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Short-term exposure to air pollutants increases the risk of ST elevation myocardial infarction and of infarct-related ventricular arrhythmias and mortality

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ABSTRACT

Background: The relation between STEMI and air pollution (AP) is scant. We aimed to investigate the short term association between AP and the incidence of STEMI, and STEMI-related ventricular arrhythmias (VA) and mortality.

Methods: The study was carried out in the area of Barcelona from January 2010 to December 2011. Daily STEMI rates and incidence of STEMI-related VA and mortality were obtained prospectively. The corresponding daily levels of the main pollutants were recorded as well as the atmospheric variables. Three cohorts were defined in order to minimize exposure bias. The magnitude of association was estimated using a time-series design and was adjusted according to atmospheric variables.

Results: The daily rate of hospital admissions for STEMI was associated with increases in PM 2.5, PM 10, lead and NO2 concentrations. VA incidence and mortality were associated with increases in PM 2.5 and PM 10 concentrations. In the most specific cohort, BCN (Barcelona) Attended & Resident, STEMI incidence was associated with increases in PM 2.5 (1.009% per 10 μg/m^3) and PM 10 concentrations (1.005% per 10 μg/m^3). VA was associated with increases in PM 2.5 (1.021%) and PM 10 (1.015%) and mortality was associated with increases in PM 2.5 (1.083%) and PM 10 (1.045%).

Conclusions: Short-term exposure to high levels of PM 2.5 and PM 10 is associated with increased daily STEMI admissions and STEMI-related VA and mortality. Exposure to high levels of lead and NO2 is associated with increased daily STEMI admissions, and NO2 with higher mortality in STEMI patients.

1. Introduction

Short-term exposure to air pollution (AP) has been associated with adverse cardiovascular outcomes in the general population, [1–14]. Considerable progress has been made in the prevention and management of ischemic heart disease but, in comparison with other well established risk factors, the role of exposure to AP as a trigger in the days and hours before the onset of an acute coronary event has received relatively little attention. However, short-term elevated particulate matter (PM) exposure has been linked with vasoconstriction, [15], increased blood coagulability, [16], and inflammation, which may contribute to acute complications of atherosclerosis including plaque rupture, thrombosis, and precipitation of acute ischemic events, [6,8].

The majority of studies reporting associations between AP and cardiovascular outcomes have used administrative databases with the corresponding diagnostic codes, which can result in a potential misclassification and reporting bias, [3,10,11]. On the other hand, we do not have the most appropriate way to measure exposure to AP, so most studies assume that the place of residence is the place where the individual is exposed, [2,17] when sometimes individuals spend a great deal of time away from their residence.

Moreover, little is known about the relationship between AP and ST elevation myocardial infarction (STEMI), [7,17–19], and there is a lack of knowledge about the relationship between AP and STEMI-related complications such as ventricular arrhythmias (VA) occurrence and mortality.

Codi IAM system of care prospectively has been collecting specific information from all confirmed STEMI cases in Catalonia since 2010.

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[1] He had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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This prospective registry of well-characterized STEMI patients provides an unbiased estimation of the daily STEMI rates in Barcelona together with their short-term complications, which can be linked to AP and climate variables. It differs when the STEMI occurs in a different place from where the patient lives.

The present study addresses the relationship between short-term AP exposure together with changes in climate variables with STEMI incidence, and with the rates of VA and mortality in patients included in the Codi IAM registry.

2. Methods

2.1. Study area and outcome data

The population studied included all STEMIs attended in Barcelona and surrounding areas recorded by Codi IAM in 2010 and 2011. Barcelona is situated in the northeast of Spain, in Catalonia. Codi IAM is a network that includes an emergency response centre in a number of healthcare facilities providing emergency care when a patient is suspected of having a heart attack and is in need of immediate reperfusion. All activities are declared and recorded by the emergency system and the hospital where emergency coronary angiography is performed and subsequently reviewed by the Health Department of the Government of Catalonia to avoid data being lost. Information on demographics, time intervals, location of each event, electrocardiogram characteristics and complications are recorded on all patients. STEMI-related VA (ventricular tachycardia and ventricular fibrillation) and mortality are defined temporarily as occurring from the first medical contact and during the first 24 h. Patients in whom a STEMI is suspected but who die before an electrocardiogram is performed are not included in the registry. Final diagnosis is reported, which enables identification and exclusion of false positive cases.

This study design was reviewed and approved by the Ethics Committee of Hospital Vall d'Hebron, Barcelona.

2.2. Ambient air quality and meteorological data

Data was provided independently according to the good functioning and quality control applied by the Meteorological Service of Catalonia and the Department of Environmental Planning and Sustainability of the Catalan Government. For the present work, ambient air quality and meteorological data for 730 days (1st January 2010–31st December 2011) were analyzed.

Meteorological data on temperature (°C), relative humidity (%), rain precipitation (mm) and barometric pressure (hPa), were obtained from the Network of meteorological equipment. Daily air concentrations of PM 10 ($\mu g/m^3$), PM 2.5 ($\mu g/m^3$), benzene ($\mu g/m^3$), cadmium (ng/m^3), nickel (ng/m^3), lead (ng/m^3), SO_2 ($\mu g/m^3$), NO ($\mu g/m^3$), NO_2 ($\mu g/m^3$), CO (mg/m^3), and O_3 ($\mu g/m^3$) were obtained from thirteen monitoring stations (Supplemental material 1). Each parameter was measured every hour and we estimated the daily 24-hour average for the analysis. Lag times from 1 to 5 days between exposure and STEMI occurrence were recorded.

