diseases has also been included in many studies. A significant association was detected in most of them. However, the results obtained in the multi-pollutant models introduce some controversy. In some cases, robust estimates are obtained,^{21–29} while in others the changes in estimates suggest that such associations may not be independent of other pollutants.^{30–31}

In the two pollutant models carried out in our study, the estimates for the association of SO₂ and NO₂ were the most sensitive to the inclusion of other pollutants. On the other hand, CO and O₃ showed the most robust estimates. These results agree with those described by other authors for CO. Thus, Burnett *et al*, in a study carried out in 10 cities in Canada²⁷ described more consistent findings for CO than for the other pollutants, although they did not include particulates. Other studies have also described the robustness of the estimators for the association between CO and cardiovascular admissions.^{17–32–34} Results for CO in Spain are similar to those

What this study adds

- This is the first multicentre study evaluating the short term effect of air pollution in cardiovascular morbidity in Spain.
- Our findings show that the number of daily hospital admissions for cardiovascular diseases increases as the concentration of air pollutants increases.
- The time sequence shows a short term impact of the increase in pollutants (lag 0 and lag 1) on cardiovascular admissions and a more delayed effect in the case of ozone.
- The risks are higher for heart diseases than for all cardiovascular diseases.
- PM₁₀, CO, and O₃ estimates were robust after controlling the potential for confounding attributable to other pollutants.
- The effect of ozone on cardiovascular admissions seems to be independent of the other pollutants.

of the Italian meta-analysis,⁶ the Melbourne study,³¹ and the London study³⁵ with a risk excess of between 2% and 2.8% for a 1 mg/m³ increase in the levels of CO-8 hours in all cardiovascular diseases. There is less evidence in the literature about the relation between ozone and cardiovascular admissions. The results of these studies are inconsistent, some described no association,^{6–35–36} and others a positive association.^{30–37–38}

What is already known on this subject

- Air pollution has been shown to be a risk factor for several health outcomes including both mortality and morbidity.
- In previous studies we described the short term effect of air pollutants on mortality rates in the Spanish urban population.
- In recent years, the potential impact of air pollution on cardiovascular health has caused considerable concern.

Policy implications

- Air pollution, even at the current levels in Spain, may represent a risk for cardiovascular health among the urban population.
- The findings from this study are similar to those obtained in other locations and support the need for policies to reduce the ambient levels of air pollutants in Spain, throughout Europe, and wherever air pollution poses a health risk.
- The methodological experience acquired, as well as the setting of a multicentre network, constitutes a valuable resource for the development of future health and environment information systems.

A common problem in studies on the effects of air pollution is the error in measurement of the exposure, because, mainly, to the differences between what is measured by the stations and the real exposure of each person within a city. However, the comparison of daily variation in particulates between the two types of measurement has shown a high correlation.³⁹ It has also been shown that a possible error in measurement would lead to an underestimation of the association.⁴⁰ Still, the above has been shown only for particulates and cannot be generalised to other pollutants.

The limitations of use of data on admissions for epidemiological studies have already been considered.^{22–41} The analysis of the quality of hospital databases on hospital admissions in Spain has shown few errors in the management of data, except as regards patients' residence.⁴¹ This problem could produce a misclassification bias, which would, in any case, be non-differential, as it does not seem logical to relate data errors concerning the residence of patients with daily variations in suspended particles. On the other hand, a study carried out in Canada⁴² showed a fair degree of agreement ($\kappa = 0.84$) in the classification of cardiac diseases.

Another problem in the use of visits and/or admission data is the possible effect of re-admissions on the air pollution estimates. In another Canadian study²² this issue was investigated building up two types of series of admissions, one for patients with only one admission during the period under study, and another for patients with several admissions. The effect estimates did not differ, or were smaller in the case of patients with more than one admission. This evaluation suggests that the effect of including repeated visits would tend to be negligible.

Given the consistency of results in population studies several physiopathological mechanisms have been proposed.⁴³ One of the main hypothesis is that particles induce the activation of some mediators which provoke an increase in blood coagulation.^{44–45} Other mechanisms studied are related to automatic cardiac control, where a significant association between particles and an increase in heart beat rate and a decrease in its variability has been shown.^{5–46–48} Another mechanism described is the association between exposure to particles and one of the major cardiovascular risk factors—that is, hypertension.⁴⁹ In an experimental study, Brook *et al*¹² reported that short term inhalation of fine particulates and also ozone at normal concentrations in an urban environment causes acute conduit artery vasoconstriction. Similar results have been found recently for patients with pre-existing cardiac disease.⁵⁰ Lastly, in experimental studies with humans, inflammatory changes at the alveolar level and an increase in fibrinogen levels, leucocytes, and platelets at the alveolar level have been found.⁵¹ Seeking the toxicant component of particles, a growing number of studies support the hypothesis that the composition of ultrafine particles^{52–53} and their contents of transition metals^{54–55} or silicon,⁵⁶ could explain their toxic capacity in the cardiovascular system.

