Assessing the Relationship Between Meteorological Parameters, Air Pollution And Cardiovascular Mortality of Mashhad City Based on Time Series Model

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ABSTRACT
Epidemiological studies conducted in the past two decades indicate that air pollution causes increase in cardiovascular, breathing and chronic bronchitis disorders and even causes cardiovascular mortality. Therefore, the aim of this study was to investigate the relationship between meteorological parameters, air pollution and cardiovascular mortality in the city of Mashhad in 2014 by a time series model. Data on mortality from cardiovascular disease, meteorological parameters and air pollution in 2014 were gathered from Paradises organization, meteorology organization and pollutant monitoring center, respectively. Then the relationship between these parameters was analyzed using correlation coefficient, generalized linear regression, time series models and comparison of means. The results of the study showed that the highest rate of cardiovascular mortality related to Sulfur dioxide, nitrogen dioxide and then $PM_{2.5}$. So that each unit increase in SO_2, NO_2 and $PM_{2.5}$ pollutants adds to the rate of cardiovascular mortality by 22.5, 2.9 and 0.69, respectively. Pressure, wind speed and rainfall have a significant association with mortality. So that each unit decrease in pressure and wind speed, increases the rate of cardiovascular mortality by 2.79 and 15.77, respectively. It was also found that in the case of one-unit increase in rainfall, the possibility of mortality from the mentioned disease goes up by 3.8 units. It was also found that one-year increase of the age increases the mortality caused by these diseases up to 0.57 percent. Furthermore, the highest rate of cardiovascular mortality related to cold periods of the year. Therefore, considering the growing trend of air pollution and its health effects on human health, performing actions and effective solutions is important in the field of controlling and reducing air pollution in Iranian metropolis including Mashhad.

Key words: Air pollutants, Meteorological parameters, Cardiovascular diseases, Mortality, Metropolis, Time Series

List of abbreviations
CO:Carbon monoxide
CO_2 :Carbon dioxide
SO_2 : Sulfur dioxide
NO_2 :Nitrogen dioxide
O_3 :Ozone
ARIMA: Autoregressive integrated moving average

INTRODUCTION
In recent decades, weather and its quality as an integral part of human life have been one of the greatest controversy and the most important environmental issues. So that, hundreds of research and reports on different aspects of air pollution and its health effects around the world showed that the live of all animals, human beings, more or less, depends on the cleanliness of the air and its quality [1-2]. In recent years, due to the process of industrialization and the increasing number of vehicles, urban air quality has had a decreasing trend in Iran. So that, due to the excessive accumulation of factories and industries in the suburban areas as well as the existence of personal vehicles inside it, the weather of cities has always been various degrees, and kinds of pollution especially air pollution [3-4]. Todays, due to the heterogeneity and diversity of air pollutants, in addition to establish a standard for each pollutant, Environmental Protection Agency uses indicators such as air quality index (AQI) to report the daily air quality that can be used to alert the public about the air quality regarding cleanliness or

pollution [5]. So, the officials and researchers analyze the air quality by measuring the air pollutants index like carbon monoxide (CO), sulfur dioxide (SO_2), nitrogen dioxide (NO_2), particulate matter smaller than 10 microns (PM_{10}) and ozone (O_3) to assess the risks and apply management practices by using the obtained results [6]. Based on the results of the study of Kermani *et al.*, AQI index values in Iran's major cities such as Tehran, Isfahan, Arak and Tabriz have been higher than the allowed standard level of environmental Protection organization of Iran in more than 80 days a year [7]. Therefore, investigating the effects of air pollution that widely and constantly overwhelm the residents' health of the contaminated area and consequently learning about the relationship between the concentrations of pollutants with human health is of particular importance.