The average daily levels of pollutants differed widely among stations, probably because of the geographic characteristics of Barcelona. Approximately half of stations systematically measured greater levels of pollutants than the other half. Thus we computed for each pollutant a low daily average concentration from those stations that systematically recorded low averages (LA) and a high daily mean concentration from those stations that systematically recorded higher averages (HA). We checked that considering their location, stations that capture more pollutants are those that are closer to roads and central city areas. Those with less pollution are near green areas.

2.3. Missing values

We selected for computation the LA and HA stations with the lowest missing values for each pollutant. Then, using the EM algorithm, [20], the missing data was imputed separately for the LA and HA stations. Missing value(s) were estimated using the available measurements in the other monitoring sites on the same day.

2.4. Statistical analysis

The results studied were the daily number of STEMIs attended in Barcelona and surrounding hospitals during the study period as well as the daily rates of STEMI-related VA and mortality.

Patients included in the study could have started their symptoms outside Barcelona, whether or not they were residents of Barcelona, and then were transferred to a Barcelona hospital for emergent coronary angiography. In order to rectify this exposure measurement error, we performed the analysis in three defined cohorts. A first cohort called "BCN Attended" was defined as all STEMI patients treated in Barcelona hospitals. A second cohort called "BCN Attended <120 min" was defined as all STEMI patients reaching the treating hospital within 2 h from the symptoms onset and a third cohort "BCN Attended & Resident" was defined as all STEMI patients who lived and were treated in Barcelona. In the two latter cohorts, a more homogeneous exposure to the corresponding AP levels was expected and so a potentially less biased estimation of the effect would be likely.

We applied the APHEA protocol (Supplemental material 2) to estimate the short-term association between atmospheric exposures and outcomes, [21]. It basically includes the time-series modeling of potential confounding factors (i.e. seasons, meteorological factors, and day of the week), choosing the "best" AP models, and applying diagnostic tools to check the adequacy of the models. The final analysis used autoregressive Poisson models allowing for overdispersion. It was assumed that overdispersion was explained by external factors such as calendar factors, time, and seasons. All pollutants were analyzed separately (unipollutant model) and jointly (multipollutant model).

Descriptive statistics included the daily average, range, standard deviation, and percentiles for each variable. Time-series graphs were plotted to depict variations over time for each variable. To describe potential functional relationships between exposures and outcomes, scatter diagrams were used.

In a first step, lineal and quadratic time-trends were included in the model for adjustment purposes, as well as the sinus and cosinus waves using different lengths (i.e. one-year, six-month and three-month waves) to model seasons. The best time-trend model was selected based on the Akaike Information Criterion (AIC). In a second step, the calendar-time effects (days, months, day of the week, hot months, etc.) were also tested in the model. Afterwards, atmospheric variables were tested. Finally, we added the pollutant exposures to the best model according to the AIC. The association of the levels of the different pollutants with dependent variables was tested one by one. We tested models using the daily average of pollutant concentrations from both LA and HA stations. Exposure effects were tested from lag 1 to lag 5 and also using the average of lag 1 to lag 5. Cross correlation function was used to assess the lag with the greatest impact. Those pollutants with greater impact and statistical significance were retained in the corresponding models. In models including VA and mortality as dependent variables, the daily number of STEMIs was included as an independent variable for adjusting purposes.

In all candidate models autocorrelation in residuals was assessed. Relative risks (RR) and attributable risks (AR) were estimated from the model coefficients.

All analyses were performed using software RStudio 0.97.551.

3. Results

3.1. Study population and exposure characteristics

Barcelona and the immediate suburban area have a population of 5.5 million inhabitants living in a 636 km^2 area. During this period, 4141 STEMI cases met inclusion criteria, which represents 82.6% of all STEMIs included in Codi IAM registry. Of them, 3689 (73.6%) corresponded to the BCN Attended <120 min cohort and 2157 (51.1%) corresponded to BCN Attended & Resident cohort (Fig. 1).

All descriptive statistics from air pollutants and environmental measurements are shown in Supplemental material 3. The median and IQR (interquartile range) for BCN Attended were 7 and 5–9 STEMI per day, for BCN Attended <120 min were 5 and 3–7 and for BCN Attended & Resident were 3 and 2–4, respectively.

3.2. Effects of particulate pollutants

PM 2.5 and PM 10 were highly correlated, whereas Nickel, SO2, NO, NO2, CO and O3 were only moderately correlated with PM 2.5 and PM 10 (Table 1).

There was a certain periodicity in the time-series distribution of the STEMIs attended (Fig. 2). Periodicity was not so evident for daily VA and mortality, although there were peaks in these outcomes as well as in peaks of STEMI.

Scatter-diagrams show the relation between AP and outcomes in the BCN Attended and BCN Attended <120 min. The most evident associations found in BCN Attended cohort were between lead levels and the rate of STEMI and its mortality. In BCN Attended <120 min cohort, PM 2.5, lead, benzene, NO, NO_2, and CO were the main AP related to STEMI rate, and PM 10 was related to STEMI mortality (Fig. 3). No evident relationships between AP and VA were found. These results were the first approximation, since no adjustment was made by potential confounders.