On the other hand, an additive part, played by other gaseous pollutants, cannot be ruled out. For example, there are few doubts about the toxicity of CO to the cardiovascular system.⁵⁷ Also, it is known that CO can produce dyspnoea and hypoxia as it provokes the formation of carboxihaemoglobin.⁵⁸

Lastly, regarding toxic mechanisms for ozone, results of some studies suggest that, besides its oxidant capacity to cause lung inflammation, ozone exposure can increase myocardial work and impair pulmonary gas exchange to a degree that might be clinically important in people with significant pre-existing cardiovascular impairment, with or without concomitant lung disease.⁵⁹ Recent research shows

an impact of ozone on mortality.^{60–63} They are four meta-analyses including an extent amount of data from different countries. As stated in accompanying editorial this amount of evidence, point to an urgent need to develop effective actions to reduce public exposure to ozone.⁶⁴

The findings from this study are similar to those obtained in other locations. They provide further information on the impact of air pollution on health, and support the need for policies to be applied all across Europe and in many other parts of the world where air pollution is a problem. Moreover, at the national level, such information may be useful for implementing public health programmes and for the development of health and environment information systems.

ACKNOWLEDGEMENTS

The authors thank all the professionals and institutions that have made this study possible by providing the essential data, in particular the Information Services of the National and Regional Health Systems, Air Pollution Networks and National Institute of Meteorology. The authors are grateful for the comments from the manuscript reviewers, and thank Susanna Pérez and Judith Williams for their help in editing the manuscript.

Authors' affiliations

F Ballester, P Rodríguez, C Iñiguez, S Pérez-Hoyos, Unit of Epidemiology and Statistics, Valencian School of Health Studies (EVES), Spain

M Saez, A Lertxundi, Grup de Recerca en Estadística, Economia Aplicada i Salut (GRECS), Universitat de Girona, Spain

A Daponte, S Toro, Escuela Andaluza de Salud Pública, Spain

I Galán, DG Salud Pública. Comunidad de Madrid, Spain

M Taracido, Universidad de Santiago. Facultad de Medicina, Spain

F Arribas, Departamento de Sanidad Aragón, Spain

J Bellido, Centro Salud Pública, Castelló, Spain

F B Cirarda, Department of Health, Basque Government, Basque Country

A Cañada, Dirección Regional de Salud Pública, Asturias, Spain

J J Guillén, Centro de Área, Cartagena, Murcia, Spain

F Guillén-Grima, Universidad Pública de Navarra, Spain

E López, DG Salud Pública, Canarias, Spain

Funding: this study has received funds from the Spanish Ministry of Health (FIS 00/0010).

Conflicts of interest: none declared.

The EMECAS group consists of F Ballester, S Pérez-Hoyos, C Iñiguez, P Rodríguez, J M Tenías, F Gómez, S Medina, J L Bosch, S Peiró (Valencia); M Saez, M A Barceló, C Saurina, A Lertxundi, L Artaco, J Sunyer, A Plasència, A Tobías (Barcelona); A Daponte, R Ocaña, S Toro, I Aguilera, J L Gurucelain, P Gutiérrez, J A Maldonado, J M Mayoral, E Caro, P López, (Granada); J M Ordóñez, E Aránguez, I Galán, A M Gandarillas, N Aragonés, M Martínez, R Fernández, P Arias, A Brezmes, F J Mantero (Madrid); K Cambra, E. Alonso, F B Cirarda, T Martínez-Rueda (Bilbao); M Taracido, A Figueiras, M R Aguiar, C Sixto, M C Sánchez (Vigo); I Aguinaga, M Y Floristan, A Guillén, M A Martínez, E Aguinaga, F J Aldaz, P Zuazo, C Moreno, A Arrazola, J J Viñes, I Serrano, M D Ugarte, A Fernández (Pamplona); J B Bellido, A Arnedo, F González, C Felis, C Herrero (Castellón); J J Guillén, L Cirera, L García, E Jiménez, M J Martínez, S Moreno, C Navarro, J Medrano, M A Martínez (Cartagena); A Cañada, C Fernández, F Fernández, J V García, I Huerta, V Rodríguez (Asturias); F Arribas, M Navarro, C Martos, M J Rabanaque, E Muniesa, J T Alcalá, J I Urraca, M Loarte (Zaragoza); E López, M D García (Canarias).