In 2012, World Health Organization's report showed that PM_{10} and SO_2 cause respiratory and cardiovascular diseases such as asthma, bronchitis, heart attacks, lung function conflicting and mortality. Furthermore, in some European cities, the mortality from PM10, for every 10 micrograms per cubic meter of concentration increase leads to a rise of 6 percent in mortality [8]. According to the Ministry of Health and Medical Education report, about 7000, 4000 and 3000 of Tehran's residence die annually due to air pollution, particulate matters and cancers, respectively [9]. Over the past two decades in Europe and around the world, many epidemiological studies have been done on the relationship between air pollution and the rate of cardiovascular mortality [10]. The results obtained from the study of Yamato *et al*. [11] in which they investigated the systematics analysis of air pollution as an effective factor in cardiovascular disease in south Asia, show a relationship between the increase in urbanization, population and air pollution and health aspects (cardiovascular) and the increase in incommunicable diseases. On the other hand, studies in various regions of the world suggest that fluctuations in meteorological have had an impact on people's lives. So that at a global scale, predicting the rate of mortality and the number of referrals for hospital admissions due to various diseases shows a direct connection regarding future meteorological change scenarios. In other words, an increase in both events (mortality and emergency admission due to various diseases) can be seen in connection with heat waves, high temperatures, high concentrations of atmospheric pollutants and stressful meteorological conditions [12]. Studies conducted in different Iranian's cities especially in Mashhad show that mortality attributed to NO_2 had the highest number in this city [13]. By reviewing the NO_x, O_3 and $PM_{2.5}$ as air pollutants and effective meteorological change on them as well as in interact with human health, Peel *et al*. [14] found that changes in temperature and precipitation pattern strengthen the duration and severity of having O_3. They found that the fire lands by rising temperatures and drought lead to increasing NO_x and $PM_{2.5}$ and has been affected human health [14]. Reviewing articles and other similar research also represents the close relationship between meteorological factors and increase or decrease on air pollution and it has shown that the increase in rainfall and wind speed effects on reduction of air pollution and therefore on more human health [15-18]. The most important effects of pollutants, especially gaseous pollutants are on the respiratory system, and so far most studies have focused on its acute and chronic effects on the respiratory system, and to a lesser extent on the cardiovascular system. However, the changes caused by long-term exposure to air pollution adds to the development of atherosclerosis and in the short term to acute cardiovascular events. It is therefore necessary to do further studies on the air mechanisms and cardiovascular effects and the related results of pollution to reduce the harmful effects of air pollution [19].

Mashhad is Iran's most important metropolis after Tehran, and annually receives millions of travelers from all over Iran and other countries that cause the increase in the air pollution in this religious metropolis of the world [20]. Therefore, considering the increasing air pollution crisis in recent decades and reducing number of healthy days, especially in metropolitan areas as well as the growing rates of disease, mortality and damage caused by it, serious measures to reduce air pollution has become a necessity in our society which is achieved through better understanding and wider study of it. Given that, not many studies have been done regarding the role of air pollutants on mortality of Mashhad citizens and since the effect of these pollutants and meteorological elements on mortality caused by cardiovascular diseases has been proved in many studies in the world, therefore, this study aims to express the role and impact of meteorological elements and air pollutants on mortality from cardiovascular disease in 2014 in the city of Mashhad.

MATERIALS AND METHODS

In this study, the 24-hour average concentration of any air pollutant index (CO, NO_2, SO_2, O_3 and $PM_{2.5}$) was prepared from the center of monitoring environmental pollutants in the Mashhad city. Data related to meteorological elements such as temperature, pressure, humidity, wind speed and precipitation were also provided from Meteorological Organization of Mashhad city. Regarding the

collected data, first, sorting the data was done based on the mean, sum, monthly and yearly minimum and maximum. Also, the mortality statistic was selected in monthly and annual time scale and for the statistical period of 2014 and it was collected by referring to Paradises' organization of Mashhad city. Statistics gathered from Paradises organization include the total statistics of mortality occurred due to accidents and different diseases including cardiovascular diseases. Then, the data was sorted based on the cause, location and age of the deceased (Mashhad city), and the number of monthly and annual mortalities extracted and finally the number of mortalities was extracted by separating age of deceased.

