Risk of Cardiovascular Hospitalizations from Exposure to Coarse Particulate Matter (PM10) Below the European Union Safety Threshold

Brief Title: Air Pollution and Cardiovascular Hospitalizations

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ABSTRACT

The association between exposure to air pollution and acute cardiovascular (CV) events is well documented, however limited data are available evaluating the public health safety of various “doses” of particular matter (PM) below currently accepted safety thresholds. We explored the cross-sectional association between PM with aerodynamic diameter less than 10 µm (PM10) and daily CV hospitalizations in Brescia, Italy using Poisson regression models adjusted for age, sex, and meteorological indices. Average daily exposure to PM10 obtained from arithmetic means of air pollution data were captured by 4 selected monitoring stations. PM10 data were expressed as daily mean (lag 0-day) or 3-day moving average (lag 3-day), and categorized according to the European Union daily limit value of 50 µg/m³. From September 2004 to September 2007, data from 6,000 acute CV admissions to a tertiary referral center were collected. An increase of 1µg/m³ PM10 at lag 0-day was independently associated with higher rates of acute hospitalizations for composite CV-related events (RR 1.003, 95% CI 1.002-1.005), acute heart failure (RR 1.004, 95% CI 1.001-1.008), acute coronary syndromes (RR 1.002, 95% CI 0.999-1.005), malignant ventricular arrhythmias (RR 1.004, 95% CI 0.999-1.010), and atrial fibrillation (RR 1.008, 95% CI 1.003-1.012). Similar results were obtained using PM10 lag 3-day data. The excess PM10 CV hospitalization risk (by lag 0-day and lag 3-day) did not vary significantly above and below the 50 µg/m³ safety threshold or by age and sex. In conclusion, increased levels of PM10, even below the current limits set by the European Union, were associated with excess risk for admissions for acute CV events.

Key Words: Acute Coronary Syndrome; Acute Heart Failure; Air Pollution; Atrial Fibrillation
Over the last several decades, rapid urbanization, motorization, and industrialization have led to a marked rise in air pollution. Despite ongoing efforts by local and global environmental and social agencies to improve air quality, the negative health impacts of air pollution remain major public health concerns (1). Major mechanisms driving inhalation-mediated cardiovascular (CV) toxicity include activation of pro-inflammatory pathways and generation of reactive oxygen species (2-3). Based on early clinical and experimental data, these adverse biologic effects may directly influence heart rate, heart rate variability, blood pressure, vascular tone, pro-coagulability, and progression of atherosclerosis (4-3).

Air pollution consists of complex mixtures of organic and inorganic toxic compounds, both in gaseous and particulate phases. Particulate matter with aerodynamic diameter less than 10 µm (PM10) has been associated with CV and respiratory morbidity and mortality, and thus represents a validated metric of air pollution (4). Recognizing this substantial CV risk, the European Union (EU) has established air quality standards and set a legal allowable limit for various pollutants in ambient air, including PM10 (less than 50 µg/m³ averaged over a 24-hour period [Directive 99/30/CE]). However, limited data are available to determine if these thresholds and regulations provide an adequate margin of safety for the general population and for more susceptible subgroups (5-7). The aims of the present study were to: 1) describe the distribution and variability of PM10 levels measured from a highly industrialized town in Northern Italy over a 3-year period; 2) examine the risk of exposure to PM10 on hospitalizations for acute CV events to a single tertiary referral center; and 3) determine if this CV hospitalization risk varies above and below the established EU safety threshold or by age and sex.

METHODS

From September 1st, 2004 to September 30th, 2007, this cross-sectional observational study assessed the association between PM10 levels and hospitalizations for acute CV events in a city with a high degree of industrialization and urbanization (~332 inhabitants/km²). The average daily concentrations of PM10 were retrieved from the official website of the regional environmental agency (Agenzia Regionale per la Prevenzione e Protezione Ambientale [ARPA]) of the Lombardy region of northern Italy (www.arpalombardia.it), which provides PM10 concentrations registered in
urban and suburban areas of the district of Brescia (covering ~1.2 million inhabitants). The daily PM10 average concentrations of this area were calculated as arithmetic means of concentration values measured by 4 monitoring stations (site A: Broletto; site B: Rezzato; site C: Sarezzo; site D: Odolo) that, according to Italian law, were not close to local sources of air pollution such as factories, industries, and high-traffic roads.

