





## The association between particulate matter 2.5 and hospitalization and mortality rates of heart failure: The CAPACITY study

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### Original Article

#### Abstract

**BACKGROUND:** Considering the high concentrations of pollutants in large cities of Iran and the high prevalence of heart failure (HF) among Iranians, especially with increasing life expectancy, this study investigated the relationship between airborne contaminants with a diameter < 2.5 µm or particulate matter 2.5 (PM<sub>2.5</sub>) and hospitalization and mortality in patients with HF in Isfahan, Iran, during 2011.

**METHODS:** This ecological study was carried out on a part of data from the CAPACITY study. A total of 275 patients with HF were randomly selected from 840 subjects with International Statistical Classification of Diseases, 10<sup>th</sup> Revision (ICD-10) diagnosis code I50 in the CAPACITY study. Patients' records were evaluated and their clinical characteristics, disease history, and laboratory and echocardiographic findings were extracted. Air pollution and climatic data were extracted from the CAPACITY study. Poisson regression was used in crude and adjusted models to evaluate the association between PM<sub>2.5</sub> and study outcomes. All analyses were performed using crude models and models adjusted for temperature, dew point, and wind speed.

**RESULTS:** 54.9% (n = 151) were men with mean age of 70.4 ± 13.7 years. While most patients (85.8%) were discharged after recovery, 14.2% of the patients died in the hospital. Blood glucose, heart rate, and ejection fraction (EF) were significantly higher on unhealthy days than normal days. Regression analysis revealed no significant relationships between hospitalization and mortality rates and PM<sub>2.5</sub> concentrations on healthy days, unhealthy days for sensitive people, and unhealthy days.

**CONCLUSION:** The model used in our study revealed no significant relationships between PM<sub>2.5</sub> concentrations and hospital admission on healthy days, unhealthy days for sensitive people, and unhealthy days.

**Keywords:** Hospitalization, Mortality, Particulate Matter

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#### Introduction

In recent years, air pollution caused by motor vehicles and industrial activities has turned into a major public health threat and an important management challenge in various countries. Numerous studies have shown a direct association between air pollution and the incidence of

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cardiovascular and pulmonary diseases and related mortality.<sup>1</sup> Short-term exposure to air pollution has been reported to increase the risk of several complications such as hypertension (HTN),<sup>2</sup> arrhythmias,<sup>3</sup> exacerbation of heart failure (HF),<sup>4</sup> and acute ischemic and atherosclerotic cardiovascular complications.<sup>5</sup> Long-term exposure is also known to lead to cardiovascular events such as atherosclerosis and deep vein thrombosis (DVT).<sup>6</sup> These complications might be caused by either acute daily changes in air pollution levels or lifetime exposure to contaminants.<sup>7</sup>

Particulate matter (PM) is a mixture of solid and liquid particles with different compositions and sizes which suspend in the air. These particles are surrounded by various gases such as ozone (O<sub>3</sub>), carbon monoxide (CO), sulfur dioxide (SO<sub>2</sub>), and nitrogen dioxide (NO<sub>2</sub>). They are divided into three categories including coarse (PM<sub>10</sub>, diameter: 2.5-10 μm), fine (PM<sub>2.5</sub>, diameter < 2.5 μm), and ultra-fine (UFP, diameter < 0.1 μm) particles.<sup>8</sup> It is widely accepted that smaller particles offer a larger surface area and hence potentially larger concentrations of adsorbed or condensed toxic air pollutants per unit mass. Hence, PM<sub>2.5</sub> was taken to be more relevant as an exposure indicator than larger particles.<sup>9</sup>