It should be noted that the methodology of the research is analytical and descriptive. So that the raw and cleaned data was collected from the center of monitoring environmental pollutants of the Mashhad, Meteorological Organization of Mashhad and Paradises' organization of Mashhad city, firstly. Then, outlier data were screened and removed from the raw data by using the Descriptive Statistical methods. The collected data was classified in terms of months and years in one dimensional table, and the monthly and yearly means were determined, then to describe the relationships between the variables, the corresponding figures were drawn. In this study, after confirming the data on air pollution, meteorological elements, and the rate of mortality in terms of time, the monthly mean of the mortality caused by the studied disease was identified and then the relationship between the mortality from cardiovascular disease and air pollution and meteorological elements was analyzed with a monthly lag thorough using Excel, R (3.3.0) and SPSS (20) softwares by statistical methods such as correlation, regression and generalized linear time series model box Jenkins (integrated model of autoregressive and moving average known as ARIMA) and mean comparisons. It should be noted that in this statistical method, meteorological elements and also air pollutants are as independent variables and on the other hand, meteorological parameters and time (day, week, month and season) are as confounding factors of the model and the mortality caused by cardiovascular diseases are as dependent variable in the study.

By utilizing the time series chart based on the ordered generalized functions such as ACF (Autocorrelation function), PACF (Partial Autocorrelation function) and EACF (Extended Autocorrelation Function), the ARIMA model is suited to data. Based on the goodness of fit model results with one upper and lower prediction limit, ARIMA has been fitted. Subsequently, the AFC and BIC (Bayesian information criterion) criteria have been computed and the model with the lowest criteria (AFC and BIC) has been chosen. Function (1), shows the equation used to calculate the final pure random model of ARIMA.

$$\mathbf{Yt = 29988.05 - 0.9819\ yt\text{-}1 - 1.565\ et\text{-}1 + 0.8769\ et\text{-}2 - 32.7926\ Pressure - 15.7707\ Wind\ speed + 3.8617\ Rainfall + 0.6967\ PM2.5 + 2.9242\ NO_2 - 16.6139\ O_3 - 151.23\ CO + 22.5133\ SO_2 + et}$$

Where Yt is mortality from cardiovascular diseases and et is pure random time series model.

In addition, after obtaining the suitable ARIMA model for the mortality, the predictor variables of air pollutants (CO, NO_2, SO_2, O_3 and $PM_{2.5}$) and meteorological elements (temperature, pressure, humidity, wind speed and precipitation) were added to the model and the coefficient of their impact on mortality prediction is achieved. In fact, a time series regression model is fitted to the data. The time series regression is modeling of short-term fluctuations in the presence of seasonal patterns, dealing with time varying confounding factors (mainly meteorological variables and time variable) and modeling monthly delayed (‘lagged’) associations between meteorological elements and air pollution as exposures with cardiovascular mortality as an outcome.

RESULTS AND DISCUSSION

Investigating the monthly relationship between meteorological elements and air pollutants in mortality caused by cardiovascular diseases.

Investigating the number of monthly mortality and the amount of meteorological elements and air pollutants' concentration in 12 months of 2014 showed that the mean of mortality caused by the mentioned diseases is 227.2 persons. Fig. 1, showed the monthly graph of mortalities from cardiovascular disease in different months in 2014. As can be seen, the highest number of mortality from the mentioned disease is obtained in February and then in April totally 378 persons and the lowest is in July with 126 persons. The high mortality in the cold months can be caused by the frequency of the inversion phenomenon in these days. As Khorshid Doost. [21] states, the number of mortalities from cardiovascular

disease in the cold months (January, February and March) which is along with cold weather, air Pressure increases, reduced solar radiation, short length of day and reduced inversion layer (temperature inversion) leads to increase the pollutants' concentration and density in the limited space of the earth and it is the main cause of mortality.

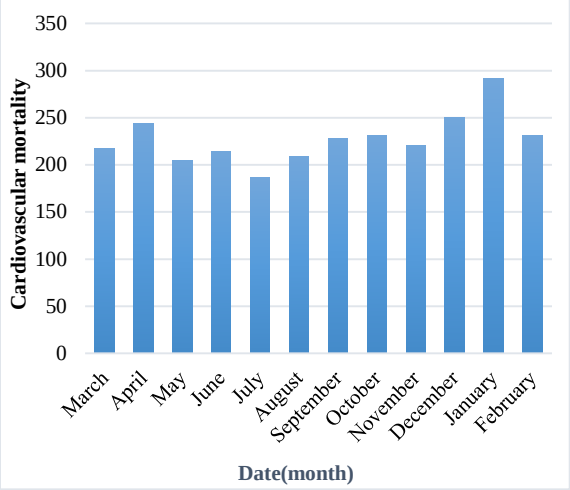

Fig 1: Number of monthly mortality from cardiovascular disease in Mashhad city in 2014

