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Association between Air Temperature and Acute Myocardial Infarction Hospitalizations in Tehran, Iran: A Time-Stratified Case-Crossover

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Abstract

Background: Although the effect of temperature on the incidence of acute myocardial infarction (AMI) has been extensively documented, no study has previously investigated the association between temperature and AMI in the Middle Eastern countries.

Objective: To examine the association between daily mean temperature and AMI admission rates in Tehran, Iran.

Methods: Data on daily number of admissions of patients with AMI to Tehran hospitals between March 21, 2013 and March 19, 2016, were retrieved from the Iranian Myocardial Infarction Registry (IMIR). Over the same period, data on daily mean temperature and relative humidity were measured at Mehrabad International Airport weather station of the Islamic Republic of Iran Meteorological Organization. Time-stratified case-crossover design was employed to investigate the short-term association between the daily mean temperature and the number of daily admissions of patients with AMI, after adjusting for public holidays, relative humidity, and air pollution.

Results: An interquartile range (IQR) increase in daily mean temperature was associated with 15.1% (95% CI 1.3 to 30.8%) and 13% (95% CI 1.9% to 25.4%) increase in the risk of AMI hospitalizations during the entire year, and in the warm months of the year, respectively. There were no significant associations between IQR increase in the two-day cumulative average up to the six-day cumulative average of the daily mean temperature and AMI during the entire year, and warm or cold months of the year.

Conclusion: An increase in temperature would increase the rate of AMI hospitalization.

Keywords: Temperature; Myocardial infarction; Risk; Case-crossover design; Iran

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Introduction

Coronary heart disease (CHD) is the most common health problem in both developed and developing countries.¹ Of the 17.5 million deaths from cardiovascular disease (CVD) worldwide in 2012, 7.4 million were attributed to CHD.^{2,3} CHD is the leading cause of mortality, morbidity, and disability in Iran, and acute myocardial infarction (AMI) is the primary cause of death for patients with CHD.^{4,5}

Considering the climate change, concerns have recently been raised about the relationship between meteorological factors and the incidence of AMI.^{6,7} Many studies conducted in several countries with different climatic conditions have documented seasonal variations in mortality and hospitalization of patients with AMI. These studies demonstrate higher AMI morbidity and mortality rates during periods of extreme high and low temperatures.⁸⁻¹⁰ In a review of 16 studies, Bhasaran, *et al*, reported a significant short-term association between temperature and occurrence of AMI at both low and high temperatures.¹¹ Eight of 12 studies that provided data on winter season, show detrimental effects of cold temperature; 7 of 13 studies report significant increased risk of AMI at higher temperatures. Significant effects of both hot and cold temperatures are reported by four studies.

The fourth assessment report of the International Panel on Climate Change (IPCC) emphasizes that climate change will lead to a general rise in temperature and frequency of severe weather events such as extreme precipitation, heat waves, and unpredictable weather.¹² The highest expected temperatures will be in the Eastern Mediterranean region and the Middle East (EMME), with about 0.37 ± 0.9 °C increase per decade, which is much faster than the expected mean rise of 2.8 °C in global tem-

perature by the end of the 21st century. The region is thus a climate change hotspot.¹³ The effect of temperature on morbidity and mortality depends on the climate of the region and the heat sensitivity, coping capacity, adaptation measures, and socio-demographic characteristics of the population.^{14,15} Furthermore, air pollution is recognized as a risk factor for the development of acute coronary disease and can fluctuate with seasons and temperature.¹⁶

The effects of temperature on the incidence of AMI have extensively been documented. To the best of our knowledge, however, no previous study has been conducted in countries of the Middle East. We conducted this study to investigate the short-term associations between daily mean temperatures and the rate of admission of patients with AMI to hospitals of Tehran, Iran, after adjusting for air pollution as a confounder.

