Air pollution and emergency hospital admissions for cardiovascular diseases in Valencia, Spain

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Abstract

Study objective—To estimate the short-term association between air pollution levels and emergency hospital admissions for cardiovascular diseases in Valencia, within 1994–1996 period.

Design—Daily levels of air pollution and emergency admissions for cardiovascular diseases were related to using an ecological time series design. The number of admissions was obtained from the hospital records database. Selected groups of causes were all cardiovascular diseases, heart admissions, and admissions for cerebrovascular diseases. The number of admissions for digestive diseases was used as control. Pollutants were black smoke, sulphur dioxide (SO_2), nitrogen dioxide (NO_2), carbon monoxide (CO) and ozone (O_3). Magnitude of association was estimated by Poisson autoregresive regression. Estimations were calculated according the hottest (May to October) and the coldest (November to April) periods.

Setting—City of Valencia, Spain, about 750 000 inhabitants.

Participants—People being admitted to the two major hospitals in the city, with a catchment area of nearly 400 000 inhabitants.

Main results—For the whole period, a significant association for SO_2-24 h was found so a rise in its levels of 10 µg/m³ was associated with an increment of 3% (95%CI 0.4 to 5.7%) in the expected number of cardiovascular admissions. A significant association for black smoke, SO_2-24 h, SO_2-1 h, and CO-1 h was found in the hottest semester. All these associations were verified with a lag of two days. The estimates of the associations for particles, SO_2, and CO were affected by the inclusion of the other pollutants in their models. NO_2 was independently associated with cerebrovascular admissions. There were no significant associations between air pollution and admissions for digestive diseases.

Conclusions—Current levels of air pollution and emergency cardiovascular admissions are significantly related in Valencia.

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The impact of air pollution on several outcomes (that is, mortality, respiratory diseases) has been studied in a considerable number of cities throughout the world. Studies on mortality impact of air pollution have shown an association with cardiovascular mortality,[1–5] however the short-term relation between cardiovascular admissions and urban air pollution has not been assessed until a few years ago. Some studies have been carried out recently in this sense, especially in North America[6–13] and also in some cities in northern or western Europe,[14–18] in Sydney, Australia,[19] and in Hong Kong, China.[20] In the Mediterranean area only one study, in Athens,[21] has examined this relation.

Most of these time series studies showed an effect predominance of particulates and carbon monoxide (CO) on cardiovascular admissions.[6–10 12 13 17 18] However, the results in some works in Europe[15 16] and in Sydney[19] suggest an independent effect of the nitrogen dioxide (NO_2) and sulphur dioxide (SO_2). Furthermore, two of the studies in Canada showed a more consistent effect for sulphates[7] or for ozone.[11]

Up to now the effect of air pollution on cardiovascular diseases morbidity has not been assessed in Spain, a country that has a mild climate, different to the climates of most of the other places studied. For this reason it seemed inadequate to extrapolate the results in other parts of the world to our particular environment. Moreover, it has been suggested that weather or, more particularly, temperature may modify the effects of air pollution on health, both high[22] and low temperatures.[12] Specifically, the results of the latter study, carried out in Chicago, USA suggest that the effect of CO on hospital admissions for heart failure may be temperature dependent, with the magnitude of the effect increasing with decreasing temperature.[12] In this sense, laboratory and further epidemiological studies in other cities with different climates are claimed in order to validate that hypothesis. In this study we explore the short-term association between air pollution levels and emergency hospital admissions for cardiovascular diseases in a Mediterranean location, the city of Valencia, Spain, for the period 1994–1996.

Methods

The study was part of an ecological time series one, where daily levels of air pollution and emergency admissions for cardiovascular disease in the two main hospitals of the city of Valencia were related controlling for the major confounding variables.

SETTING

Valencia is located on the Mediterranean coast and has a mesothermal climate (mild climate). The air pollution mainly derives from motor

Table 1 Summary of the daily figures for the number of hospital admissions for cardiovascular and digestive causes, the concentrations of air pollutants, the meteorological variables and the flu incidence. Valencia, Spain (1994–1996)

	Whole period					Semesters	
	Mean	Minimum	P50	Maximum	n	hottest Mean	coldest Mean
Cardiovascular diseases	7.0	0	7.0	20	1080	6.6	7.4
Heart diseases	3.9	0	4.0	13	1080	3.7	4.2
Cerebrovascular diseases	1.5	0	1	7	1080	1.5	1.6
Digestive diseases	5.6	1	5	15	1076	5.7	5.5
Mean temperature (°C)	18.7	6.6	18.4	33.8	1080	22.9	14.4
Relative humidity (%)	63.1	23.0	65.0	96.0	1080	65.3	60.7
Black smoke 24 h ($\mu g/m^3$)	43.7	8.0	40.4	136.2	1080	37.2	50.7
SO_2 24 h ($\mu g/m^3$)	25.6	4.4	25.0	68.4	1073	21.6	29.8
NO_2 24 h ($\mu g/m^3$)	66.8	11.9	64.7	155.1	1072	66.8	66.9
NO_2 1 h ($\mu g/m^3$)	116.1	31.1	113.2	469.0	1072	116.3	116.0
O_3 8 h ($\mu g/m^3$)	45.9	10.2	45.0	125.0	1071	54.2	37.2
CO 1 h (mg/m^3)	6.2	0.6	5.7	17.8	1078	5.1	7.4
Cases of influenza	167.5	3.0	120.0	660.0	1080	68.6	270.9

n: number of days with valid observations.