Monthly average of meteorological elements of pressure, humidity, temperature and wind speed as well as sum total of rainfall is 903.3 Hpa, 49.1% , 16.04oc, 6.83m/s, and 23.66mm, and the value of the concentration of $PM_{2.5}$, NO_2, O_3, CO and SO_2 is respectively 22.6µg/m^3, 22.21ppb, 14.87ppb, 1.81ppm, , and 13.63ppb. The greatest amount of pressure and humidity is in December and the highest temperature and wind speed is in July, the lowest pressure, humidity, temperature, wind speed, are respectively in the months of July, August, November, December. Also, the highest concentration of $PM_{2.5}$, NO_2, O_3, CO and SO_2 is respectively in October, November, February, March, April and May and the lowest concentration of pollutants are respectively in March, June, December, August and September. Furthermore, it should be noted that the concentration of all mentioned pollutants are below the standard threshold of Health Act in 2009. It was also found that in individual days, the amount of pollutants is much higher than its monthly average. For example, in some days, the concentration of NO_2 and SO_2 is respectively 0.06 ppm and 0.05 ppm and the $PM_{2.5}$ concentration is 105.1µg/m^3.

The time series model of the monthly relationship between mortality from cardiovascular diseases and meteorological elements and air pollutants was performed by using pure random model of ARIMA (1, 0, 2), and the results are shown in Table 1. In general the pure random model of ARIMA (1, 0, 2) was achieved based on Table 1.

Table 1: The parameters of the final model of determining the relationship between monthly mortality due to cardiovascular disease with meteorological elements and air pollution

Variable's name		The estimated coefficient	Standard Error	P-value[d]
Coefficient	ar1[a]	-0.9819	0.0201	< 0.0001
	ma1[b]	-1.5654	0.4012	< 0.0001
	ma2[b]	0.8769	0.2724	0.0012
	Intercept[c]	29988.05	745.6541	< 0.0001
Meteorological elements	Pressure	-32.7926	0.8552	< 0.0001
	Wind speed	-15.7707	1.6357	< 0.0001
	Rainfall	3.8617	0.1232	< 0.0001
Air pollutants	$PM_{2.5}$	0.6967	0.2331	0.0028
	NO_2	2.9242	0.2278	< 0.0001
	O_3	-16.6139	0.7196	< 0.0001
	CO	-151.23	9.2706	< 0.0001
	SO_2	22.5133	0.6267	< 0.0001

a= ar1 is autoregressive component of the first stage
b = ma1 and ma2 are second-order moving average model components
c= Intercept is width from source
d= The meaningful of parameters on the model is measured by p-value where the H_0 for example in art1 is ar1=1 and H_1 is ar1≠0.

It should be noted that, time series regression studies have been widely used in environmental epidemiology, notably in investigating the short-term associations between exposures such as air pollution, weather variables or pollen, and health outcomes such as mortality, myocardial infarction or disease-specific hospital admissions. Typically, for both exposure and outcome, data are available at regular time intervals (e.g. daily pollution levels and daily mortality counts) and the aim is to explore short term

associations between them. One of the most important merits of time series studies is removing the effect of confounding factors on outcome [22].