Materials and Methods

Data Collection

Data on the number of adult (≥ 18 years of age) patients with a diagnosis of AMI admitted to Tehran hospitals from March 21, 2013 to March 19, 2016 were retrieved from the Iranian Myocardial Infarction Registry (IMIR). The registry was founded in 2009 by the Office of Cardiovascular Diseases of the Iranian Ministry of Health and Medical Education, and its coverage was completed by the end of 2011.¹⁷ The IMIR is a patient-centred registry system that is compatible with the Iranian Electronic Health Record, which is locally called SEPAS. The data interchange protocol between the IMIR and SEPAS is based on the international standard ISO 13606, which enables the patient encounters to be stored in a nation-wide repository.¹⁸ The selection of the period for this study was determined by the availability of complete and accurate air pollution

For more information on the effect of temperature on daily mortality in Harbin, China see <http://www.theijoem.com/ijoem/index.php/ijoem/article/view/979>



data.

Data for 10 740 patients admitted with a primary diagnosis of AMI (code I21-I22, according to the 10th revision of the International Classification of Diseases [ICD-10]) were collected. We excluded hospital admissions due to AMI that occurred within 28 days of the initial AMI admission—they were not considered new episodes.¹⁹

Data pertaining to the daily mean temperature and relative humidity during the study period were retrieved from Mehrabad International Airport weather station affiliated to the IR Iran Meteorological Organization. To adjust for the confounding effect of air pollution on AMI, air pollution data were acquired from the Iranian Department of Environment. The air pollution data collection process included measurement of 24-hour averages (midnight to midnight) of particulate matter <10 µm in diameter (PM₁₀), nitrogen dioxide (NO₂), nitrogen monoxide (NO), carbon monoxide (CO), sulfur dioxide (SO₂), and ozone (O₃). During the study period, there were no missing values for temperature and relative humidity. However, from March 3, 2016 to March 19, 2016, we had 17 days with no air pollution data. These days were thus excluded from the analysis.

Statistical Analysis

We used the time-stratified case-crossover design to investigate the short-term association between the mean daily temperature and the daily number of hospital admissions of patients with a primary diagnosis of AMI. The model has previously been used extensively to assess this problem.^{14,20,21}

The case-crossover design is a variant of the matched case-control study method, which uses each patient as his or her own control and is appropriate for assessing the association between a short-term exposure and the risk of an acute event. By comparing the temperature on the day of

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- Increases in temperature are associated with increase in AMI hospitalizations.
- There was no association between temperature and AMI admissions during the cold months.
- There was no association between cumulative average temperature and AMI admissions during the entire year, and warm and cold months.
- The effects of temperature on AMI admissions could vary with local climate.

the hospital admission (case period) with the temperatures on other days, when hospital admission does not occur (referent period), the confounders pertaining to individual characteristics that do not vary over a short period are controlled.²² In addition, by selecting a referent period close to the case period, seasonality and confounders related to individual characteristics that vary slowly over time (*eg*, body mass index and smoking status) are also controlled.²³⁻²⁵

In order to control the seasonality and day of the week, time stratified case-crossover design was applied to restrict the referent period to the same day of the week, month, and year as the case period.

To investigate the lag effect of average daily temperature on AMI-related admissions, we examined mean daily temperature of the same day (Lag0), the day before the admission (Lag1), and up to five days prior to the day of admission (Lag5). Two-day cumulative average (CA2 = mean of Lag0 and Lag1) to six-day cumulative average (CA6 = mean of Lag0, Lag1, ..., Lag5) were also investigated.

Public holidays (as a binary variable) and relative humidity (same lag as the temperature) were considered in all models. In addition, we also examined the possibility of confounding by PM₁₀, NO₂, NO,

CO, SO₂, and O₃. All pollutants were adjusted as linear terms based on previous studies.^{14,21,26}

All analyses were performed by Stata ver 14. Using conditional logistic regression, ORs and their corresponding 95% CIs per an IQR increase in temperature and pollutant were calculated. The same lag was used for temperature, relative humidity, and pollutants. Separate analyses for the entire year, in both warm (April to October) and cold (November to March) months were performed. The following equation was used to calculate percentage of excess risk in AMI hospitalizations per IQR increase in temperature and pollutant levels.²¹

$$(e^{\beta \times IQR} - 1) \times 100\%$$

where β is the estimated coefficient in the model. A p value <0.05 was considered statistically significant.