Graphical representation of the concentration of main pollutants and the outcomes rates are shown in Supplemental material 4. RR and AR of AP variables significantly associated with outcomes in Poisson regression models were in concordance in the three cohorts analyzed. The outcomes of the most relevant pollutants (PM 2.5, PM 10, and NO2) are shown in Table 2. PM 2.5 was common in all three cohorts as a statistically significant trigger of STEMI on the same day of exposure. In BCN attended cohort, lead (lag 1, H; RR 1.0260, 95% CI: 1.0027–1.0480) and NO (lag 4, H, 95% CI: 1.0140 1.0009–1.0270) were also significantly associated with STEMI rate. In BCN Attended <120 min NO2 was also significantly associated.

Concerning mortality, PM 2.5 and PM 10 were associated in the three cohorts on the same day of exposure. In BCN Attended & Resident cohort, NO2 was also associated with mortality.

Finally, PM 2.5 was associated with a higher incidence of VA in the three cohorts and PM 10 only in BCN Attended & Resident cohort.

4. Discussion

The present time-series study conducted in a cohort of patients with STEMI in a closed geographical area shows an association between AP and the rate of STEMI and their acute main complications, even after adjusting for seasonal, meteorological factors, and time-calendar variables. Specifically, an increase in PM 2.5 levels was associated with a higher rate of STEMI, VA and mortality in the three cohorts as

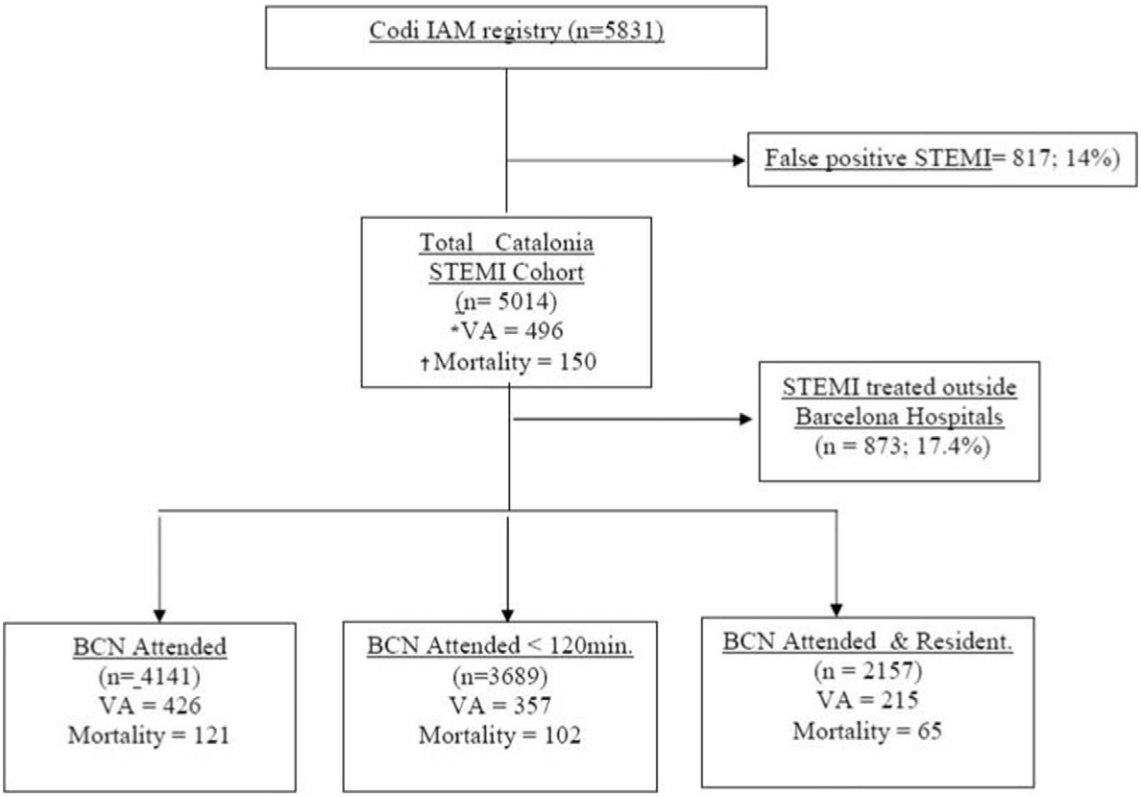

Fig. 1. Patients selection flow chart from the Codi IAM STEMI Registry between January 2010 and December 2011. False positive STEMI includes patients with other final diagnoses (takotsubo syndrome, pericarditis, myocarditis, early repolarization, vasospasm and others). Total Catalonia STEMI cohort includes all STEMIs of the registry. BCN Attended cohort includes all STEMI patients attended in Barcelona and surrounding hospitals. BCN Attended <120 min cohort includes all STEMI patients attended in Barcelona and surrounding hospitals within 120 min from the symptoms onset. BCN Attended & Resident includes all STEMI patients who lived and were treated in Barcelona *VA: ventricular tachycardia and ventricular fibrillation from the first medical contact and during the first 24 h. †Mortality: mortality from the first medical contact and during the first 24 h.

Table 1
Correlations between independent variables (pollutants).