Based on Table 1, the ARIMA model showed that among meteorological elements of pressure, wind speed and Rainfall and all air pollutants, there is a significant relationship with mortality from cardiovascular diseases with error level less than 0.05. According to the model shows that, among meteorological elements, pressure and wind speed have significant and negative effect, and rainfall has significant and positive effect (i.e. having reduced the pressure and wind speed and increased rainfall accelerates mortality). The minimum and maximum amount of pressure in Mashhad city is 888.7 and 920.7 Hpa, respectively. This fluctuation in air pressure can cause to surface persistent change which makes the air pollutant's accumulation in troposphere and therefore serious health effects such as exacerbation of various diseases. However, the observed negative relationship between pressure and mortality in this study might be due to the result of other factors that have not been seen in the study [21, 22, 23]. Wind speed has a reverse effect (-15.77) and we see it can be seen that as the wind speed decreases the rate of mortalities from cardiovascular disease will increase. The results of this study show that with each unit decrease in wind speed, 15.77 unit of mortality probability from cardiovascular disease increases (Table 1). Wind speed reduction and its inability to discharges and transport pollutants lead to the concentration of pollutants in the city, and will increase the potential for pollution. So, the dominant wind direction and wind speed play a decisive role in reducing or increasing air pollution [23]. It was also found that in the case of one-unit increase in rainfall, the possibility of mortality from the mentioned disease goes up by 3.8 units (Table 1). Precipitation role in the city's pollution is critically important so that the days with precipitation greater than 5 mm/day have greater importance in urban air cleaning. While the intensity of rainfall less than 5mm per day, not only cleanse the city but also result in pollution [23]. Average days with precipitation more than the mentioned amount in Mashhad in April, February and March have been respectively 6, 2 and 4 days. This means that during the cold period of the year in Mashhad weather has been refined more by precipitation. This situation, however, cleans the air, the atmospheric leaching of suspended matter to the soil, causes soil contamination [23].

In relation to air pollutants, the most damaging effect belongs to SO_2 with the coefficient of 22.5133 and for each unit increase, 22.5 units will add to mortality from cardiovascular. NO_2 and $PM_{2.5}$ pollutants with the coefficient of 2.9242 and 0.6967 such as SO_2 have a significant positive effect. So that each unit increase in NO_2 and $PM_{2.5}$ pollutants adds to the rate of mortality by 2.9 and 0.69, respectively. But O_3 and CO pollutants have a reverse relationship with the mortality rate of these patients (Table 1). Various reports indicate that even very low concentrations of SO_2 can increase the heart beat and chest pain. It is also known that the $PM_{2.5}$ is of important pollutants in creating heart disease. Many polluting particles exit from the nose by small hair-like appendages, however very small particles may stay in the lungs for several weeks, months or years. Air pollution affects lung function and damaging lung prevent purification process and create respiratory and cardiovascular disease. Also, people who have been exposed to ultrafine particles in air pollution, experience significant reduction in blood flow of the supplying arteries of the heart and the strength of its contractions. In addition, the risk of arrhythmias (changes in regular heart rate) and increased heart rate in these patients is higher. It was also reported that NO_2 can alter the kidney, liver and heart tissues [24].

The existence of a reverse relationship between some pollutants and the rate of mortality from cardiovascular disease in analyzing the current model can be the result of simultaneous consideration of meteorological elements and air pollutants' role in the mortality rate, the influence of some confounding factors like smoking, gender, level of education, having vehicle, unsuitable diet, lack of movement, type of job, social and economic stresses, the duration of being out, and etc, more sensitivity of the mentioned pollutants to the confounding factors including meteorological elements, and their high intra correlation [22]. On the other hand, the current study shows that these pollutants together with meteorological factors have a long-term impact (i.e. monthly here) and not immediate or short-term (i.e. in daily and weekly) (results do not show) on human health therefore, this issue should be considered in epidemiological studies of air pollution and in similar studies, longer time periods (yearly) should be used.

A study conducted in 15 Italian cities showed that cardiovascular mortality increased by 1.9, 1.0, 0.5 and 0.4 percent for an increase of 10 micrograms per cubic meter NO_2, 1mg per cubic meter CO, 10 micrograms per cubic meter SO_2 and 10 micrograms per cubic meter PM_{10}. In Boston there is a significant association between NO_2 and $PM_{2.5}$ and the risk of acute myocardial infarction [19]. Khorshid Doost *et al*. [21] also found that there is a significant relationship between the mortality from stroke and coronary heart with temperature and air pressure [21]. A survey conducted in Shiraz showed that SO_2 and NO_2 gas concentrations are associated with heart