Using the Hospital Discharge Database, which includes date of admission and discharge from the hospital, the primary discharge diagnosis, classified according to the International Classification of Diseases, Ninth Revision (ICD-9), and the diagnosis-related group code, we identified patients who experienced hospitalizations for CV disease during the study period. Consistent with prior data (8), hospitalizations for acute heart failure (AHF; ICD-9 428), acute coronary syndromes (ACS; ICD-9 410-413), malignant ventricular arrhythmias and/or implanted cardiac defibrillator requirement (MVA; ICD-9 427.1, 427.41, 427.42), and atrial fibrillation (AF; ICD-9 427.31, 427.32) were extracted.

The cross-sectional association between daily average concentrations of PM10 and hospitalization rate for acute CV events were analyzed by a generalized linear model. We applied the Poisson regression with the log link function since daily counts of hospitalizations were assumed to follow a Poisson distribution. Concentrations of PM10 were analyzed as a daily 24-hour average (lag 0-day) and as a 3-day moving average (lag 3-day). In each model, lag 0-day pollution effects were evaluated using the arithmetic means of PM10 values obtained on the same admission day, whereas lag 3-day effects were investigated using the arithmetic means of values obtained on the same day, and from the 3 days preceding the admission date. This time-series approach is expected to attenuate day-to-day variation of the exposure variable and minimize the influence of changes in individual-level cardiovascular risk profiles of admitted patients (9). In order to evaluate the influence of the EU daily limit, lag 0-day PM10 values were also assessed as a dichotomous variable above and below 50µg/m³.

Seasonal variation (10,11) and specific meteorological factors (12,13) are known to influence cardiovascular risk. As such, all models were adjusted for age, sex, prior CV
hospitalizations, and meteoclimatic variables (mean daily air temperature (°C), relative humidity (%), atmospheric pressure (mbar), and wind speed (km/h). Age was expressed as a dichotomous variable (<65 years or ≥65 years). Contemporaneous data regarding meteorological variables were obtained from the National Meteorological Institute of the Air Force located in Ghedi (Brescia, Italy) (www.meteoam.it). Interaction analyses were performed to determine if the CV hospitalization risk associated with PM10 was modified by the EU safety limit or by age and sex.

Effect sizes were expressed as relative risks (RR) and 95% confidence intervals (CI), determined by Poisson regression models. Means and standard deviations (SD) of admissions were calculated according to the Poisson distribution, i.e. SD were obtained as square roots of means. Covariates in the final models were age, sex, meteorological indices (temperature, relative humidity, wind speed, rain, and atmospheric pressure), and the PM10*age and PM10*sex interaction terms. Normality of the PM10 distribution was tested based on Kolmogorov-Smirnov testing. P<0.05 was considered statistically significant. All statistical analyses were performed using IBM PASW 19 (IBM Corporation, Armonk, NY, USA).

RESULTS
From September 1st, 2004 to September 30th, 2007, the distribution of PM10 values was log-normal. The geometric mean of lag 0-day PM10 values was 40.2 ± 1.8µg/m³ (range: 5th percentile 15 µg/m³ and 95th percentile 108.5 µg/m³). The corresponding geometric mean of lag 3-day PM10 values was 41.3 ± 1.7µg/m³ (range: 5th percentile 17.3 µg/m³ and 95th percentile 102.1 µg/m³). Of the total 1,125 days surveyed, 413 (36.7%) included PM10 measurements above the EU safety threshold of 50µg/m³.

During the study time-frame, there were a total of 6,000 urgent CV admissions: 23% with a primary diagnosis of AHF, 54% with ACS, 9% with MVA, and 14% with AF (Table 1). Older patients and men were more likely to be admitted for all CV events, except MVA. In terms of meteorological parameters, temperature was negatively associated with all causes of CV admissions, with the exception of AF. Atmospheric pressure was negatively associated with AHF and MVA, while rain was positively associated with AF (Table 2).
Table 3 summarizes the CV admission risk associated with lag 0-day PM10 values as a continuous function, lag 0-day PM10 categorized according to the EU daily limit value of 50 µg/m$^3$ (above vs. below), and the lag 3-day PM10 values. An increase of 1µg/m$^3$ PM10 at lag 0-day was independently associated with higher rates of acute hospitalizations for composite CV-related events (RR 1.003, 95% CI 1.002-1.005), AHF (RR 1.004, 95% CI 1.001-1.008), ACS (RR 1.002, 95% CI 0.999-1.005), MVA (RR 1.004, 95% CI 0.999-1.010), and AF (RR 1.008, 95% CI 1.003-1.012). Similar results for CV hospitalization risk were obtained using PM10 lag 3-day data (as a continuous function) and when PM10 lag 0-day values were dichotomized (≥ 50 µg/m$^3$ compared with <50 µg/m$^3$). No significant interaction was observed for PM10 CV hospitalization risk (by lag 0-day and lag 3-day) above and below the 50 µg/m$^3$ safety threshold or by age and sex.