	PM 10 (μg/m^3)	PM 2.5 (μg/m^3)	Benzene (μg/m^3)	Cadmium (ng/m^3)	Nickel (ng/m^3)	Lead (ng/m^3)	SO2 (μg/m^3)	NO (μg/m^3)	NO2 (μg/m^3)	CO (mg/m^3)
PM 2.5 (μg/m^3)	0.677**									
Benzene (μg/m^3)	0.180**	0.123**								
Cadmium (ng/m^3)	0.148**	0.155**	0.118**							
Nickel (ng/m^3)	0.552**	0.402**	0.087*	0.024						
Lead (ng/m^3)	0.314**	0.328**	0.077*	0.079*	0.221**					
SO2 (μg/m^3)	0.416**	0.416**	0.152**	0.007	0.321**	0.215**				
NO (μg/m^3)	0.448**	0.467**	0.507**	0.086*	0.219**	0.174**	0.512**			
NO2 (μg/m^3)	0.552**	0.524**	0.460**	0.104**	0.445**	0.197**	0.493**	0.765**		
CO (mg/m^3)	0.497**	0.507**	0.499**	0.089*	0.300**	0.158**	0.486**	0.914**	0.878**	
O3 (μg/m^3)	0.417**	0.418**	0.153**	0.007	0.323**	0.215**	0.186**	0.514**	0.497**	0.489**

m^3: cubic meter; μg: micrograms; ng: nanograms; PM: particulate matter.
* p-value ≤ 0.05.
** p-value ≤ 0.001.

well PM 10 with mortality, which indicates that they are the most harmful pollutants. The fact that the association with a pollutant in the BCN Attended cohort is maintained in the other 2 cohorts provides robustness to the results and goes against the bias exposure. Other associations were also present but were less consistent as the results were not present in all three cohorts. In general, these associations were higher in BCN Attended & Resident cohort, despite having fewer STEMIs, which could go hand in hand with the least biased cohort. On the other hand, the fact that we did not find any pollutant in particular in the multipollutant model leads us to believe that the events are associated with pollution in general and pollutants are strongly correlated with each other.

4.1. Selected study population

While epidemiological and experimental studies have consistently demonstrated adverse effects of PM exposure on human health, [15,22,23], the mechanism of the effect is still unclear. One of the major controversial issues is whether the cardiovascular toxicity of particles resides or not, in some specific fraction of the particle as defined by its chemical composition or size. However, since the chemical composition of particles is constantly changing and varies greatly between different geographical, meteorological, and source-specific variables, the epidemiological relationship between AP concentration and events could be biased. In order to reduce this exposure bias, we focused on a specific population circumscribed to a closed geographic area instead of assessing larger areas where pollutant concentration varies widely, [7,22] and defined three cohorts with the aim of reducing exposure bias.

4.2. Comparison with other studies

In general, our results increase the growing evidence on the relationship between AP and hospital admissions for cardiovascular diseases, [6,8], and specifically between short-term PM exposure and cardiovascular events, [3,15], including acute myocardial infarction (AMI), [9,10,24]. Although some of these relationships have already been described, controversy exists basically because of the potential confounder of these studies, [2,7,18]. Really, most studies reporting associations between AP and cardiovascular outcomes have used administrative databases with the corresponding diagnostic codes, which may imply a risk of bias, including misclassification and reporting bias, [3,10,11].To our knowledge, our study is the first one that uses an exhaustive STEMI registry to assess at the same time the risk and the prognosis of STEMI associated with AP variations. Our PM results are in line with the recent huge MED PARTICLES project where there is clear evidence of the effects of fine PM on both mortality and morbidity, [14].

Another point of criticism has been the heterogeneous methods used to assess the relationship between AP levels and the incidence of AMI and the risk of death, [6]. There is a wide variability in the number of monitors used, sample size of studies, the comorbidities included, the method of pollution measurement, and the level of ambient concentration, [2,8,9,24]. While some studies used only one central urban air pollution monitoring station as an exposure estimate for the entire population, [3], assuming that the exposure is homogenous across the whole area, other studies measured AP at the nearest air pollution monitoring site to the place of residence, [4,7]. Finally, measurements also varied, from hourly to every six days, [22]. In our study the average of thirteen monitoring stations in a relatively close area with measurements taken every hour was used in order to reflect the exposure variation in the best way.

Correlations between the main pollutants studied were similar to others estimated in big European cities like Paris, [18] and Rome, [26]. To highlight the correlation between PM 2.5 and PM 10 it was higher in Paris than in Barcelona. Less correlation in Barcelona indicates that the source of these pollutants is different and could explain in part the different effect on the incidence of STEMI, VA and mortality.

4.3. Air pollutants and STEMI

A lack of differentiation of AMI categories in STEMI and non-STEMI has been common in epidemiological studies on AP and cardiovascular risk, [3,4]. One of the strengths of our study is that data were prospectively collected by cardiologists thereby ensuring the diagnosis of STEMI. In this sense, most studies have been conducted retrospectively and using data coded according to the International Classification of Diseases, [2,4,22]. In addition, different criteria of AMI such as increased cardiac biomarkers, Q waves, ECG changes or other variables have usually been used with the subsequent risk of bias. Even considering these limitations, in a recent meta-analysis, [9], PM 10 and PM 2.5 were significantly associated with an increase in AMI risk, with RR of 1.006 (95% CI, 1.002–1.009) and 1.025 (95% CI, 1.015–1.036) respectively. Even though the evidence of the higher rates of AMI admissions associated with the increase of PM 10 and PM 2.5 is strong, [3,25], to our knowledge there are only four studies reporting the effects of short-term effects of AP variations in STEMI patients. The biggest was conducted in England and Wales and included nearly 190,000 STEMIs, [7]. In this study the diagnosis of STEMI at discharge was based on clinical history, presence of electrocardiographic changes of ST elevation consistent with infarction and elevated enzyme or troponin levels. Using lags up to 4 days and controlling temperature, no association between AP variations and STEMI incidence was found. The large area of study, resulting in a large variability in pollutants composition and climate conditions, probably explains the absence of findings. Recently, a large population-based registry in Paris with angiographically proven STEMI found no significant relationship between AP levels and STEMI