disease [25]. Mohammadi [26] did various studies at Tehran University on Tehran air pollutants associated with mortality from cardiovascular diseases. Their results showed that there is a strong and significant correlation between meteorological elements such as temperature, pressure and relative humidity and heart disease mortality. Moreover, this is particularly significant and strong correlation between the monthly average of these elements and the number of deceased from heart disease. Along with the results of this study, Peters (2001) analysis in Harvard University on 772 heart patients showed that there is a direct relationship between the increase in the pollutants' particles in the air and heart stroke and the raise in the time of exposure with these particles increases the occurrence of heart stroke [27]. In the study of Dehghani *et al.* [11] on the impact of air pollution on heart patients hospitalized in Shiraz, the results indicate the lack of correlation between the mean of PM_{10}, SO_2 and O_3 and admission increase of people with heart disease. Also air pollutants' relationship (CO, SO_2, PM_{10}) with mortality in the study on increased air pollution and mortality in people over the age of 64 years in Tehran is reported to be significant in the final model [22]. Several studies in various institutes and universities have been done on this topic and conflicting results have been obtained. For example, Douglas *et al*., investigated the relationship between air pollution and mortality in six provinces of the United States of America with random sampling and controlling other confounding factors (alcohol, cigarettes, etc.). They concluded that the influence of other risk factors cannot be completely removed but the relationship between mortality from heart diseases and SO_2 particle existed in air pollution can be definitely confirmed [28].

Investigating the relationship between age and mortality from cardiovascular diseases .

Reviewing the number of monthly mortalities based on different ages in 2014 showed that the average age of mortality from cardiovascular disease over the period of study is 53.5 years. The minimum age is 1 year and the maximum is 106 years and the standard deviation of monthly mortalities caused by the disease is 3.6.

For statistical analysis of age and mortality from cardiovascular disease, a linear regression model (generalized) was used. It can be seen from results of that age has had a significant impact on the mortality of the disease at a significant level of 0.05. Since the estimated coefficient for this variable are a positive value, so age has a direct impact on patient mortality rates. That is, as the age increases the rate of mortality from cardiovascular diseases will rise, so that if the age increases by one unit (year), the rate of mortality from cardiovascular diseases will increase by 0.56 coefficient. Relevant factors as well as their relationship with the result are shown in Table 2.

Table 2: Parameters of the model determining the relationship between age and monthly mortality due to cardiovascular diseases

Variable's name	Coefficient estimate	Standard Error	t-test	p-value
Intercept	3.42	4.81	0.71	0.47
Age	0.56	0.08	7.20	<0.0001

*= In the linear regression model (generalized), the H_0 is there is no any relationship between age and monthly mortality due to cardiovascular diseases and the H_1 is there is a relationship between age and monthly mortality due to cardiovascular diseases, and therefore the T-test and P-value is measured the meaningful of these hypothesis.

The correlation coefficient between age and mortality from cardiovascular disease is shown in Table 3. Considering the amount of correlation between two variables which is 0.576, it can be concluded that there is a significant relationship between age and mortality from cardiovascular diseases. Mortality and human diseases greatly and relate to meteorological patterns, in many ways. The frequency and severity of maximum temperatures have the most influence on mortality rates, especially among elderly [26]. Studying the impact of meteorological elements and air pollution on heart disease, the effect of weather on mortality from heart attack has been shown significant in both men and women. It also significantly increased with aging, but no significant relationship was observed between age at a younger stage (0-20) and mortality from heart stroke [29]. Asefzadeh *et al*. [30] also evaluated the socio-economic situation of deceased due to cardiovascular disease in the city of Qazvin and determined that with increasing of age, the incidence of mortality has increased. Also, Robert Brook's studies at University of Michigan in America on air pollution particles and O_3 and Coronary Heart Disease on adult health in 2013 showed that exposure to the mentioned pollutants results in the clogging of arteries [25].

Table 3: The correlation coefficient between age and mortality from cardiovascular disease

Correlation coefficient between age and mortality from cardiovascular disease	0.576

Investigating the effect of the seasons on mortalities from cardiovascular disease.

Quantitative studies was done on the relationship between air pollution and mortality in different seasons of the year (cold, and warm), because the amount of air pollution is altered in various seasons of the year and therefore the rate of disease as well as mortality will be different. So the present study has

been investigated the effect of season on mortality caused by cardiovascular diseases. The number of mortality based on different seasons in the city of Mashhad in 2014 shows that the average mortality from cardiovascular disease in the studied year was about 681.8 of persons. Moreover, its standard deviation was 33.86 persons, its minimum and maximum was respectively 610 and 773 persons. The effect of different seasons on mortalities from cardiovascular disease is done by comparing the average of several independent groups (ANOVA). Table 4 shows sum of squares, degrees of freedom, mean squares, t-test and p value.