Preliminary results of this work have been presented at the Joint Meeting between International Epidemiological Association European Federation and the Spanish Society of Epidemiology, Toledo October 2003; at the II AIRNET Conference, Rome, November 2003; at the XVI Conference of the International Society for Environmental Epidemiology, New York August 2004; and at the V Conference of Urban Air Quality, Valencia, March 2005.

REFERENCES

- 1 Brunekreef B, Holgate ST. Air pollution and health. *Lancet* 2002;**360**:1233–42.

2. **Katsouyanni K**, Touloumi G, Samoli E, et al. Confounding and effect modification in the short-term effects of ambient particles on total mortality: results from 29 European cities within the APHEA2 project. *Epidemiology* 2001;12:521-31.
3. **Le Tertre A**, Medina S, Samoli E, et al. Short-term effects of particulate air pollution on cardiovascular diseases in eight European cities. *J Epidemiol Community Health* 2002;56:773-9.
4. **Samet JM**, Dominici F, Zeger S, et al. The national morbidity, mortality, and air pollution study. Part I: methods and methodologic issues. *Research Report Health Effects Institute* 2000;93:1-70.
5. **Quenel P**, Cassadou S, Declercq C, et al. *Surveillance des effets sur la santé liés à la pollution atmosphérique en milieu urbain*. Paris: Rapport Surveillance épidémiologique "Air and Santé", 1999.
6. **Biggeri A**, Bellini P, Terracini B. Meta-analysis of the Italian studies on short-term effects of air pollution. *Epidemiol Prev* 2001;25(suppl):1-71.
7. **Ballester F**, Sáez M, Alonso E, et al. El proyecto EMECAM: estudio español sobre la relación entre la contaminación atmosférica y la mortalidad. Antecedentes, participantes, objetivos, material y métodos. *Revista Española de Salud Pública* 1999;73:165-75.
8. **Schwartz J**, Ballester F, Saez M, et al. The concentration-response relation between air pollution and daily deaths. *Environ Health Perspect* 2001;109:1001-6.
9. **Ballester F**, Saez M, Perez-Hoyos S, et al. The EMECAM project: a multi-center study on air pollution and mortality in Spain. Combined results for particulates and for sulphur dioxide. *Occup Environ Med* 2002;59:300-8.
10. **Saez M**, Ballester F, Barceló MA, et al. A combined analysis of the short-term effects of photochemical air pollutants on mortality within the EMECAM project. *Environ Health Perspect* 2002;110:221-8.
11. **Brook RD**, Franklin B, Cascio W, et al. Air pollution and cardiovascular disease. A statement for Healthcare Professionals From the Expert Panel on Population and Prevention Science of the American Heart Association. *Circulation* 2004;109:2655-71.
12. **Brook RD**, Brook JR, Urch B, et al. Inhalation of fine particulate air pollution and ozone causes acute arterial vasoconstriction in healthy adults. *Circulation* 2002;105:1534-6.
13. **Nemmar A**, Nemery B, Hoet PH, et al. Pulmonary inflammation and thrombogenicity caused by diesel particles in hamsters: role of histamine. *Am J Respir Crit Care Med* 2003;168:1366-72.
14. **Dominici F**, McDermott A, Zeger SL, et al. On the use of generalized additive models in time-series studies of air pollution and health. *Am J Epidemiol* 2002;156:193-203.
15. **DerSimonian R**, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177-88.
16. **Spector TD**, Thompson SG. The Potential and limitations of meta-analysis. *J Epidemiol Community Health* 1990;45:89-92.
17. **Schwartz J**. Air pollution and hospital admissions for heart disease in eight US counties. *Epidemiology* 1999;10:17-22.
18. **Zanobetti A**, Schwartz J, Dockery DW. Airborne particles are a risk factor for hospital admissions for heart and lung disease. *Environ Health Perspect* 2000;108:1071-7.
19. **Samet JM**, Zeger SL, Dominici F, et al. The national morbidity, mortality, and air pollution study. Part II: morbidity and mortality from air pollution in the United States. *Research Report Health Effects Institute* 2000;94:1-70.