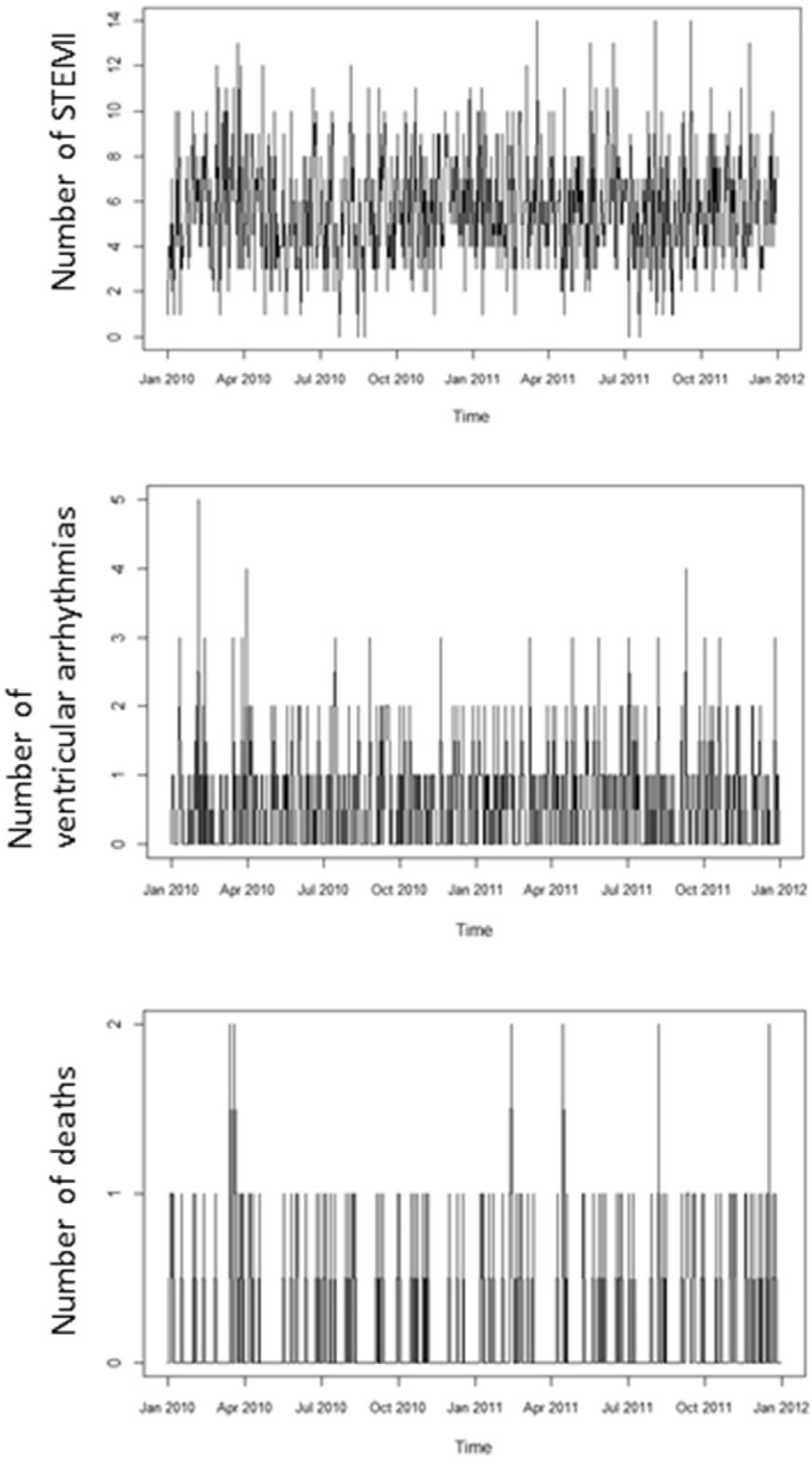

Fig. 2. Time-series graphs of daily number of STEMIs, daily ventricular arrhythmias and daily mortality in BCN Attended cohort.

incidence, [18]. Different exposure levels of air pollutants (e.g. mean PM 10 23.7 and 27.5 μg/m^3; mean PM 2.5 15.2 and 17.4 μg/m^3 in Paris and Barcelona, respectively) could explain at least in part the discrepancy between these results and ours. In fact, the mean PM concentration varies substantially in different European large cities, [11,18,26]. A third study with a small number of patients found that an increased fine particle concentration in the hour prior to acute coronary syndrome onset was associated with an increased risk of STEMI, [19]. Finally, a recent study observed increased odds associated with each 7.1 μg/m^3 increase in PM 2.5 (OR, 95% CI: 1.17, 0.99–1.39) as a STEMI trigger, [27].