vehicle exhaust emissions, with industrial pollution playing a smaller part. The analysis took place in the Hospital Clínico Universitario, and Hospital Universitario La Fe. These hospitals have an urban catchment area of 376 681 inhabitants (total population of the city 750 000 inhabitants). Because both hospitals are part of the public health service network, access to emergency health services is universal. In a previous study we found that people attending a different hospital emergency department for respiratory diseases to their reference one in Valencia represented less than 3% (unpublished data).

DATA

Health measures
The number of daily admissions was obtained from the registry databases of the two hospitals, being selected the admissions for residents of Valencia city with a primary discharge diagnosis of the following causes (codes of International Classification of Diseases, 9th revision, ICD-9): cardiovascular diseases (ICD-9: 390–459); heart diseases (ICD-9: 410–414, 427, 428); cerebrovascular diseases (ICD 9: 430–438); and admissions for digestive disease excluding vascular related ones (ICD 9: 530–534,5 40–543, 560–569, 571–572, 574–578). The latter was selected as a control series. We preferred the use of broad categories rather than more specific ones in order to obtain more precision in results[13] and seeking to reduce likelihood of misclassification.[19]

Exposure data
The pollution data were obtained from the city's air pollution monitoring network, which consists of 14 manual and five automatic monitoring stations. From the manual network the 24 hour average levels for black smoke (reflectometry method) were obtained and from the automatic network the 24 hour average and the one hour maximum levels for NO_2 (chemiluminescence), SO_2 (ultraviolet fluorescence) and CO (infrared absorption) as well as the eight hours moving average and the one hour maximum levels for ozone (UV absorption). Only the data obtained from those stations with valid readings on more than 75% of days were used in this investigation. The results of this calculation were ruled out if less than 75% of data for that day was available. Using these criteria, seven manual and the five automatic monitoring stations were finally selected. The correlation between the measurements at different stations varied from 0.30 to 0.62 in the manual network (that is, black
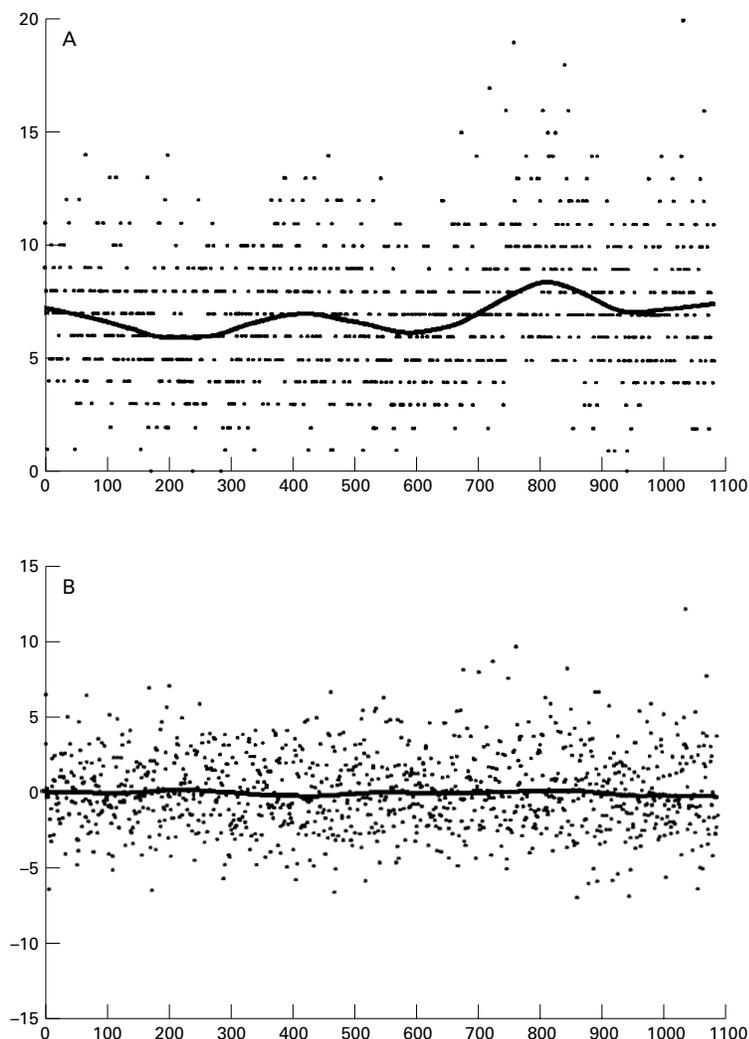

Figure 1 Raw (A) and residual after adjusting for the core model (B) series of the daily number of admissions for cardiovascular diseases in Valencia (1994–1996). Adjusted line: loess with a width of 20%.