Chronic HF (CHF) is one of the most common causes of mortality from cardiovascular diseases (CVDs) and its related hospitalization rates have remarkably increased during the past two decades.<sup>10</sup> The hospitalization and one-year mortality rates due to CHF are about 2% and 30%, respectively.<sup>11</sup> In patients with HF, hospitalization occurs following decompensation caused by various factors such as inadequate treatment, uncontrolled HTN, and arrhythmias.<sup>12</sup> PM contributes to the pathogenesis of HF through several biological mechanisms. Oxidative inflammation and endothelial dysfunction can increase the number and activity of platelets, elevate the levels of inflammatory and coagulation factors, and cause autonomic nerve disorders.<sup>13</sup> A combination of these factors intensifies ventricular remodeling and myocardial fibrosis and causes left ventricular dysfunction (LVD), increased pulmonary capillary wedge pressure (PCWP), and repeated decompensation attacks in the long-term.<sup>14</sup>

In Iran, as a developing country, the level of air pollutants has increased gradually since the beginning of industrialization in the 1970s, but it has reached a very harmful level in some megacities such as Tehran, Mashhad, Tabriz, Isfahan, Ahvaz, Arak, and Karaj, Iran, over the past two decades.<sup>15</sup> Isfahan is the second most polluted city in Iran and

one of the most polluted cities in the world.<sup>16</sup> Various factors such as Isfahan's specific geographic location, the presence of industrial units and contaminating firms, and the large number of motor vehicles and related traffic problems increase the risk of exposure to air pollution in the residents of the city. Since air pollution and thus hospitalization and mortality rates due to HF are on the rise in Isfahan,<sup>17</sup> this study investigated the relationship between airborne contaminants (particularly PM<sub>2.5</sub>) and hospitalization and mortality rates in patients with HF in Isfahan during 2011.

## Materials and Methods

This study was a part of the CAPACITY study which focused on participants with HF and was carried out in Isfahan from March 20, 2011 to March 20, 2012. It sought to clarify the association between hospitalization caused by cardiovascular and respiratory diseases and air pollutants. The CAPACITY study collected data from all patients who had been diagnosed with and hospitalized for cardiovascular and respiratory diseases based on International Statistical Classification of Diseases, 10<sup>th</sup> Revision (ICD-10) codes in Isfahan. PM, SO<sub>2</sub>, NO<sub>2</sub>, CO, and O<sub>3</sub> levels measured by six fixed pollution monitoring stations were retrieved from Isfahan Department of Environment (DOE). The methodology of the CAPACITY study has been fully described elsewhere.<sup>18</sup>

HF had already been diagnosed by the patient's physician at the time of admission and the records were documented in the health information system (HIS) based on ICD-10 codes and ejection fraction (EF) of 40% or less as HF with reduced EF.<sup>19</sup> Of all patients with ICD-10 diagnosis code I50 in the CAPACITY study, 275 subjects who were hospitalized for acute HF (AHF) during March 20, 2011 to March 20, 2012 were randomly selected. The participants' records were evaluated by project executive and patient information including admission time, demographic information (e.g., age, gender, and place of residence), history of diabetes, HTN, ischemic heart disease (IHD), chronic obstructive pulmonary disease (COPD), smoking, and medication use, vital signs at the time of admission [i.e., systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate, respiratory rate, and oxygen saturation], and troponin, blood urea nitrogen (BUN), creatinine (Cr), blood sugar, and hemoglobin (Hb) levels was recorded in a checklist. Echocardiographic data including left ventricular EF (LVEF), mitral and

tricuspid valve regurgitation (MR and TR, respectively), and systolic pulmonary arterial pressure (SPAP), as well as discharge/death dates were also recorded.