Results

There were 10 740 patients with primary diagnosis of AMI during the 1078 study days. The daily number of AMI hospital admissions varied from 1 to 33. Table 1 shows the descriptive statistics for daily temperature, relative humidity, and air pollutant levels on the same day (Lago) in Tehran during the study period. The daily mean temperature was 19.1 (range -5.7 to 36.5) °C during the entire study period, 25.9 (range 7.3 to 36.5) °C during the warm months (April to October), and 8.8 (range -5.7 to 21.5) °C during the cold months (November to March). On average, levels of relative humidity, PM₁₀, NO₂, NO, CO, and SO₂ were higher during the cold period, while O₃ levels were higher during the warm period.

Table 2 shows the Pearson's correlation coefficients matrix for mean daily temperature, relative humidity, and air

pollutants in the study period. There was a highly negative correlation ($r = -0.81$) between the average daily temperature and the relative humidity. O₃ levels had a weak positive correlation with mean daily temperature and a weak negative correlation with relative humidity. The mean daily temperature showed weak negative correlation with NO₂ and NO, but it had no correlation with PM₁₀.

Table 3 presents percentage change in AMI occurrence per IQR increase in daily mean temperature after adjusting for public holidays, relative humidity, and all pollutants. We found a significant linear increase in the risk of AMI per IQR increase in daily mean temperature on the same day (Lago) in the entire year and in the warm months. During the entire year, an IQR increase (18.6 °C) in Lago of daily mean temperature was associated with 15.1% (95% CI 1.3% to 30.8%) increase in the risk of AMI hospitalizations. In the warm months, an IQR increase (9 °C) in Lago of daily mean temperature was associated with 13% (95% CI 1.9% to 25.4%) increase in the risk of AMI hospitalizations. In the cold months, the change in AMI hospitalizations for an IQR increase (5 °C) in daily mean temperature was 3.2% (95% CI -2% to 8.7%), which was insignificant.

In the entire year and in the warm months, an IQR increase in two-day cumulative average of daily mean temperature was associated with an insignificant decrease in AMI admission. In the cold months, the association was positive (increase of 0.3%, 95% CI -17.1 to 21%), but still insignificant. In general, we find no significant associations between an IQR increase in CA2–CA6 of daily mean temperature and AMI during the entire year, warm or cold month.

Figure 1 shows the percentage change in the AMI admissions per IQR increase in different lags of daily mean temperature during the entire year, warm and cold

Table 1: Summary statistics for daily levels of meteorological variables and air pollutant levels (Lag0) in Tehran (March 21, 2013 to March 2, 2016)