Table 2   Pearson correlation coefficients among the environmental variables. Valencia, 1994–1996

Variable	Temperature	Humidity	Black smoke	SO₂ 24 h	NO₂ 1 h	CO 24 h	O₃ 8 h
Temperature	1	0.07	−0.41	−0.42	−0.10	−0.55	0.45
Humidity		1	0.07	−0.18	−0.10	−0.02*	−0.10
Black smoke			1	0.63	0.33	0.64	−0.57
SO₂ 24 h				1	0.22	0.74	−0.35
NO₂ 1 h					1	0.03*	−0.26
CO 24 h						1	−0.42
O₃ 8 h							1

24 h daily average; 1 h: daily one hour maximum level; 8 h daily eight hours moving average maximum level. *p>0.05.

smoke), and from 0.46 to 0.78 in the automatic one (gaseous pollutants).

Data of control variables
The daily data for temperature and relative humidity were obtained from Valencia's meteorological station, located within an urban garden. The weekly influenza cases were taken from the registers of notified diseases. Local holidays and the period of strike action by medical staff during May 1995 were also taken into consideration.

ANALYSIS
Magnitude of association was estimated by Poisson autoregresive regression following the standardised methodology of the APHEA project[23–25] with some modifications introduced in the Spanish EMECAM project.[26 27] With this approach we assume counts of daily admissions follow a non-stationary overdispersed Poisson process where variations could be explained in part for some factors varying in time (that is, long term trend and seasonality, temperature and humidity, week days, flu incidence, special events, or air pollution). The effect of the former variables must be taken into account to avoid confusion in the estimation of the relation between admissions and air pollution. Therefore, using Poisson regression we analysed data in two steps. Firstly, a core model was built for each outcome variable (that is, the series of daily admissions) controlling for the main confounding variables Secondly, the association with air pollutants was estimated examining the delayed relation up to the fifth lag of pollutants. To control residual overdispersion serial autocorrelation in the final models autoregressive terms up to the fifth order were checked, including them in the model when significant.

The relation between air pollutants and admissions does not have to be linear. Therefore, besides the linear model, a non-parametric model, including a loess term for the pollutant, has been fitted. This kind of model does not assume any shape of the relation. The depart from the linearity was

checked comparing the deviance of both models by means of a χ² test with the difference of degree of freedoms between the models.

Furthermore, estimations were calculated for the hottest (May to October) and coldest (November to April) semester. Lastly, to analyse the independence of the associations, two pollutant models were also fitted. The effect of pollution was calculated using the relative risk (RR) corresponding to an increase in 10 μg/m³ in air pollutant indicators (1 mg/m³ for CO).

Results
Table 1 shows the summary statistics of the health and environmental data in Valencia. The mean daily number of cardiovascular admissions was seven, most of them attributable to heart diseases (3.9), and to cerebrovascular diseases (1.5). These figures would correspond to a daily rate of 18.6, 10.4, and 4, respectively, for a hypothetical population of one million inhabitants.

Levels of pollutants are, in general, moderate. However, if we examine them in the light of the recent European Directive relating on limit values for some pollutants[28] it would be difficult to meet some of them, especially for NO₂ (limit value for the annual mean of NO₂: 40 μg/m³).

The cardiovascular admissions series presented a seasonal trend with higher numbers in the coldest months. This pattern was removed after adjusting for the control variables (fig 1). Black smoke, SO₂, and CO showed the same seasonal pattern as cardiovascular admissions, and high correlation among them (table 2). Ozone presented positive correlation with temperature and negative correlation with the other pollutants. Nitrogen dioxide did not show a clear pattern.

Table 3 shows the estimates for the association between air pollutants and the three groups of emergency cardiovascular admissions for the whole period. A significant association was found for SO₂ 24 h, lag 2, so that a rise in its levels of 10 μg/m³ was associated with an increment of 3.0% (95% confidence intervals, (95%CI 0.4 to 5.7%) and 3.6%

Table 3   Association between air pollution and the number of emergency hospital admissions for the three groups of cardiovascular diseases and the one of digestive admissions. Valencia 1994–1996. Results expressed as the relative risk (and the 95%CI) in admissions for an increase in the pollutant levels of 10 μg/m³ (1 mg/m³ for CO)