DISCUSSION

This single-center, cross-sectional study of 6,000 CV hospitalizations revealed 3 major findings: 1) PM10 measurements exceeded the established EU safety threshold of 50 µg/m$^3$ in over a third of sampled days; 2) contemporaneously sampled PM10 levels in the ambient air were independently associated with risk of CV hospitalization (regardless of cause); 3) PM10 was consistently associated with risk of CV hospitalization above and below the established EU safety threshold and across age and sex subgroups.

The adverse health consequences of short-term exposure to increased levels of PM10 observed in this analysis are consistent with prior data. Scarinzi et al. demonstrated a significant association between air pollution and hospital admissions in 25 Italian cities participating in the Epi Air (Epidemiological surveillance of air pollution effects among Italian cities) project (14). A meta-analysis of 34 studies corroborated this significant association between major air pollutants and ACS risk with a RR of 1.006 (95% CI 1.002-1.009) for PM10 (as a continuous function, per 10 µg/m$^3$) (15). In our study, the CV hospitalization risk was estimated to be higher with a RR of 1.003 (95% CI 1.002-1.005) per 1µg/m$^3$ increase in PM10. A possible explanation for these findings may be related to the characteristics of air pollution in the studied urban area. Brescia is a city with a high degree of industrialization.
and urbanization (~332 inhabitants/km²). According to recent data from the National Statistics Institute (ISTAT), which is based on the Airbase Database of the European Environment Agency (EEA), Brescia is one of the most polluted European cities.

The majority of data evaluating the adverse cardiovascular health effects of air pollution focus on risk of ACS. We also found a significant relationship between higher PM10 levels and an increased risk of hospitalization for AHF, which is consistent with data from a recent meta-analysis (16). Airborne particles may worsen HF through alterations in cardiac hemodynamics related to myocardial ischemia, promote adverse ventricular remodelling (17,18), and elevate filling pressures (19). Formal testing of interventions that may modulate these adverse air pollution-related effects in HF are underway. FILTER-HF (Effects of Air Pollution Exposure Reduction by Filter Mask on Heart Failure; ClinicalTrials.gov NCT01960920), a small randomized, prospective, double-blind, controlled study, demonstrated that use of a respiratory filter attenuated endothelial dysfunction and rises in natriuretic peptides during controlled diesel exhaust exposure in patients with HF (20). PM10 may also trigger ventricular or supraventricular arrhythmias, but the molecular pathways mediating this risk have not been entirely defined. Potential mechanisms lending to increased arrhythmogenicity may include autonomic imbalances, decreased oxygen carrying capacity, and direct electrophysiological effects (21).

The association between PM10 air pollution and CV hospitalization risk appears to occur at concentrations below current European environmental quality standards. Our data support the concept that “lower is better” and that there may be no safe level of PM10 since every incremental increase in short-term exposure increases risk of CV hospitalizations. This data are consistent with a large prospective analysis of over 300,000 people that suggested that every 10 ug/m³ increase in PM10 conferred a 22% increase in rates of lung cancer, regardless of initial “dose” (22).

Although the magnitude of the PM10-associated risk observed in our study is relatively small, as compared to major CV risk factors, it should not be ignored when considering the population at risk and area of exposure. Future prospective data, perhaps including contemporary pooled data from multiple cities, are required to clarify 1) whether short-term air pollutants confer long-term CV risk; and 2) whether this attributable risk is modifiable by population-level interventions and regulations; and
3) whether a more optimal safety threshold for PM10 can be established. Our data may inform future policy efforts to set local and regional standards aimed at attenuating the CV-related risk associated with air pollutants.

We acknowledge several limitations to our study. First, we used a single pollutant model in spite of possible interaction between multiple ambient pollutants. Second, as with all population-based air surveillance analyses, we assumed that air pollutant concentrations measured at a community level serve as a surrogate for the average personal exposure during the respective time period. Factors such as time spent in traffic, indoor air emission sources, and smoking may affect the validity of this assumption (23). Our models did not account for individual CV risk factors, laboratory or imaging data that may have influence hospitalization risk. Furthermore, we did not collect specific information related to the area of residence of hospitalized patients. As such, it is possible that a proportion of patients may in fact reside outside of Brescia, potentially contributing to misclassification of the primary exposure. Third, temporal misclassification of exposure likely resulted in bias towards the null. In this study, exposures were assigned based on 00:00 am to 11:59 pm daily averages, such that for individuals admitted at 1 am, the assigned 24-hour average “current day” exposure would have actually occurred after admission. Symons et al. (24) found that associations based on an 8-hour lagged exposure period were stronger than associations based on 24-hour lagged exposure. Fourth, data were not available for other important causes of CV hospitalizations including stroke, transient ischemic attack, and venous thromboembolism. Fifth, our data were collected over a decade ago, and as such more contemporary surveys are required to substantiate the observed findings. Finally, the use of listed discharge diagnoses may not adequately reflect the “true” reasons underlying each CV hospitalization (25).