In the study year, only one station in the center of Isfahan measured hourly PM<sub>2.5</sub> concentrations. The station is located in one of the busiest areas of Isfahan near Naqshe-e Jahan Square (a historical site) and a specialty cardiac hospital (established in 2010). This station continuously monitored the concentrations of PM<sub>2.5</sub> and gas contaminants [sulfur oxides (SOX), nitrogen oxides (NOX), CO, and O<sub>3</sub>] and recorded the data as mean hourly values. PM<sub>2.5</sub> concentrations were measured through beta attenuation monitoring (BAM) method. Considering the effects of weather conditions on air pollution, in order to eliminate their confounding effects on PM<sub>2.5</sub> concentrations, we adjusted dataset for climatic variables (wind speed, temperature, and humidity). The hourly average values, for 24 hours during March 20, 2011 to March 20, 2012 for temperature (in Fahrenheit), dew point (in percent), and wind speed [in meters per second (m/s)] were also collected from Isfahan Meteorological Organization and were compared with available satellite data (an archive of all climatic data recorded at meteorological stations since 1950).

All data were entered into SPSS software (version 23, IBM Corporation, Armonk, NY, USA) and data about PM<sub>2.5</sub> concentrations and anthropometric factors were merged with patient information based on the patient's hospitalization date. Data were shown as mean  $\pm$  standard deviation (SD) for quantitative variables or frequency and percentage for qualitative variables. Before the analyses, the days of the year were categorized as "good or moderate", "unhealthy for sensitive people", and "unhealthy" or "hazardous" based on PM<sub>2.5</sub> levels and air quality index (AQI) classifications.<sup>20</sup> Hospitalization data and disease history in patients admitted on good or moderate (PM<sub>2.5</sub> < 40.5), unhealthy for sensitive people (PM<sub>2.5</sub> = 40.5-65.5), and unhealthy or hazardous (PM<sub>2.5</sub> > 66) days were compared by chi-square test and one-way analysis of variance (ANOVA).

Poisson regression model was performed to investigate crude and adjusted effect of PM<sub>2.5</sub> on mortality or hospitalization rate of HF. Age, temperature, dew point, and wind speed were added to model as adjustments also for hospitalization rate models were performed separately for each gender. Data analysis was conducted using SPSS and Stata (version 12, Stata

Corporation, College Station, TX, USA) and P-values less than 0.05 were considered significant.

## Results

Of 16990 patients with CVDs who were enrolled in the CAPACITY study during March 20, 2011 to March 20, 2012, 840 patients had HF. A total of 275 individuals with HF, including 151 men (54.9%) and 124 women (45.1%), were randomly selected from this population and included in the present research. The patients' mean age was 70.4  $\pm$  13.7 years. Most patients (n = 236, 85.8%) were discharged from the hospital and 39 patients (14.2%) died. Table 1 presents the patients' history and clinical characteristics at the time of admission.

**Table 1.** Patients' history and clinical characteristics at the time of admission

Variable	Value
Gender	275 (100)
Male	151 (54.9)
Female	124 (45.1)
Viability	275 (100)
Alive	236 (85.8)
Died	39 (14.2)
Past history	
Diabetes	103 (37.5)
HTN	148 (53.8)
IHD	161 (85.5)
COPD	68 (24.7)
Smoking	59 (21.5)
Physical examination	
SBP (mmHg)	125.04 $\pm$ 30.34
DBP (mmHg)	76.07 $\pm$ 15.95
Heart rate (per minute)	87.96 $\pm$ 21.37
Respiratory rate (per minute)	23.03 $\pm$ 8.15
O <sub>2</sub> saturation (percent)	90.64 $\pm$ 68.46
Laboratory data	
Urea (mg/dl)	35.08 $\pm$ 62.36
Creatinine (mg/dl)	1.67 $\pm$ 1.21
Blood glucose (mg/dl)	160.32 $\pm$ 87.17
Hb (mg/dl)	14.82 $\pm$ 12.59
Positive troponin	21 (7.6)
Echocardiography	
EF (percent)	32.48 $\pm$ 13.76
SPAP (mmHg)	41.34 $\pm$ 17.69
MR	259 (94.2)
TR	255 (92.7)

Values are mean  $\pm$  standard deviation (SD) for quantitative variables and number (%) for qualitative variables.