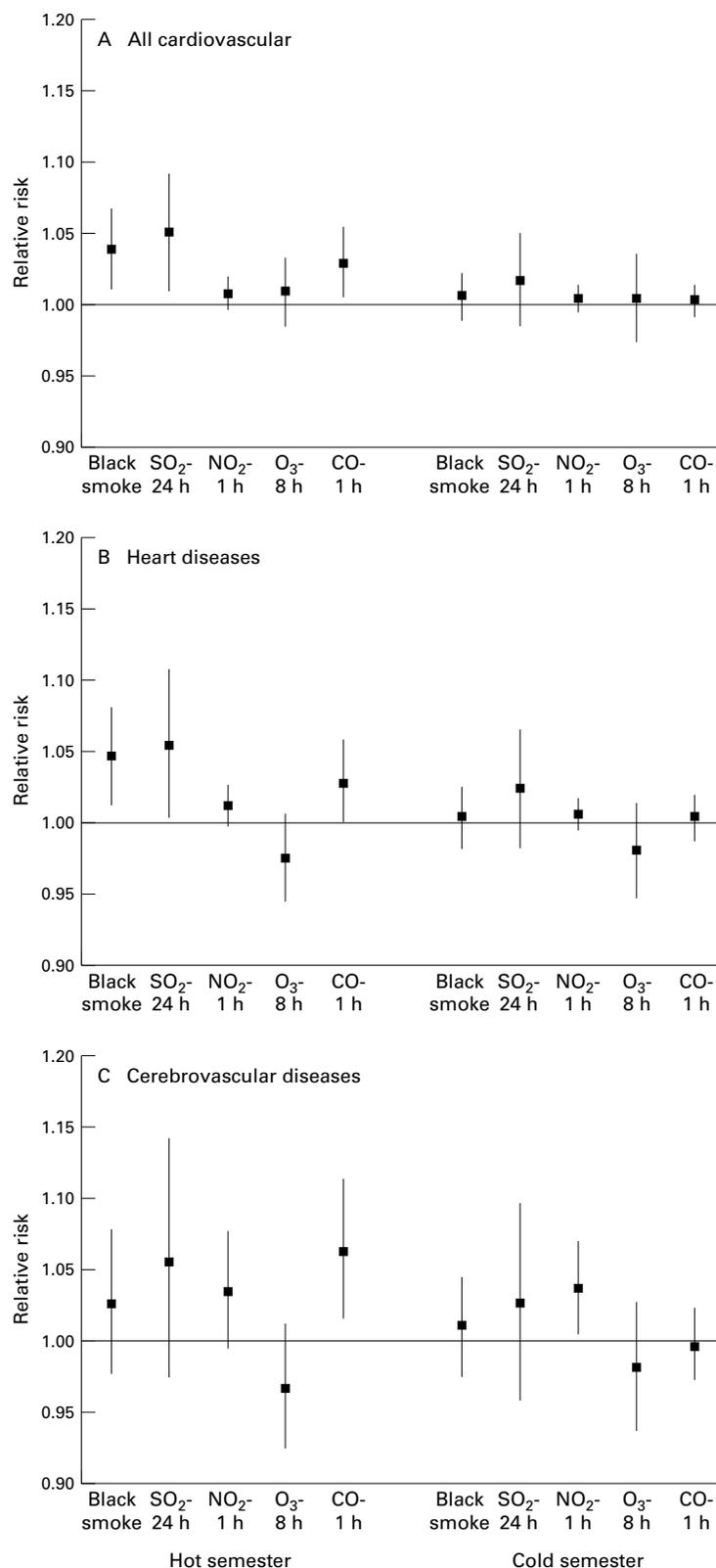| Pollutants	All cardiovascular diseases	L	Heart diseases	L	Cerebrovascular diseases	L	Digestive diseases	L
Black smoke	1.0145 (0.9996;1.0297)	2	1.0149 (0.9953;1.0349)	2	1.0156 (0.9860;1.0461)	5	0.9905 (0.9750;1.0063)	3
SO₂ 24 h	1.0302 (1.0042;1.0568)	2	1.0357 (1.0012;1.0714)	2	1.0378 (0.9844;1.0940)	5	1.0234 (0.9958;1.0518)	1
NO₂ 1 h	1.0065 (0.9982;1.0148)	0	1.0085 (0.9984;1.0188)	2	1.0362* (1.0066;1.0667)	4	0.9970 (0.9909;1.0031)	2
O₃ 8 h	0.9905 (0.9710;1.0104)	2	0.9786 (0.9535;1.0044)	5	0.9760 (0.9464;1.0066)	2	1.0051 (0.9896;1.0210)	4
CO 1 h	1.0077 (0.9912;1.0138)	2	1.0092 (0.9945;1.0242)	1	0.9874 (0.9646;1.0107)	1	0.9937 (0.9823;1.0052)	3

L: lag with the best fit. *NO₂-24 h.

Figure 2 Association between air pollution and the number of emergency admissions for selected causes of cardiovascular diseases. Analysis for semesters. Valencia (1994–1996). Hot semester: May; October. Cold Semester: November; April. (A) All cardiovascular disease admissions; (B) heart disease admissions; and (C) cerebrovascular disease admissions. Results expressed as the relative risk (and the 95% CI) in admissions for an increase in the pollutant levels of 10 μg/m³ (1 mg/m³ for CO).

24 h, lag 4, was associated with an increment of 3.6% (95%CI 0.7 to 6.7%) in the expected number of admissions for cerebrovascular diseases. There were no significant associations between air pollution and admissions for digestive diseases. On the other hand, the fit of the model did not change significantly after including the air pollutant indicators in a non-parametric way. In that sense the estimated models conducted to assume the linear relation between air pollution indicators and hospital admissions.