20. **Dominici F**, Zanobetti A, Zeger SL, et al. Hierarchical bivariate time series models: a combined analysis of the effects of particulate matter on morbidity and mortality. *Biostatistics* 2004;5:41-60.
21. **Burnett RT**, Smith-Doiron M, et al. Effects of particulate and gaseous air pollution on cardiorespiratory hospitalizations. *Arch Environ Health* 1999;54:130-9.
22. **Lippmann M**, Ito K, Nadas A, et al. Association of particulate matter components with daily mortality and morbidity in urban populations. *Research Report Health Effects Institute* 2000;95:5-72.
23. **Schwartz J**. Air pollution and hospital admissions for cardiovascular disease in Tucson. *Epidemiology* 1997;8:371-7.
24. **Anderson HR**, Bremner SA, Atkinson RW, et al. Particulate matter and daily mortality and hospital admissions in the West Midlands conurbation of the United Kingdom: associations with fine and coarse particles, black smoke and sulphate. *Occup Environ Med* 2001;58:504-10.
25. **Wong TW**, Lau TS, Yu TS, et al. Air pollution and hospital admissions for respiratory and cardiovascular diseases in Hong Kong. *Occup Environ Med* 1999;56:679-83.
26. **Schwartz J**, Morris RD. Air pollution and hospital admissions for cardiovascular disease in Detroit, Michigan. *Am J Epidemiol* 1995;142:23-35.
27. **Burnett RT**, Dales RE, Brook JR, et al. Association between ambient carbon monoxide levels and hospitalizations for congestive heart failure in the elderly in 10 Canadian cities. *Epidemiology* 1996;8:162-7.
28. **Sunyer J**, Ballester F, Tertre, et al. The association of daily sulfur dioxide air pollution levels with hospital admissions for cardiovascular diseases in Europe (the Aphea-II study). *Eur Heart J* 2003;24:752-60.
29. **Morgan G**, Corbett S, Włodarczyk J. Air pollution and hospital admissions in Sydney, Australia, 1990 to 1994. *Am J Public Health* 1998;88:1761-6.
30. **Atkinson RW**, Bremner SA, Anderson HR, et al. Short-term associations between emergency hospital admissions for respiratory and cardiovascular disease and outdoor air pollution in London. *Arch Environ Health* 1999;54:398-411.
31. **Denison L**, Simpson R, Petroeshevsky A, et al. *Ambient air pollution and daily hospital admissions in Melbourne, 1994-1997*. Southbank, Australia: EPA Victoria, 2001:1-81.
32. **Morris RD**, Naumova EN. Carbon monoxide and hospital admissions for congestive heart failure: evidence of an increase effect at low temperatures. *Environ Health Perspect* 1998;106:649-53.
33. **Moolgavkar SH**. Air pollution and hospital admissions for diseases of the circulatory system in three US metropolitan areas. *J Air Waste Manag Assoc* 2000;50:1199-206.
34. **Mann JK**, Tager IB, Lurmann F, et al. Air pollution and hospital admissions for ischemic heart disease in persons with congestive heart failure or arrhythmia. *Environ Health Perspect* 2002;110:1247-52.
35. **Poloniecki JD**, Atkinson RW, Ponce A, et al. Daily time series for cardiovascular hospital admissions and previous day's air pollution in London, UK. *Occup Environ Med* 1997;54:535-40.
36. **Gwynn RC**, Burnett RT, Thurston GD. A time-series analysis of acidic particulate matter and daily mortality and morbidity in the Buffalo, New York, region. *Environ Health Perspect* 2000;108:125-33.
37. **Wong C**, Ma S, Hedley AJ, et al. Does ozone have any effect on daily hospital admissions for circulatory diseases? *J Epidemiol Community Health* 1999;53:580-1.
38. **Stieb DM**, Beveridge RC, Brook JR, et al. Air pollution, aeroallergens and cardiorespiratory emergency department visits in Saint John, Canada. *J Expo Anal Environ Epidemiol* 2000;10:461-77.
39. **Janssen NA**, Hoek G, Brunekreef B, et al. Personal sampling of particles in adults: relation among personal, indoor, and outdoor air concentrations. *Am J Epidemiol* 1998;147:537-47.
40. **Zeger S**, Thomas D, Dominici F, et al. Exposure measurement error in time-series studies of air pollution: concepts and consequences. *Environ Health Perspect* 2000;108:419-26.