Variables	Mean (SD)	Minimum	Percentile			IQR	Maximum
			25 th	50 th	75 th		
Entire year(1078 days)							
Daily mean temperature	19.1 (10.0)	-5.7	9.8	19.3	28.4	18.6	36.5
Relative humidity (%)	31.8 (16.8)	7.5	17.5	28.6	42.2	24.6	85.1
CO (ppm)	2.4 (0.6)	0.7	2.0	2.4	2.8	0.8	4.0
NO ₂ (ppb)	36.7 (9.1)	15.5	28.7	37.3	43.3	14.6	67.3
NO (ppb)	35.2 (18.2)	8.2	22.8	30.0	43.4	20.6	121.9
PM ₁₀ (µg/m ³)	96.6 (39.7)	31.8	69.4	86.6	112.7	43.3	364.4
SO ₂ (ppb)	20.0 (6.4)	9.3	15.0	18.6	23.3	8.4	50.1
O ₃ (ppb)	25.0 (8.3)	6.4	20.1	25.4	30.2	10.1	53.7
Warm period (648 days)							
Daily mean temperature	25.9 (6.3)	7.3	21.8	26.9	30.9	9.0	36.5
Relative humidity (%)	22.1 (10.4)	7.5	15.1	19.0	27.1	12.0	76.6
CO (ppm)	2.4 (0.5)	1.2	2	2.4	2.7	0.7	3.7
NO ₂ (ppb)	35.3 (9.1)	15.5	27.7	35.7	42.5	14.8	63.1
NO (ppb)	32.5 (16.9)	9.4	21.1	28.3	39.1	18.0	112.5
PM ₁₀ (µg/m ³)	93.0 (35.5)	31.8	67.5	86.7	112.4	44.9	364.4
SO ₂ (ppb)	19.3 (5.6)	10.5	15.2	18.1	22.3	7.1	41.3
O ₃ (ppb)	26.1 (7.3)	7.6	21.2	25.7	30.6	9.4	53.7
Cold period (430 days)							
Average daily temperature	8.8 (3.7)	-5.7	6.1	8.8	11.0	5.0	21.5
Relative humidity (%)	46.4 (13.7)	1.3	35.9	44.3	53.8	17.9	85.1
CO (ppm)	2.4 (0.6)	0.7	2.0	2.4	2.8	0.8	4.0
NO ₂ (ppb)	38.8 (8.7)	21.5	31.9	39.3	45.3	13.4	67.3
NO (ppb)	39.4 (19.4)	8.2	25.8	33.5	51.3	25.5	121.9
PM ₁₀ (µg/m ³)	102.1 (44.9)	43.4	71.8	86.0	117.9	46.0	290.3
SO ₂ (ppb)	21.0 (7.4)	9.3	14.8	19.5	26.1	11.4	50.1
O ₃ (ppb)	23.4 (9.5)	6.4	17.5	24.6	29.4	11.9	48.4

months, adjusted for public holidays, relative humidity, and all pollutants simulta-

neously. Only IQR increase in daily mean temperature in Lag0 was significantly as-

Table 2: Correlations between average daily temperature (ADT), levels of air pollutants and relative humidity (RH)

	ADT	RH	CO	NO ₂	NO	PM ₁₀	SO ₂
RH	-0.810**	1					
CO	-0.072	0.113**	1				
NO ₂	-0.245**	0.114**	0.242**	1			
NO	-0.193**	0.145**	0.408**	0.671**	1		
PM ₁₀	-0.048	0.117*	0.512**	0.086*	0.284**	1	
SO ₂	-0.077	0.066	0.037	0.038	-0.134**	0.070*	1
O ₃	0.142**	-0.210**	-0.499**	-0.021	-0.332**	-0.414**	0.235**

*p<0.05, **p<0.001

sociated with AMI admissions in the entire year and in the warm months. There was no significant association for Lag1 to Lag5, and CA2 to CA6 during the entire year, and warm and cold months.

Discussion

In our study, an IQR increase in daily mean temperature, after adjustment for relative humidity, public holidays, NO₂, CO, NO, PM₁₀, and SO₂ concentrations, was associated with 15.1% increase in the risk of AMI hospitalizations during the entire year and 13% increase in the warm months of year.

No significant association was found between same-day mean temperature

(Lago) and the frequency of AMI admission during the cold months. We did also not find any significant associations between cumulative average temperature (CA2 to CA6) and AMI admission rate during the entire year, and warm or cold months of year.

The observed increase in AMI admission rate in this study on the same day of exposure to higher mean temperature was consistent with results reported by other studies. A study conducted in the USA reveals that hospital admissions for heart disease increase with increase in mean temperature on the same day throughout the entire year.²⁷ The significant positive association between same-day apparent

Table 3: Relationship between an IQR increase in mean daily temperature and occurrence of acute myocardial infarction (AMI) in the entire year, warm months and cold months of year. Figures are percentage (95% CI), adjusted for public holidays, relative humidity and all the pollutants.