Table 4: Analysis of the Variance for investigating the effect of the seasons on mortalities from cardiovascular disease

	Sum of Squares	df	Mean Square	F	P-value
Between Groups	218.618	3	72.873	8.893	.000
Within Groups	2958.330	361	8.195		
Total	3176.948	364			

The Ho hypothesis states that there is no significant relationship between groups, since in this part; the p value is less than 0.05 so the mean of mortality from cardiovascular diseases in different seasons of the year has had a significant difference.

According to the obtained results and the existence of a significant difference in different seasons, LSD post hoc test has been carried out in order to identify the difference between groups (Table 5).

Table 5: Post hoc tests (LSD) to investigate the difference between mortality from cardiovascular disease in different seasons

Post hoc test	Season(I)*	Season(J)*	Mean Difference (I-J)	Std. Error	P-value	95% Confidence Interval	
						Lower Bound	Upper Bound
LSD	1.0	2.0	.5914	.4198	.160	-.234	1.417
		3.0	-.3939	.4233	.353	-1.226	.439
		4.0	-1.5349*	.4245	.000	-2.370	-.700
	2.0	1.0	-.5914	.4198	.160	-1.417	.234
		3.0	-.9853*	.4233	.020	-1.818	-.153
		4.0	-2.1263*	.4245	.000	-2.961	-1.291
	3.0	1.0	.3939	.4233	.353	-.439	1.226
		2.0	.9853*	.4233	.020	.153	1.818
		4.0	-1.1409*	.4279	.008	-1.983	-.299
	4.0	1.0	1.5349*	.4245	.000	.700	2.370
		2.0	2.1263*	.4245	.000	1.291	2.961
		3.0	1.1409*	.4279	.008	.299	1.983

Season 1= Spring, 2 = Summer, 3= Autumn and 4= Winter

*= I and J are not abbreviated; they are used only for a symbol as the number of groups. In this study, there are 4 groups (seasons), so that each group is compared with other groups, respectively in LSD post hoc test.

The results suggest that the rate of mortalities from cardiovascular disease is not significantly different` in the spring, summer and fall ($p > 0.05$) and the number of mortality were higher in spring than summer and in autumn it was slightly more than spring. There is also a significant difference in mortality rate in summer and autumn ($p < 0.05$) and the number of mortalities was greater in autumn than summer. It should be noted that the number of mortalities from cardiovascular disease has a significant difference in the spring and winter ($p>0.05$). Also, the mortality rate in summer and autumn is significantly different from winter (p-value is less than 0.05) and the number of mortalities was higher in winter than summer and autumn. In general, the results of this study showed that the highest mortality from cardiovascular disease in the studied year is related to winter, fall, spring, and summer, respectively. As it can be seen, the highest rate of mortality caused by cardiovascular diseases is recorded in cold seasons of the year especially winter that can be caused by inversion phenomenon this season, long nights and therefore the increase in pollutants' concentration. As mentioned earlier, the highest monthly concentration of $PM_{2.5}$ and NO_2 also relates to the second half of the year and cold seasons. The researchers of environmental health research center in Munich in Germany analyzed 5000 samples on 1000 patients and found that cold weather helps the increase in the number of heart stroke occurrence by increasing Body inflammatory marker [31]. In western Europe and America's countries, most mortality from heart diseases occurs in January and February, and the least occurs in August and July [32]. The impact of refrigeration and air pollution following the inversion phenomenon (in cold seasons) is very significant in heart attacks, so that the number of visits to cardiovascular clinics on cold and snowy days is growing every year. Given that by temperature reduction in compensatory mechanism,

the body's metabolism increases to generate heat and cope with the cold, so along with it the heart activity increases and the individual faces the risk of heart stroke. Some cases referred to specialists of heart disease have been reported during snow removal, chain replacement or pushing vehicles in snowy days and work-related accidents increase during periods of meteorological change [33]. Therefore, people with underlying heart disease should refrain from doing heavy activity in cold weather because this activity is a factor to impose additional pressure on the heart. The results of the studies conducted so far indicate that lower temperatures increase the incidence of heart attacks and the chance of dying from it. Heart muscle begins more activities at low temperatures than normal situation to deal with a drop in body temperature and also, at low temperature, heart coronary arteries contracts and pumping blood to the heart has been disrupted and thus the risk of stroke, especially in patients with a history of heart disease increases. This kind of diseases have been reported the first cause of mortality, in the city Ahar [33].