4.4. New relations between particular air pollutants and STEMI

To the best of our knowledge, we describe for the first time a potential deleterious effect of exposure to ambient lead and NO on STEMI incidence, even though the effect was only found in BCN Attended

cohort. There has been considerable debate in recent years about the health effects of exposure to particular common environmental pollutants including PM, O3, CO, NO2 and SO2. Even though it has been reported that exposure to lead concentrations exceeding 0.225 ug/m^3 tends to increase AMI risk by 12% (95% CI 0.94–1.34), [28], the interest on the effects of this pollutant on health has been decreased once its concentration in gasoline and paints has been significantly reduced.

On the other hand, although the effects of NO2 have been studied, [10,25], there has been little interest in studying NO effects possibly because it is a highly unstable molecule in the air, as it is rapidly oxidized in oxygen becoming NO2, which complicates its measurement. On the known harmful effects of NO2 we found that the NO is also associated with a higher incidence of STEMI.

4.5. Effects of air pollutants on STEMI ventricular arrhythmias

PM exposure can trigger changes in cardiac electrophysiology which could eventually increase the risk of arrhythmias, [5]. Studying patients with cardiac disease and implantable cardioverter defibrillators has clarified the association between air pollution and arrhythmias, [29]. In the context of AMI, the relation between arrhythmias and AP has been poorly studied. In this sense, our results are consistent with a previous study linking PM 2.5 exposure with an increased risk of arrhythmias, [7]. Moreover, the relationship between PM 2.5 exposure and the risk of VA occurring within 24 h in STEMI is described for the first time in the present study.

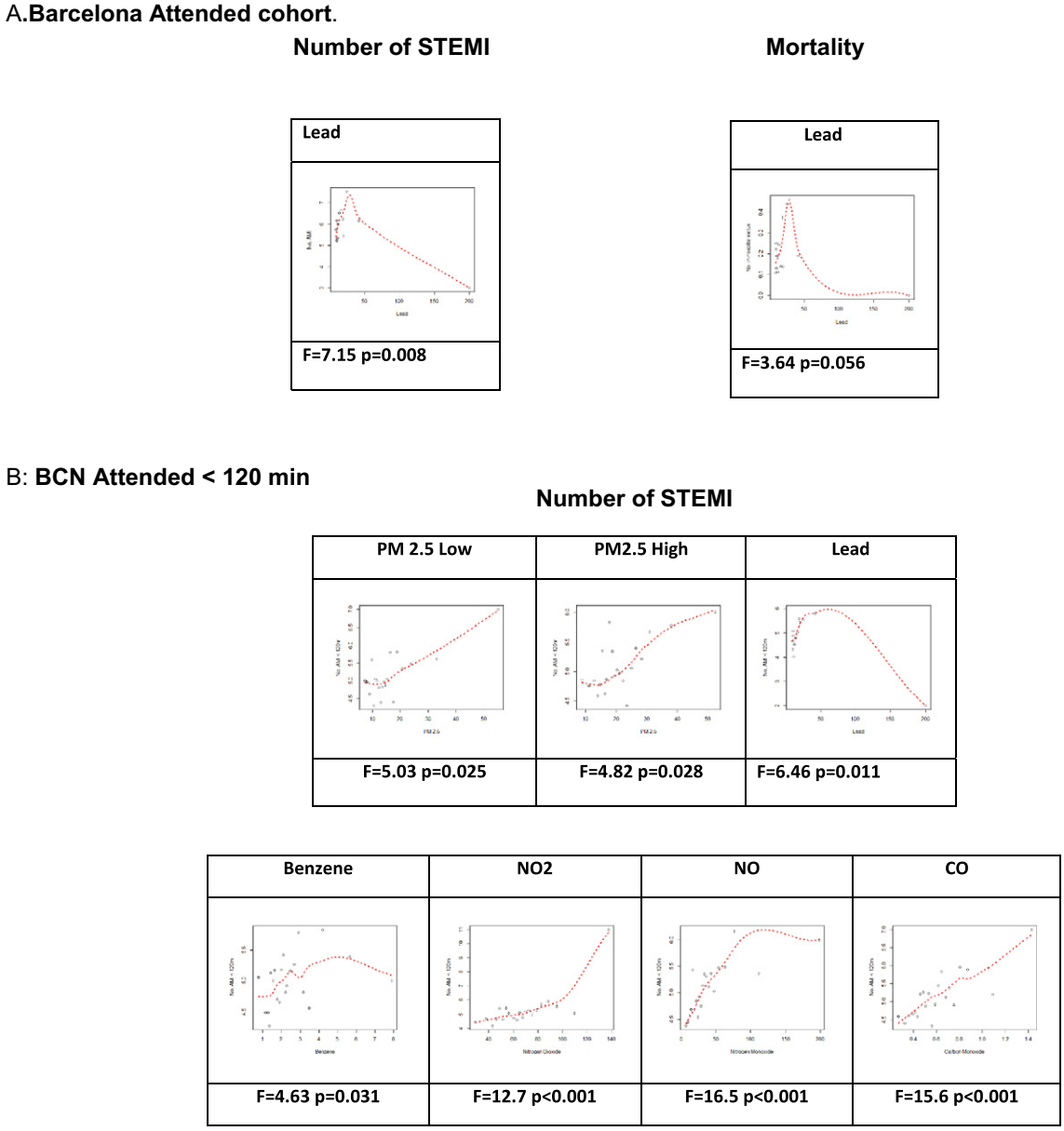

Fig. 3. Scatter-diagrams of the most evident associations found between pollutants and outcomes. F: F of the regression; STEMI: ST elevation myocardial infarction.