As shown in figure 2, in the analysis for semesters some effect modifications were verified. Thus, the association of cardiovascular admissions with black smoke, SO_2, and CO was higher in the hottest semester. For the group of all cardiovascular admissions (fig 2A) a significant association for black smoke (RR 10 μg/m³: 1.038; 95% CI 1.011 to 1.067) was found in the hottest semester. It was also found for SO_2 24 h (RR 10 μg/m³: 1.050; 95%CI 1.010 to 1.092), for SO_2 1 h (RR 10 μg/m³: 1.017; 95%CI 1.002 to 1.032), and for CO 1 h (RR 1 mg/m³: 1.029; 95%CI 1.005 to 1.055). All these estimates were verified for a lag of two days. No significant association was found in the coldest semester. A similar pattern was observed for heart disease admissions (fig 2B). That is to say, significant associations were found in the hottest semester for black smoke (RR 10 μg/m³: 1.047; 95%CI 1.013 to 1.028), for SO_2 24 h (RR 10 μg/m³: 1.054; 95%CI 1.003 to 1.107), and for CO 1 h (RR 1 mg/m³: 1.029; 95%CI 1.000 to 1.058). Lastly, admissions for cerebrovascular diseases presented some different results (fig 2C). The most consistent association was with NO_2 24 h at lag 4, with significance in the coldest semester (RR 10μg/m³: 1.037; 95% CI 1.005 to 1.070) and quite similar estimates in the hottest one (RR 10μg/m³: 1.034; 95% CI 0.993 to 1.077). The only significant relation in the hot semester was for CO 1 h (RR 1 mg/m3: 1.064; 95% CI 1.015 to 1.114).

Regarding the two pollutant models they provide changes in some estimates. As can be seen in figure 3 (A and B) the estimations of CO and black smoke associations with admissions for all cardiovascular diseases and for hearth disease, respectively, were modified after the inclusion of SO_2 in their models. The association of NO_2 with admissions for cerebrovascular disease (fig 3C) did not change after controlling for other pollutants. In the stratified analysis by semesters, the two pollutant models yielded a similar pattern to the one provided for the whole period.

Discussion

To our knowledge, this is the first study on the short-term relation between air pollution and emergency hospital admissions for cardiovascular diseases in a Spanish city. Our results suggest that current levels of air pollution and emergency cardiovascular admissions are positive and significantly related in the city of Valencia. Four of the five pollutants studied presented a statistical significant association with cardiovascular admissions. Both black

(95%CI 0.1 to 7.1%) in the expected number of all cardiovascular and heart diseases admissions, respectively. A similar increase in NO_2
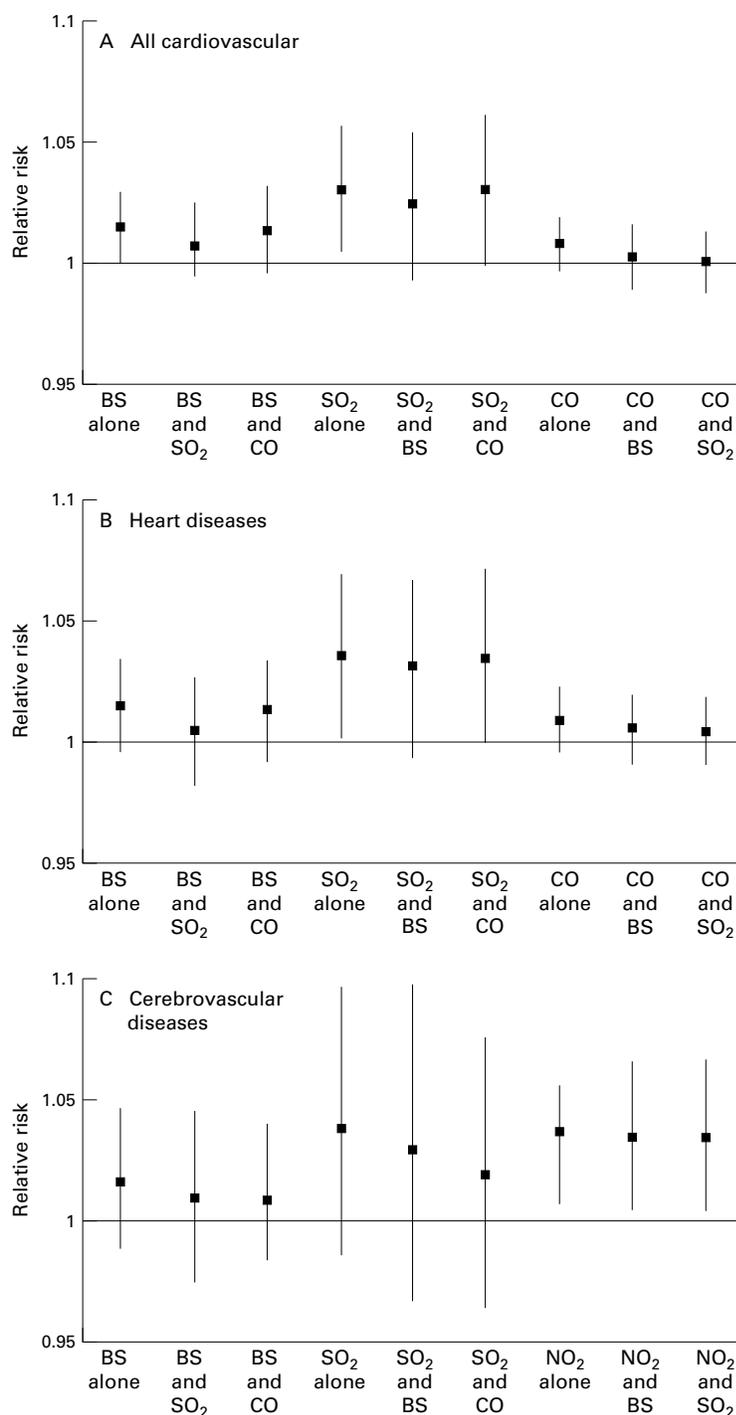
Figure 3   Association between air pollution and the number of emergency admissions for selected causes of cardiovascular diseases. Two pollutant models. Valencia (1994–1996): (A) all cardiovascular disease admissions; (B) heart disease admissions; and (C) cerebrovascular disease admissions. Results expressed as the relative risk (and the 95% CI) in admissions for an increase in the pollutant levels of 10 µg/m³ (1 mg/m³ for CO).