Occurrence of AMI	Entire year	Warm months	Cold months
Same day	15.1 (1.3 to 30.8)	13.0 (1.9 to 25.4)	3.2 (-2.0 to 8.7)
2-day cumulative average (Lag0–Lag1)	-35.0 (-58.8 to 2.4)	-12.6 (-38.1 to 23.4)	0.3 (-17.1 to 21.0)
3-day cumulative average (Lag0–Lag2)	-19.9 (-40.5 to 8.0)	2.1 (-20.1 to 30.5)	0.8 (-10.9 to 14.2)
4-day cumulative average (Lag0–Lag3)	-16.9 (-35.6 to 7.1)	0.2 (-19.5 to 24.7)	-0.4 (-10.4 to 10.7)
5-day cumulative average (Lag0–Lag4)	-16.9 (-34.5 to 5.4)	-0.9 (-19.8 to 22.3)	-1.4 (-10.8 to 8.9)
6-day cumulative average (Lag0–Lag5)	-16.5 (-33.7 to 5.3)	3.4 (-18.6 to 27.1)	-3.7 (-12.5 to 6.0)

temperature and incidence of ischemic heart disease was also reported by Basu, *et al*,²⁸ in a study conducted in California. They found 1.7% excess risk in CVD emergency admissions per 10 °F increase in apparent temperature during the warm season. Consistent with our findings, in a recent systematic review, seven out of 13 studies reported significant increases in the risk of AMI admission on days with higher temperatures.¹¹ Unlike our study, several studies failed to find any association between temperature and AMI admission rate during the entire year^{14,29,30} or warm season^{14,16,31}. Moreover, a number of studies reported a significant inverse association between temperature and AMI admission rate in the warm period.^{21,26,31,32}

We did not observe any increased risk of AMI admission per IQR increase in temperature during the cold months, which was consistent with the results of studies from Sweden and Denmark.^{21,31} Nonetheless, an apparent protective effect of higher temperature on the risk of AMI admission in the cold season was reported in other studies.^{14,16,32,33}

The heterogeneity in the results of various studies may be related to many factors. There are many methodological differences (*eg*, statistical methods, lag structure, and level of adjustment for potential confounding factors such as air pollution, the day of the week, and seasonality, *etc*) across studies. Additionally, there are variations in the ascertainment and validation of AMI outcome events, definition of temperature (*eg*, minimum, maximum, mean, or apparent temperature), the demographic profile of the study population (*eg*, age, sex, and socio-economic status), and the climate of the study location.

The magnitude and direction of the detrimental effect of temperature on AMI could also be affected by the number of air conditioning or central heating units in different locations.¹¹ Madrigano, *et al*,¹⁶