HTN: Hypertension; IHD: Ischemic heart disease; COPD: Chronic obstructive pulmonary disease; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; Hb: Hemoglobin; EF: Ejection fraction; SPAP: Systolic pulmonary artery pressure; MR: Mitral regurgitation; TR: Tricuspid regurgitation

As seen, over 90% of the patients had MR and TR, 85.5% had a history of IHD, and 53.8% had HTN. The patients' SBP, DBP, and blood glucose were within the acceptable ranges at the time of admission. Positive troponin, as an indicator of acute coronary event, was detected in 7.6% of the patients at the time of admission.

Table 2 shows the mean PM<sub>2.5</sub> concentrations, temperature, wind speed, humidity, and visibility for all days, as well as healthy, unhealthy for sensitive people, and unhealthy days. As seen, the largest number of admissions belonged to unhealthy days for sensitive people.

**Table 2.** Climatic variables and particulate matter 2.5 (PM<sub>2.5</sub>) concentrations

Variable	Value
Wind speed (m/s)	5.55 ± 2.83
Temperature (Fahrenheit)	57.73 ± 19.35
Humidity (percent)	27.40 ± 9.19
Visibility (km)	4.52 ± 1.15
PM <sub>2.5</sub> concentrations (µg/m <sup>3</sup> )	55.36 ± 32.12
Frequency of hospitalization	275 (100)
Good or moderate	68 (24.7)
Unhealthy for sensitive people	149 (54.2)
Unhealthy or hazardous	58 (21.1)

Values are mean ± standard deviation (SD) for quantitative variables and number (%) for qualitative variables.

PM: Particulate matter

Table 3 compares the study variables on healthy, unhealthy for sensitive people, and unhealthy days. According to the provided data, EF, blood glucose, and heart rate at the time of admission were significantly higher on unhealthy days than healthy days.

Table 4 presents the association between the mean PM<sub>2.5</sub> concentrations and hospitalization due to HF in the whole population and the two genders based on Poisson regression analysis (crude models and models adjusted for temperature, humidity, wind speed, and visibility). After adjustment for climatic variables (wind speed, temperature, visibility, and humidity), a positive relationship was observed between PM<sub>2.5</sub> concentration and hospitalization rate both in the whole population and in women. However, no significant relationships were found in good or moderate, unhealthy for sensitive people, and unhealthy or hazardous ranges.

## Discussion

The results of this study showed no significant correlations between PM<sub>2.5</sub> concentrations and hospitalization due to HF on healthy days, unhealthy days for sensitive people, and unhealthy days.

**Table 3.** Comparison of patient characteristics at the time of admission in particulate matter 2.5 (PM<sub>2.5</sub>) groups

Patient characteristics	Good or moderate	Unhealthy for sensitive people	Unhealthy or hazardous	P
HTN	40 (60.6)	80 (54.8)	28 (49.1)	0.441*
Diabetes	30 (46.2)	57 (39.6)	16 (28.1)	0.117*
IHD	42 (64.6)	91 (64.1)	28 (50.9)	0.195*
COPD	18 (28.6)	36 (25.7)	14 (25.9)	0.908*
Smoking	19 (30.6)	30 (22.2)	10 (18.2)	0.252*
Positive troponin	7 (10.1)	13 (9.8)	1 (2.0)	0.203*
Died	11 (16.2)	21 (14.1)	7 (12.1)	0.804*
Age (year)	72.22 ± 12.06	69.98 ± 14.12	69.36 ± 14.48	0.435**
SBP (mmHg)	125.94 ± 24.14	126.09 ± 31.43	121.40 ± 33.93	0.588**
DBP (mmHg)	74.89 ± 15.41	77.57 ± 16.14	73.64 ± 15.93	0.226**
Heart rate (per minute)	80.00 ± 21.48	88.81 ± 20.72	93.09 ± 20.73	0.002**
Creatinine (mg/dl)	1.45 ± 0.78	1.82 ± 1.46	1.53 ± 0.86	0.076**
Blood glucose (mg/dl)	134.48 ± 55.18	161.43 ± 86.12	180.81 ± 106.12	0.014**
Hb (mg/dl)	12.90 ± 2.15	14.78 ± 12.52	17.15 ± 18.37	0.175**
EF (percent)	28.32 ± 12.18	31.08 ± 14.42	35.00 ± 13.82	0.028**
SPAP (mmHg)	41.81 ± 17.52	40.35 ± 18.51	43.18 ± 15.94	0.598**

Values are mean ± standard deviation (SD) for quantitative variables and number (%) for qualitative variables.