Moreover, other studies have shown that the highest correlation between air pollution and mortality belongs to autumn [19]. Farajzadeh and Darand. [34] also found that the greatest number of cardiovascular mortality has been occurred during the cold months (December, January and February), so that the increase caused by cardiovascular diseases in the cold months shows this. A study conducted by Berga *et al.* stated that there is a significant positive relationship between heart attack disease and temperature [21]. The results analyzing the concentration of pollutants in the city of Tabriz in four studied seasons show that concentration of PM_{10} has the highest and lowest amounts in the spring and summer, respectively. Also, SO_2 in autumn and summer had the highest and lowest concentrations, respectively and therefore, heart patients have increased by rising in PM_{10} and SO_2 [35]. The temperature impacts on mortality in elderly and children especially because of cardiovascular, Vascular-cerebral and respiratory diseases are more prominent than patients with other disease and therefore the relationship between mortality and temperature for daily mortalities is clearly visible [36]. The results of the studies conducted so far indicate that a lower temperature increases the incidence of heart attacks and the chance of dying from it. Heart muscle begins more activities at low temperatures than normal situation to deal with a drop in body temperature and also, at low temperature, heart coronary arteries contracts and pumping blood to the heart has been disrupted and thus the risk of stroke, especially in patients with a history of heart disease increases [33].

CONCLUSION

The analysis of a wide range of epidemiological and experimental studies shows that air pollution is among new risk factors for cardiovascular disease. Time series studies, which are the relation between the level of day-to-day/week-to-week/ month-to-month air pollutants and health endpoint (mortality) consistently shows a correlation between all causes of mortality. So the aim of this study is to remove the specific confounding factors (mainly meteorological variables and time variable) and also considering other characteristics of time series data to address investigating the relationship between meteorological elements and air pollution with cardiovascular mortality. The results of an ARIMA model (1,0,2), indicate a significant relationship between the monthly mean of the pollutants of SO_2, NO_2 and $PM_{2.5}$, as well as meteorological elements such as pressure, wind speed and rainfall and cardiovascular mortality. On the other hand, the study shows that these pollutant along with meteorological factors have a long-term impact (i.e. monthly here) and not immediate or short-term (i.e. daily and weekly) on human health and therefore this issue should be considered in epidemiological studies of air pollution and other studies should focus on longer time periods (yearly). It was also identified that the harmful effects of air pollution is mostly observed in elderly, so that the rate of mortality from cardiovascular has increased by increasing age and if the age increases by one unit (year), the rate of mortality from the mentioned diseases will increase by 0.56. The results of this study showed that there is a significant difference between the mean of mortality due to cardiovascular in different seasons of the year and the highest rate of mortality from the mentioned diseases in the studied year occurred in winter, fall, spring, and summer, respectively. This may be due to inversion phenomenon in winter, the long nights and thus increase in the concentration of pollutants. The highest monthly concentration of $PM_{2.5}$ and NO_2 also relates to the second half of the year and cold season. Meanwhile, by cold air on the city of Mashhad and also high pressure flow, air pollution intensifies and inversion occurs. The inversion of the city of Mashhad almost coincides with the penetration of cold air pressure on Iran. Regarding the results of this study, it can be stated that air pollution is a problem that has a great impact on human health especially on cardiovascular system and it is one of the problems that can reduce the damages threatening the society's health by adopting appropriate measures of law enforcement.

ETHICAL ISSUES
Ethical issues such plagiarisms have been observed by the authors.

COMPETING INTEREST
The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTIONS
All authors of this study have a complete and equal contribution for data collection, data analyses and manuscript writing.

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