ACKNOWLEDGEMENTS

None


Table 1. Reasons for urgent cardiovascular hospitalizations by sex

<table>
<thead>
<tr>
<th>Diagnoses</th>
<th>Men</th>
<th>Women</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=4,201</td>
<td>n=1,799</td>
<td>n=6,000</td>
</tr>
<tr>
<td>Acute heart failure</td>
<td>902 (21%)</td>
<td>484 (27%)</td>
<td>1,386 (23%)</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>2,423 (58%)</td>
<td>830 (46%)</td>
<td>3,253 (54%)</td>
</tr>
<tr>
<td>Malignant ventricular arrhythmia</td>
<td>316 (8%)</td>
<td>215 (12%)</td>
<td>531 (9%)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>560 (13%)</td>
<td>270 (15%)</td>
<td>830 (14%)</td>
</tr>
</tbody>
</table>
Table 2. Association between demographic and environmental factors and causes for cardiovascular hospitalizations

<table>
<thead>
<tr>
<th>Variables</th>
<th>Acute heart failure</th>
<th>Acute coronary syndrome</th>
<th>Malignant ventricular arrhythmia</th>
<th>Atrial fibrillation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR</td>
<td>95% CI</td>
<td>RR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Male</td>
<td>1.864</td>
<td>1.669-2.081</td>
<td>2.919</td>
<td>2.698-3.159</td>
</tr>
<tr>
<td>Age&lt;65 years</td>
<td>0.535</td>
<td>0.479-0.597</td>
<td>0.860</td>
<td>0.803-0.921</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>0.988</td>
<td>0.980-0.996</td>
<td>0.990</td>
<td>0.985-0.995</td>
</tr>
<tr>
<td>Relative humidity (%)</td>
<td>0.998</td>
<td>0.994-1.003</td>
<td>0.999</td>
<td>0.996-1.001</td>
</tr>
<tr>
<td>Wind speed (km/h)</td>
<td>1.029</td>
<td>0.994-1.066</td>
<td>0.982</td>
<td>0.959-1.005</td>
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<tr>
<td>Rain (mm)</td>
<td>0.996</td>
<td>0.972-1.022</td>
<td>1.005</td>
<td>0.989-1.021</td>
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<tr>
<td>Atmospheric pressure (mbar)</td>
<td>0.992</td>
<td>0.984-1.000</td>
<td>0.999</td>
<td>0.993-1.004</td>
</tr>
</tbody>
</table>

Relative risks (RR) and 95% confident intervals (CI) estimated by Poisson regression models.

* P<0.05
** P<0.01
*** P<0.001
Table 3. Multivariate regression models evaluating association between PM10 and cardiovascular hospitalizations

<table>
<thead>
<tr>
<th></th>
<th>PM10(≥ vs. &lt; 50 µg/m³)</th>
<th>PM10 lag 3-day (per 1µg/m³ increase)</th>
<th>PM10 lag 0-day (per 1 µg/m³ increase)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR</td>
<td>95% CI</td>
<td>RR</td>
</tr>
<tr>
<td>Acute heart failure</td>
<td>1.32***</td>
<td>1.15-1.52</td>
<td>1.002</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>1.14**</td>
<td>1.04-1.25</td>
<td>1.002</td>
</tr>
<tr>
<td>Malignant ventricular arrhythmia</td>
<td>1.39**</td>
<td>1.12-1.74</td>
<td>1.002</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1.57***</td>
<td>1.32-1.87</td>
<td>1.008***</td>
</tr>
</tbody>
</table>

Relative risks (RR) and 95% confident intervals (CI) estimated by Poisson regression models. Particulate matter with aerodynamic diameter less than 10 µm (PM10) values were analyzed as a 1) categorical variable dichotomized based on the European Union safety limit of 50 µg/m³; 2) daily mean (lag 0-day), expressed as every 1 µg/m³ increase in PM10; 3) mean concentrations on the day of admission and in the previous 3 days (lag 3-day), expressed as every 1 µg/m³ increase in PM10. Covariates in the Poisson regression models were: age, sex, and meteorological variables (temperature, relative humidity, wind speed, rain, atmospheric pressure), and the PM10*age and PM10*sex interaction terms.

* P<0.05  
** P<0.01  
*** P<0.001