\*Chi-square test or Fisher's exact test were used where appropriate.

\*\*One-way analysis of variance (ANOVA) was used.

HTN: Hypertension; IHD: Ischemic heart disease; COPD: Chronic obstructive pulmonary disease; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; Hb: Hemoglobin; EF: Ejection fraction; SPAP: Systolic pulmonary artery pressure

**Table 4.** Crude and adjusted effect of particulate matter 2.5 (PM<sub>2.5</sub>) on mortality or hospitalization rate of heart failure (HF)

Events	PM <sub>2.5</sub> level	Crude model		Adjusted model*	
		OR (95% CI)	P	OR (95% CI)	P
Total	Good or moderate	1		1	
	Unhealthy for sensitive people	1.19 (0.69-2.08)	0.510	0.99 (0.56-1.79)	0.990
	Unhealthy or hazardous	1.25 (0.62-2.53)	0.530	1.08 (0.52-2.24)	0.830
Female	Good or moderate	1		1	
	Unhealthy for sensitive people	1.40 (0.64-3.06)	0.380	1.09 (0.46-2.59)	0.830
	Unhealthy or hazardous	1.76 (0.60-5.16)	0.300	1.18 (0.34-3.99)	0.780
Male	Good or moderate	1		1	
	Unhealthy for sensitive people	1.01 (0.46-2.23)	0.960	0.79 (0.33-1.87)	0.600
	Unhealthy or hazardous	0.94 (0.36-2.44)	0.910	0.64 (0.23-1.79)	0.400
Mortality	Good or moderate	1		1	
	Unhealthy for sensitive people	2.33 (0.40-13.45)	0.340	3.55 (0.46-27.30)	0.220
	Unhealthy or hazardous	1.00 (0.11-9.27)	0.990	1.63 (0.13-20.7)	0.700

\* Adjusted for age, temperature (°F), dew point (percent), and wind speed (m/s)

PM: Particulate matter; OR: Odds ratio; CI: Confidence interval

However, a comparison between patients' clinical characteristics at the time of admission revealed that heart rate and blood glucose levels of patients hospitalized on unhealthy days were significantly higher than those of patients admitted on healthy days. Likewise, significantly higher EF was observed in patients admitted on unhealthy days than those hospitalized on healthy days. This finding suggests that patients with more stable conditions experienced decompensation on more contaminated days.

Yang et al. investigated the long-term effects of air pollution on LV function during 2005-2009. They observed significant relationships between PM<sub>2.5</sub> and age, plasma glucose, prevalence of diabetes, and LV function variables (e.g., age-standardized EF and longitudinal strain rate).<sup>21</sup> Since EF does not change in the absence of an acute coronary artery attack within 24 hours and the reduction in this parameter is more pronounced over time,<sup>22</sup> long-term comparisons of EF would be possible if we followed the admitted patients. In Jackson Heart Study (JHS), echocardiography was performed on 4866 patients. The patients' exposure to pollutants was also evaluated according to their distance from highways. Various analyses did not show any significant differences in LVEF, E velocity, isovolumic relaxation time (IVRT), and left atrium size.<sup>23</sup>