Table 2
Relative risk (RR) and attributable risk percent (AR%) of STEMIs, deaths and ventricular arrhythmias attended for each increase (10 units) in the concentration of the independent variable in the three cohorts analyzed.

Outcome	Unipollutant			Multipollutant		
	Variable	RR (95% CI)	AR% (95% CI)	Variable	RR (95% CI)	AR% (95% CI)
BCN Attended						
Number of STEMI[a]	PM 10 (low–lag 2)	1.004 (1.000–1.007)	0.39% (0.06%; 0.70%)	PM 10 (low–lag 2)	1.002 (0.998–1.006)	0.21% (−0.19%; 0.60%)
	PM 2.5 (low)	1.005 (1.001–1.010)	0.54% (0.07%; 1.00%)	PM 2.5 (low)	1.003 (0.998–1.008)	0.32% (−0.21%; 0.83%)
	NO2 (high–lag 2)	1.002 (1.000–1.003)	0.17% (0.00%; 0.33%)	NO2 (high–lag 2)	1.001 (0.999–1.003)	0.09% (−0.10%; 0.27%)
Number of acute deaths[b]	PM 10 (mean low)	1.036 (1.011–1.059)	3.43% (1.13%; 5.55%)	PM 10 (mean low)	1.030 (0.981–1.081)	2.93% (−1.96%; 7.47%)
	PM 2.5 (mean low)	1.042 (1.012–1.070)	4.05% (1.17%; 6.56%)	PM 2.5 (mean low)	1.022 (0.959–1.086)	2.14% (−4.22%; 7.92%)
	NO2 (mean low)	1.009 (0.991–1.026)	0.87% (−0.89%; 2.54%)	NO2 (mean low)	0.988 (0.966–1.011)	−1.17% (−3.48%; 1.04%)
Number of ventricular arrhythmias[c]	PM 10 (low–lag 3)	1.009 (0.999–1.020)	0.92% (−0.05%; 1.95%)	PM 10 (low–lag 3)	1.004 (0.990–1.017)	0.38% (−0.98%; 1.68%)
	PM 2.5 (high–lag 3)	1.016 (1.003–1.028)	1.53% (2.52%; 2.77%)	PM 2.5 (high–lag 3)	1.016 (0.998–1.035)	1.62% (−0.17%; 3.26%)
	NO2 (high–lag 2)	0.998 (0.993–1.003)	−0.20% (−0.69%; 0.29%)	NO2 (high–lag 2)	0.995 (0.990–1.001)	−0.46% (−0.98%; 0.07%)
BCN Attended <120 min						
Number of STEMI[d]	PM 10 (low)	1.004 (1.000–1.007)	0.37% (0.02%; 0.72%)	PM 10 (low)	1.001 (0.996–1.006)	0.08% (−0.40%; 0.55%)
	PM 2.5 (high)	1.005 (1.001–1.010)	0.52% (0.07%; 0.98%)	PM 2.5 (high)	1.002 (0.995–1.008)	0.17% (−0.46%; 0.81%)
	NO2 (high)	1.002 (1.001–1.004)	0.25% (0.08%; 0.41%)	NO2 (high)	1.002 (1.000–1.004)	0.20% (−0.00%; 0.40%)
Number of acute deaths[e]	PM 10 (mean low)	1.034 (1.010–1. 058)	3.33% (0.95%; 5.49%)	PM 10 (mean low)	1.039 (0.988–1.092)	3.75% (−1.24%; 8.46%)
	PM 2.5 (mean low)	1.039 (1.006–1.070)	3.79% (0.62%; 6.54%)	PM 2.5 (mean low)	0.988 (0.921–1.056)	−1.22% (−8.56%; 5.35%)
	NO2 (low–lag 5)	1.011 (0.999–1.023)	1.13% (−0.13%; 2.29%)	NO2 (low–lag 5)	1.007 (0.993–1.020)	0.71% (−0.66%; 1.97%)
Number of ventricular arrhythmias[f]	PM 10 (low–lag 3)	1010 (0.999–1.021)	1.01% (−0.04%; 2.01%)	PM 10 (low–lag 3)	1.001 (0.986–1.015)	0.09% (−1.41%; 1.51%)
	PM 2.5 (high–lag 3)	1.019 (1.005–1.033)	1.84% (0.45%; 3.16%)	PM 2.5 (high–lag 3)	1.017 (0.998–1.037)	1.69% (−0.24%; 3.57%)
	NO2 (high–lag 4)	1.003 (0.998–1.008)	0.32% (−0.21%; 0.84%)	NO2 (high–lag 4)	1.001 (0.995–1.006)	0.06% (−0.52%; 0.63%)
BCN Attended & Residents						
Number of STEMI[g]	PM 10 (low)	1.005 (1.001–1.009)	0.51% (0.07%; 0.93%)	PM 10 (low)	0.999 (0.991–1.007)	−0.12% (−0.95%; 0.69%)
	PM 2.5 (low)	1.009 (1.002–1.015)	0.88% (0.25%; 1.49%)	PM 2.5 (low)	1.009 (0.997–1.021)	0.86% (−0.32%; 2.02%)
	NO2 (high–lag 1)	1.002 (0.999–1.004)	0.22% (−0.00%; 0.44%)	NO2 (high–lag 1)	1.001 (0.999–1.004)	0.13% (−0.12%; 0.37%)
Number of acute deaths[h]	PM 10 (mean high)	1.045 (1.010–1.080)	4.29% (1.02%; 7.39%)	PM 10 (mean high)	1.003 (0.951–1.057)	0.33% (−5.12%; 5.38%)
	PM 2.5 (mean low)	1.083 (1.034–1.135)	7.67% (3.28%; 11.9%)	PM 2.5 (mean low)	1.072 (0.995–1.157)	6.70% (−4.69%; 13.59%)
	NO2 (low–lag 5)	1.022 (1.006–1.037)	2.16% (0.06%; 3.60%)	NO2 (low–lag 5)	1.017 (0.997–1.033)	1.64% (−0.03%; 3.17%)
Number of ventricular arrhythmias[i]	PM 10 (low–lag 3)	1.015 (1.001–1.028)	1.46% (0.14%; 2.72%)	PM 10 (low–lag 3)	1.011 (0.995–1.028)	1.14% (−0.54%; 2.74%)
	PM 2.5 (high–lag 4)	1.021 (1.003–1.039)	2.09% (0.32%; 3.76%)	PM 2.5 (high–lag 4)	1.017 (0.996–1.039)	1.71% (−0.42%; 3.75%)
	NO2 (mean low)	1.003 (0.990–1.016)	0.29% (−1.01%; 1.54%)	NO2 (mean low)	0.993 (0.979–1.008)	−0.69% (−2.18%; 0.76%)