ant. Lastly, ozone did not present any significant association with the outcomes.

Particulates (such as PM10, black smoke or other indicators), CO and SO_2 are among the pollutants that have been most studied in relation to their cardiovascular impact. Attention has been especially paid to the possibility that the association found among some of these pollutants with cardiovascular admissions was independent of the other pollutants. In table 4 the main results of the revised papers including the same outcomes as our study are shown.

In the majority of studies carried out in North America, results show that SO_2 does not seem to have an independent role in the association with admissions for cardiovascular diseases. Thus, Schwartz and Morris in a study in Detroit, USA,[6] found an independent association of PM_{10} with daily admissions for ischaemic heart disease in people 65 years and older, and no independent contributions of SO_2, CO and ozone for this outcome. CO, as particles, presented an independent association with heart failure admissions. Similarly, in Tucson, USA, where the correlation between particles and SO_2 was low ($r = 0.095$) Schwartz[10] showed an independent and additive association between both PM_{10} and CO with cardiovascular admissions in people over 65. Simultaneously, Burnett *et al*, in the 10 major Canadian cities,[9] reported CO as the only gaseous pollutant independently associated with heart failure. In another study carried out by Burnett *et al* in Toronto, Canada,[11] the apparent association between particles and cardiorespiratory hospitalisation disappeared after adjustment for O_3, NO_2 and SO_2. In Chicago, USA, Morris and Naumova[12] found a strong association of CO with congestive heart disease admissions in elderly people. Finally, Schwartz, in a study in eight US counties (including eastern and western ones) found independent effects (to weather or other pollutants) of PM_{10} and CO on hospital admissions for heart disease in people aged 65 and more.[13]

In contrast, results of the few studies carried out in Europe, are not so conclusive concerning the role of each pollutant. Thus, in London, Poloniecki *et al*[17] found an association between SO_2 and acute myocardial infarction and all circulatory diseases. For acute myocardial infarction they also obtained positive associations for black smoke, CO, and NO_2, but the most consistent results in the two pollutant models were for SO_2. In Athens, Pantazopoulou *et al* did not include SO_2 in their study arguing that its levels were low. In the Greek study the magnitude of the association for black smoke, CO and NO_2 with cardiac admissions was of the same order as the one carried out in Valencia.

The results of the European study APHEA,[5] have shown that SO_2 together with the particles contribute to cardiovascular mortality. Furthermore, in this collaborative study, the summary estimates for cardiovascular mortality associated with SO_2 were not substantially altered when particles were also included in the model, confirming that in the cities included in this study SO_2 was more consistent

smoke and SO_2 were more specifically related with heart disease admissions. NO_2 showed a clearer association with cerebrovascular disease, and CO was related with both groups of cardiovascular diseases. The associations with black smoke and CO were significant only for the hottest months. Because of the high correlation between three of the pollutants studied (black smoke, CO, SO_2), it is difficult to assign the potential causal role to an isolated pollut-

Table 4 Results from articles studying the association between cardiovascular hospital admissions and air pollution

Author/s (year of publication)	Site	Outcome	Pollutant	Increase (%) in admissions*
Schwartz J and Morris R[6]	Detroit, USA	Ischaemic heart disease	PM10	0.6
Schwartz J[10]	Tucson, USA	All cardiovascular	PM10	1.8
Burnett R et al[11]	Toronto	Heart disease	Sulphates	2.1
Schwartz J[13]	eight counties USA	All cardiovascular	PM10	1.0
			CO	1.4
Poloniecki JD et al[16]	London, UK	All cardiovascular	BS	1.6
			SO₂	0.5
			NO₂	0.4
			CO	2.1
Wordley J et al[17]	Birmingham, UK	All cardiovascular	PM10	2.1
Morgan G et al[19]	Sydney, Australia	Heart disease	PM10	0.8
			NO₂	2.0
Wong T et al[20]	Hong Kong, China	All cardiovascular	PM10	0.6
			SO₂	1.6
			NO₂	1.3
			O₃	1.3