Different biological studies have shown that circulating adhesion molecules [E-selectin (endothelium-derived), P-selectin (platelet-derived), vascular cell adhesion molecule (VCAM), and intercellular adhesion molecule (ICAM)] create a systemic inflammatory condition and play an important role in the development of adverse cardiovascular effects.<sup>24</sup> Through the release of the

mentioned inflammatory mediators, the respiratory system triggers endothelial dysfunction, decreases NO-dependent vasodilation, promotes pulmonary arteriole remodeling, and ultimately increases pulmonary vascular resistance and decreases venous return to the left atrium. According to Frank-Starling Law, these hemodynamic changes in pulmonary circulation reduce atrial contraction and may exacerbate patients' dyspnea regardless of their EF.<sup>25</sup> Moreover, pulmonary inflammation caused by air pollution can stimulate vagal afferents in the lungs and cause autonomic dysfunction. The consequent transfer of inflammatory mediators from the lungs to the systemic circulation affects cardiac neurotransmission and changes the heart rate (i.e., decreases heart rate variability).<sup>26</sup>

This study presented evidence of a correlation between PM<sub>2.5</sub> levels and hospitalization and mortality rates due to HF. However, this relationship was not statistically significant. Milojevic et al. investigated the short-term effects of air pollution on hospitalization and mortality caused by cardiovascular events during 2003-2008. Consistent with our findings, they reported PM<sub>2.5</sub> concentrations to have no significant effects on 335000 hospitalizations and 37000 deaths caused by HF.<sup>27</sup> Nevertheless, a recent meta-analysis of 32 studies on the relationship between air pollution and HF concluded that every 10 µg/cm<sup>3</sup> increase in PM<sub>2.5</sub> concentration increased hospitalization and mortality rates in patients with HF by 12.2%.<sup>28</sup> The differences between various studies can be attributed to different methods of data analysis and disease diagnosis recording. In the present study, the relationship between air pollution and HF did not depend on the history of diabetes, HTN, and smoking. Similar findings were reported by Annesi-Maesano et al.<sup>29</sup>

One strength point of this study was collecting data from government departments (HIS from the Deputy of Treatment, air pollutant data from the DOE, and weather data from the Meteorological Organization) which reduced the cost of the research. Given the fact that almost all national data are currently collected and recorded online, research costs can be reduced by using different data recording systems. One of the limitations of this study was time-dependent confounding effects, including day, month, weather conditions, stress, and physical activity. In addition, due to the elimination of cases of deterioration and death at home or attribution of dyspnea to other respiratory diseases, the estimated values might be lower than the actual rates. Therefore, correct recording of the information and an accurate final diagnosis are highly important in determining the relationship between HF and air pollution. Nevertheless, air pollution seems to have greater impacts on patients with previously-diagnosed HF than the new cases of the disease.<sup>30</sup> Thus, further studies with this goal are recommended in the future. Furthermore, since we collected the data over a specific period of time, future studies are recommended to collect more information through longer follow-up of the patients.

Patients hospitalized for HF had significant differences in terms of echocardiographic EF, blood glucose, and heart rate at the time of admission. This finding can indicate that patients with more stable conditions experience decompensation events on more polluted days. However, an increase in 24-hour PM<sub>2.5</sub> concentrations was not significantly related to patients' hospitalization and mortality rates and no differences in the levels of moderating variables were observed in this regard. Considering the important role of air pollution in the incidence of cardiovascular and respiratory diseases, more effective strategies should be adopted to reduce these contaminants. Meanwhile, high-risk patients should be advised to take care of measures and avoid exposure to air pollution. According to the findings of the present study, case-crossover models, similar to that used in the CAPACITY study for the examination of all patients, are recommended for the elimination of the effects of many patient-related confounders. In addition, longitudinal studies on patients hospitalized for HF are warranted to investigate the long-term impacts of PM<sub>2.5</sub> on changes in heart function (including EF).

## Conclusion

The model used in our study revealed no significant relationships between PM<sub>2.5</sub> concentrations and hospital admission on healthy days, unhealthy days for sensitive people, and unhealthy day.

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## Conflict of Interests

Authors have no conflict of interests.

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