AR%: attributable risk percent; NO2: nitrogen dioxide; PM: particulate matter; RR: Relative risk; STEMI: ST elevation myocardial infarction.
[a] Adjusted by cos.t, Tuesday, Wednesday, Thursday and Friday.
[b] Adjusted by Thursday, Friday and atmospheric pressure lag 3.
[c] Adjusted by atmospheric pressure.
[d] Adjusted by cos.t, sin.t and Monday.
[e] Adjusted by atmospheric pressure.
[f] Adjusted by August.
[g] Adjusted by cos.t, Monday and Saturday.
[h] Adjusted by cos.t and month (as factor).
[i] Is not adjusted for any variables.

4.6. Effects of air pollutants on STEMI mortality

The association of AP changes with acute STEMI mortality has not been described in literature up to date. We did not specifically record unrecovered out-of-hospital sudden death, which in any case is highly in consonance with AMI. However, a relationship between out-of-hospital coronary death and increased PM 10 and PM 2.5 levels has been described, [26,30]. In this sense, we have found a clear association between STEMI mortality and increased levels of PM 2.5 and PM 10. Our results are similar to those found in Madrid, Spain, where a RR of 1.066 (CI 1.032–1.100) has been reported at lag 6 exposure PM 2.5 for AMI mortality, [11].

4.7. Multipollutant model

The fact that there is a strong association between pollutants, as shown in Table 1, implies that if one pollutant concentration increases, the variation of the other pollutant goes in the same direction. For this reason, in the mutipollutant model, the harmful effect of a given pollutant is neutralized at a statistical level, because the effect of the other pollutants goes in the same direction by its correlation effect.

4.8. Study limitations

Our study has several limitations. We used thirteen fixed monitoring sites and calculated the average measurements to represent AP exposure. This may not accurately reflect personal exposure as people move through the day and AP composition varies between very short geographical points. To circumvent these potential limitations we repeated all analyses in two other cohorts in order to reduce this variability. It is hard to elucidate which AP component has a higher potential as a trigger for STEMI and STEMI-related events, as PM contains multiple heterogeneous elements. However, we found NO and lead as isolated elements that can trigger STEMI. We only investigated outside contamination. Inside contamination may be also important as people spend a great part of the time at home or in other closed spaces. For the sake of homogeneity and diagnostic accuracy, we did not register suspected fatal heart attacks before the first medical attention. Previous studies have explored the relation between AP and out-of-hospital cardiac arrest. Although there are inconsistent results, most studies support an association, mainly for exposure to PM 2.5, whereas an association was found for lags 2 or 4 before the event, [12,31], which may be consistent with our findings even though we did not include non-recovered sudden STEMI deaths.

We can infer that there is a clear association between the pollutants analyzed and the outcomes assessed. In addition, there is a biological rationale that supports that this association may be causal. However, we cannot rule out some sources of bias as mentioned in the manuscript. Moreover, residual confounding is also possible.

5. Conclusion

A reduction in mean AP levels and its transient elevations in PM concentration may have a significant effect in reducing STEMI incidence and its serious complications. Understanding the role of AP in increasing the risk of STEMI and its major complications is important to improve public health. Although we found a slightly significant association of pollutants as triggers of STEMI, the impact on health is obvious because 100% of the target population is exposed.

More studies are needed in particular geographical areas, because the results might not apply to other populations due to the variability in atmospheric conditions and AP composition.

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Contributors

Jordi Bañeras planned the study, obtained funding and contributed to provided local cohort data, the study design, data analyses, and drafted the report. Ignacio Ferreira-González and Josep Ramon Marsal contributed to the study design, quality control, statistical script, data analyses and draft the report. José A. Barrabés and Aida Ribera contributed to the study design and data analyses. Rosa Maria Lidón. Enric Domingo and Gerard Martí contributed to provided local cohort data. David Garcia-Dorado contributed to provided data analyses. All authors contributed to critical reading of, and commented on, the report, helped to interpret the data, and approved the final draft.

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Conflict-of-interest

We declare that we have no conflicts of interest.

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