*Results expressed as the increase (%) in admissions for an increase in the pollutant levels of 10 μg/m³ (1 mg/m³ for CO). The results shown here are the significant results from single pollutant models.

than particles were. If SO_2 has any impact on mortality through cardiovascular diseases, it is coherent to think that it can play a part in the triggering of cardiovascular disease. However, in previous studies carried out in Valencia, results have shown a clearer effect of particles on mortality than SO_2,[29 30] both in the all cause group of mortality and in the circulatory diseases one.

In this study, the two pollutant models showed the complex relation between the air pollution indicators and the outcomes studied. In fact, because of the high correlation between three of the pollutants studied (black smoke, CO, SO_2), it is difficult to assign the potential causal role to an isolated pollutant. Notwithstanding that, considering our results, the estimations of the association with cardiovascular diseases were a little more robust for SO_2. All in all, it is possible that any of these three pollutants (or other elements that they may represent such as "proxy") may cause cardiovascular stress when reaching the cardiorespiratory system, increasing the probability of clinical symptoms. In this sense, provided the local characteristics of Valencia (high correlation between these three pollutants) any of them represents an indicator of a type of "mixture" of atmospheric pollution.

In general we found that the estimates for these three pollutants (black smoke, SO_2, and CO) were higher in the hottest semester than in the coldest one. We have found an effect modification for period on the relation between cardiovascular admissions and CO. Our estimates for CO are only significant for the hottest months.

Conversely, in their study in Chicago, Morris and Naumova[12] found that the association of CO with congestive heart disease admissions was temperature dependent, with the magnitude of the effect increasing with decreasing temperature. There are some epidemiological evidence relating to an interaction between temperature and air pollution, both with low temperatures and high ones. In the study in Toronto, Burnett et al,[11] described relatively weaker associations in summertime than in year round ones. They argued that it may be attributable to low summertime concentrations. This could not be the case in Valencia. In fact, the summer CO mean concentration in

Toronto was 2.1 mg/ml, and the mean concentration in Valencia in the hottest semester was 5.1 mg/ml. On the other hand, an interaction between air pollution and high temperatures in their relation with mortality was also described in the study in Athens.[22]

The results presented here are coherent with the findings of other studies carried out in Valencia on the short-term effect of air pollution on mortality. So, in the context of the Spanish multi-centred EMECAM Project[26] the results for the association between CO and cardiovascular mortality in Valencia[30] showed positive and significant estimates for the hottest months (RR for a 1 mg/m³ increase in the daily CO concentration of 1.068; 95%CI: 1.007 to 1.133), which was not found during the rest of the year (RR 1 mg/m³ CO: 0.990; 95%CI: 0.959 to 1.022). In a previous study we found the same pattern of effect modification for SO_2 and total and cardiovascular mortality: its relation was significant in the hot period but not in the cold one.[29]

In some other Mediterranean cities the risk estimates for the relation between air pollution and mortality were higher in the warmer season.[31 32] Besides the potential for biological interaction between air pollution and mortality, other possible explanations have been argued. One derives from the fact that during the warmer months people could modify their activity patterns.[33] This includes people spending more time outdoors and windows being left open for longer, so the actual exposure could be more correlated with outdoor concentrations. Another reason could be that, during the warmer period, other stronger determinants of daily mortality and morbidity (such as acute respiratory infections) are less influential.[32] Lastly, one local potential reason for this pattern could be that the climate in Valencia is very mild, without extreme cold temperatures. In fact, the lowest daily average temperature registered during the study period (6.6ºC) was superior to the cut point for stratification corresponding to the lowest temperature strata analysed in Chicago (4.4ºC) for the daily maximum temperature.[12] That is to say, it is difficult to have an interaction between air pollution and low extreme temperatures because they almost do not exist in Valencia.

Our data provide some indication of an independent association between NO_2 and hospitalisations for cerebrovascular disease. The correlation of NO_2 with weather and other pollutants in Valencia is low, and daily level series of NO_2 did not show a defined seasonal pattern. Furthermore, the estimates of that association did not change after adjusting for other pollutants. All this supports the idea that these results are not confounded for other factors varying in time

In contrast with cardiac disease, the relation between air pollution and cerebrovascular diseases has been explored in only a few studies. Pönka and Virtanen reported in Helsinki[15] a similar relation between NO_2 and cerebrovascular diseases than the one found in Valencia. In a study in Birmingham only including PM10 as air pollution indicator, Wordley *et al*[17] showed an association of particulates with admissions for cerebrovascular diseases and not with other cardiovascular disease groupings. In another paper studying this diseases' group, Poloniecki *et al*[16] did not find any evidence of its association with black smoke, ozone, NO_2, SO_2, or CO, but it could be relevant to mention that these authors only explored the first lag of pollutants. In Hong Kong, China, Wong *et al*[20] showed a significant relation of NO_2, O_3, SO_2 and PM_{10} with hospital admissions for cardiovascular diseases. In their analysis for specific causes ischaemic heart disease and cerebrovascular diseases were not significantly associated with any of the pollutants; however NO_2 showed the highest effect with cerebrovascular diseases (RR for an increase of 10 $\mu g/m^3$: 1.008, 95%CI 0.998 to 1.018).