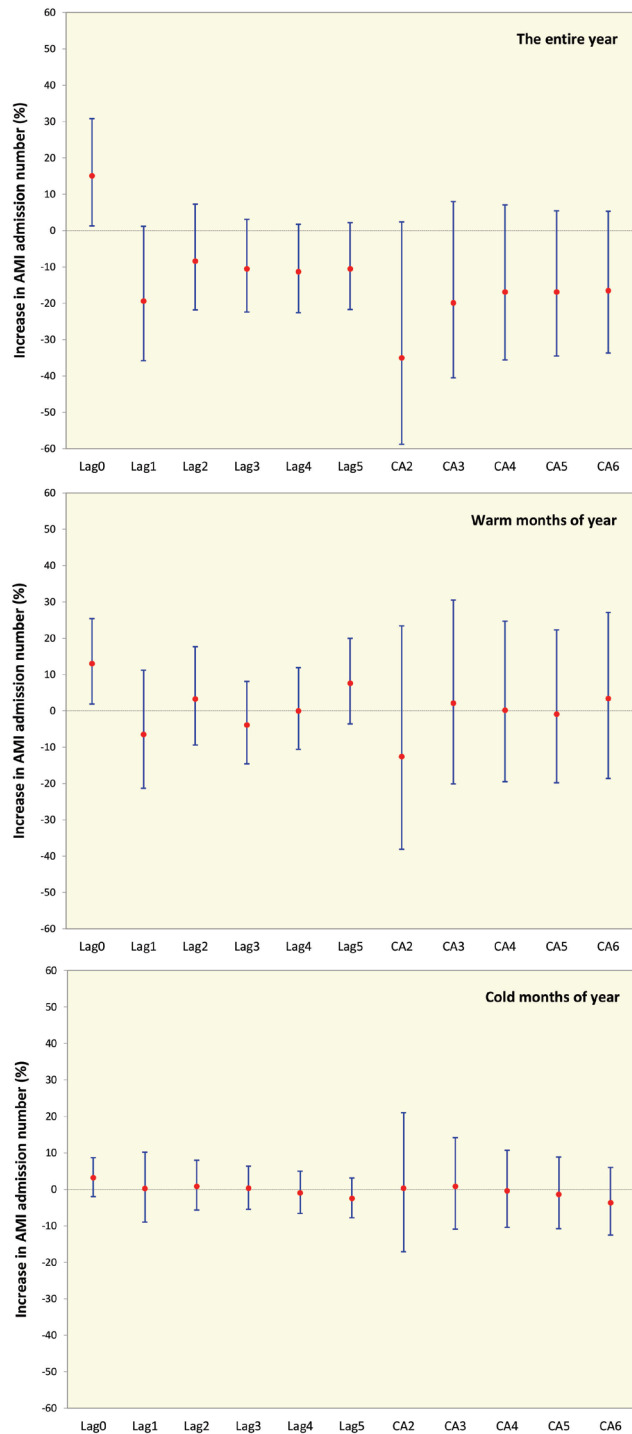


Figure 1: Percent change in the acute myocardial infarction (AMI) admission number per IQR increase in daily mean temperature in different lags, adjusted for public holidays, relative humidity and all pollutants. Error bars represent 95% CI.

reported greater effect of heat on both AMI occurrence and mortality in people living in areas with a higher proportion of poverty. Furthermore, since weather patterns and adaptive abilities vary with latitude, the effects of temperature could vary with latitude and local climate.³⁴ Barnett, *et al*,³⁵ in a multinational study (21 countries), suggested that 28% of the variations in estimated effect of temperature across the countries are related to local mean temperature. A strong association between the temperature-mortality relation and latitude has been found in a study from 11 large eastern US cities.³⁶ The location of our study may justify why we failed to detect any association between temperature and AMI admissions in the cold months. The minimum and 25th percentile of temperature in cold months during this study were -5.72 °C and 6.11 °C, respectively. Conceivably, decreases in temperature in our study were not adequate for developing detrimental effects in the cold months.

The increased risk of AMI in association with elevated temperature could be explained by some mechanisms. In case of exposure to high temperature, blood flow switches from the body core to subcutaneous areas in order to cool the body.^{37,38} As a result, blood pressure may increase and insert stress over the cardiovascular and respiratory systems.³⁹ Increase in blood pressure would lead to a fall in myocardial oxygen supply and possible myocardial ischemia, especially among elderly people with limited adaptive responses and vulnerable myocardium.²⁰ Moreover, dehydration, elevated low-density lipoprotein levels, and lose of water and salt from sweating during exposure to high temperatures, can cause increased blood viscosity and may promote thrombosis.^{38,40,41}

On the other hand, exposure to cold could result in an increased heart rate, blood pressure, and peripheral vasoconstriction, as well as thrombogenic fac-

tors, such as plasma viscosity, fibrinogen concentrations, platelet aggregation, red blood cell count and serum cholesterol levels.⁴²⁻⁴⁵ All these factors are associated with increased risk of AMI, especially among susceptible people.

The current study had several strengths. Unlike most studies, we examined confounding by air pollution. We also used detailed air pollution and meteorological data. Moreover, the quality of data retrieved from the IMIR was reported "suitable for a diagnosis of AMI."⁴⁶

Our study had also some limitations. First, due to data constraints, we did not consider sex, age, socio-economic status, and pre-existing disease or comorbidities. These factors could affect the relationship between temperature and morbidity. Second, in this study, we used ecological design, so there was some potential exposure error. We acquired temperature and humidity data from a single monitoring station instead of measuring individual exposure. This might not necessarily represent the actual indoor temperature and individual exposure and could lead to exposure misclassification.

In conclusion, we found that an increase in temperature was associated with an increase in AMI hospitalization rate in the entire year and in the warm months of year. This was the first study to investigate the short-term association between temperature and AMI hospital admissions in Iran. More research should be done to shed light on the role of local climatic variables in developing AMI and identify vulnerable subgroups.

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Conflicts of Interest: None declared.

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