41. **Librero J**, Ordinaña R, Peiró S. Análisis automatizado de la calidad del conjunto mínimo de datos básicos. Implicaciones para los sistemas de ajuste de riesgos. *Gac Sanit* 1998;12:9-21.
42. **Stieb DM**, Beveridge RC, Rowe BH, et al. Assessing diagnostic classification in an emergency department: implications for daily time series studies of air pollution. *Am J Epidemiol* 1998;148:666-70.
43. **Seaton A**, MacNee W, Donaldson K, et al. Particulate air pollution and acute health effects. *Lancet* 1995;345:176-8.
44. **Peters A**, Döring A, Wichmann HE, et al. Increased plasma viscosity during an air pollution episode: a link to mortality? *Lancet* 1997;349:1582-7.
45. **Schwartz J**. Air pollution and blood markers of cardiovascular risk. *Environ Health Perspect* 2001;109(suppl 3):405-9.
46. **Liao D**, Creason J, Shy C, et al. Daily Variation of particulate air pollution and poor cardiac autonomic control in the elderly. *Environ Health Perspect* 1999;107:521-5.
47. **Peters A**, Perz S, Döring A, et al. Increases in heart rate during an air pollution episode. *Am J Epidemiol* 1999;150:1094-8.
48. **Holguin F**, Tellez-Rojo MM, Hernandez M, et al. Air pollution and heart rate variability among the elderly in Mexico City. *Epidemiology* 2003;14:521-7.
49. **Ibald-Mulli A**, Stieber J, Wichmann HE, et al. Effects of air pollution on blood pressure: a population-based approach. *Am J Public Health* 2001;91:571-7.
50. **Zanobetti A**, Canner MJ, Stone PH, et al. Ambient pollution and blood pressure in cardiac rehabilitation patients. *Circulation* 2004;110:2184-9.
51. **Salvi S**, Blomberg A, Rudell B, et al. Acute inflammatory responses in the airways and peripheral blood after short-term exposure to diesel exhaust in healthy human volunteers. *Am J Respir Crit Care Med* 1999;159:702-9.
52. **Donaldson K**, Stone V, Seaton A, et al. Ambient particle inhalation and the cardiovascular system: potential mechanisms. *Environ Health Perspect* 2001;109(suppl 4):523-7.
53. **Frampton MW**. Systemic and cardiovascular effects of airway injury and inflammation: ultrafine particle exposure in humans. *Environ Health Perspect* 2001;109(suppl 4):529-32.
54. **Costa DL**, Dreher KL. Bioavailable transition metals in particulate matter mediate cardiopulmonary injury in healthy and compromised animal models. *Environ Health Perspect* 1997;105(suppl 5):1053-60.
55. **Magari SR**, Schwartz J, Williams PL, et al. The association of particulate air metal concentrations with heart rate variability. *Environ Health Perspect* 2002;110:875-80.
56. **Wellenius GA**, Coull BA, Godleski JJ, et al. Inhalation of concentrated ambient air particles exacerbates myocardial ischemia in conscious dogs. *Environ Health Perspect* 2003;111:402-8.
57. **Allred E**, Blecker E, Chaitman B, et al. Effects of carbon monoxide on myocardial ischemia. *Environ Health Perspect* 1991;91:89-132.
58. **Maynard RL**, Waller RE. Carbon monoxide. In: Holgate ST, Samet JM, Koren H, et al. *Air pollution and health*. San Diego, CA: Academic Press, 1999:749-96.
59. **Gong HJ**, Wong R, Sarma RJ, et al. Cardiovascular effects of ozone exposure in human volunteers. *Am J Respir Crit Care Med* 1998;158:538-46.
60. **Gryparis A**, Forsberg B, Katsouyanni K, et al. Acute effects of ozone on mortality from the "Air pollution and health: a European approach" project. *Am J Respir Crit Care Med* 2004;170:1080-7.
61. **Levy JI**, Chemerynski SM, Sarnat JA. Ozone exposure and mortality: an empiric bayes metaregression analysis. *Epidemiology* 2005;16:458-68.
62. **Ito K**, De Leon SF, Lippmann M. Associations between ozone and daily mortality: analysis and meta-analysis. *Epidemiology* 2005;16:446-57.
63. **Bell ML**, Dominici F, Samet JM. A meta-analysis of time-series studies of ozone and mortality with comparison to the national morbidity, mortality, and air pollution study. *Epidemiology* 2005;16:436-45.
64. **Bates DV**. Ambient ozone and mortality. *Epidemiology* 2005;16:427-9.