In a considerable number of studies, ozone has been linked with respiratory toxicity including increase of mortality,[5] emergency respiratory visits,[34 35] and hospital admissions for respiratory morbidity.[11 36] In Valencia we have described such a significant association with emergency visits for asthma[37] and for chronic obstructive pulmonary disease.[38] However, there is little evidence of an association between ozone and cardiovascular morbidity. Our results do not suggest an impact of ozone on the number of hospitalisations attributable to cardiovascular disease. These results agree with those obtained in other studies[6 8 10 12 16 19] in that all of them did not find an association with cardiovascular hospital admissions. Only three of the studies reviewed showed evidence of a consistent association between ozone and cardiovascular admissions. In the study of Burnett *et al* in Toronto,[11] ozone was the most clearly and strongly associated with hospitalisation for cardiac diseases in summer. In the study of Pönka and Virtanen in Helsinki,[15] ozone, besides nitric oxide, was the most clearly associated pollutant with the number of emergent admissions for ischaemic cardiac diseases. Lastly, Wong *et al*[20] in Hong Kong, found a significant relation of O_3 with hospital admissions for cardiovascular diseases.

In contrast, Prescott *et al*[18] found a negative association of O_3 with cardiovascular admissions in ages over 65. The authors argued that,

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KEY POINTS
- Current levels of air pollution and emergency cardiovascular admissions are significantly associated in Valencia.
- The independent effect of some correlated pollutants (that is, particles, SO_2, and CO) is difficult to evaluate, as they represent proxies of the quality of ambient air.
- NO_2 could play a part in the development of cerebrovascular diseases; this hypothesis needs further investigation.

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because of the complex relation between O_3 and NO and NO_2, their central estimate at the fixed sampling point could provide an inaccurate reflection of the actual exposure for most of the population. This fact may have happened in other cities where studies of the effect of ozone on health have been carried out. Because it is a secondary pollutant, generated from precursors such as nitrogen oxide and volatile organic compounds through exposure to solar radiation, it reaches its concentration maximum far from the emitting focus (mainly traffic). For that reason, to evaluate the impact of ozone on health more precisely, it would be suitable to have monitoring stations located in peripherical areas where the population is likely to be exposed to the highest levels of ozone.[39]

In the past years a great advance has been made concerning the possible biological mechanism of the impairment of air pollution in cardiovascular health. Results of studies that have explored the possible physiopathological mechanisms have given evidence that fine particulates in suspension can lead to systemic effect, such as an increase of plasma viscosity[40] or heartbeat alterations.[41] Toxicological studies have found biological alterations in rats after exposure to filtered air or concentrated ambient particulate matter.[42] Abnormalities in the electrocardiogram after exposure to fine particles have also been found in dogs.[43]

The possible role of CO in causing cardiovascular disease has been investigated for many years.[44] People occupationally exposed to high levels of CO presented high risk of arteriosclerosis heart disease.[45] But even exposure to low doses of CO can produce significant effects on cardiac function during exercise in subjects with coronary artery disease, as showed by Allred *et al*.[46 47]

The physiopathological mechanisms of SO_2 and NO_2 causing cardiovascular damages are insufficiently understood, and more research is needed in this way. Probably these pollutants, as also particles and CO, could play a part among other not yet studied components of air pollution as sulphates or volatile organic aerosols from automotive or other sources.

The use of a database designed for other means may have a limited application in other different fields. In the case of time series epidemiological studies, the key aspects would be exhaustivity of registers, perseverance of specific clinical information and the fulfilment of

date variable.[48] The hospital database quality of Valencian Community has been analysed showing very few errors in the administration variables, except for the residence.[48] This problem may result in a misclassification bias, which would be non-differential in any case, as it does not seem logical for patient residence data errors to be connected with daily atmospheric pollution levels. On the other hand, a study carried out in Canada[49] showed a good agreement (κ index: 0.84) in the classification of visits attributable to heart disease, and there was no evidence of diagnostic bias in relation to daily air pollution levels.

In conclusion, these results add more evidence to the knowledge about the impact of air pollution on cardiovascular health, in this case in a Spanish Mediterranean city, a different climate to the ones already studied. Results show that an increase in pollution levels attributable to SO_2, black smoke or CO are associated with an increase in the number of emergency admissions for heart diseases in Valencia. Furthermore, an association between environment levels of NO_2 and the number of urgent admissions for cerebrovascular diseases has been found, although this aspect needs further investigation to enable adequate quantification. Moreover, the results presented here are coherent with previous studies on mortality carried out in Valencia. These evidences of preventable disease linked to air pollution must be a key element in the process of decision making related with public health policies.

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