Short-term effects of ambient (outdoor) air pollution on cardiovascular death in Tehran, Iran – a time series study

Azizallah Dehghan, Narges Khanjani, Abbas Bahrampour, Gholamreza Goudarzi and Masoud Yunesian

ABSTRACT
The aim of this study was to estimate the effect of ambient air pollutants on cardiovascular deaths in Tehran, Iran. In this time series study, air pollutant data were acquired from the Environmental Protection Agency. Meteorological data were acquired from the meteorological organization, and death data were acquired from the Tehran's cemetery registration. Generalized Additive Models (GAM) were used for estimating the Rate Ratio. NO2, SO2 and PM10 were associated with total cardiovascular deaths. PM10 and NO2 showed stronger relations with deaths in the elder age group. The result of this study showed that NO2, SO2, PM10 and O3 are probably responsible for part of the cardiovascular deaths that happen daily in Tehran.

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Air pollution; cardiovascular; death; particulate matter; Tehran

Introduction
Air pollution is composed of a heterogeneous mixture of compounds including carbon monoxide (CO), ozone (O3), nitrogen oxides (NOx), sulfur dioxide (SO2), particulate matter (PM) and liquids (Sun et al. 2010).

Air pollution is a main environmental hazard and a threat to human health. The rising health consequences of air pollution have attracted the attention of researchers in the last decades. In 2014, 91% of the global population lived in places where the levels of air pollutants failed to meet the World Health Organization’s air quality standards. The World Health Organization (WHO) reported that in 2016 around 4.2 million people lost their lives because of inhaling outdoor polluted air. These facts confirm that air pollution is now the world’s largest single environmental health risk (WHO, 2018).

Air pollution in developing countries is mainly related to their increased population, wrong ways of regulating vehicles, vast usage of fossil fuels, urban sprawl, immigration to big cities and inappropriate expansion of industries without appropriate site selection (Roushan et al. 2009, Rezaei et al. 2016).


Although the Rate Ratio of mortality caused by air pollution is low, the proportion of deaths related to air pollution is high because of the high number of exposed and sensible populations (Qorbani and Yunesian 2010). Air pollution shows a nations environmental health and quality control problems. Although there are many studies done in the world about air pollution, the study is the first to analyze the relation between the short-term changes in air pollution, and cardiovascular death in Tehran.
pollution and its health effects, but there have been fewer studies from developing countries; and, therefore, studying the various aspects of air pollution in developing countries is essential (Santus et al. 2012).

Tehran is the capital and the biggest city of Iran, with a population of about 8.5 million people, from the 80 million people who live in Iran. The area of Tehran is 1500 km². This city is very densely populated and suffers from air pollution due to its specific geographical conditions (topography and meteorology), social and cultural problems (population distribution, traffic), urban development and abundant consumption of energy in transportation and industry. Controlling air pollution has been complicated in Tehran and investigation about the different aspects of air pollution and its health effects is still necessary (Hosseinpoor et al. 2005, Khalilzadeh et al. 2009).

Given the importance of air pollution in Tehran, this time series study was carried out to find about the short-term effects of air pollution on deaths due to cardiovascular disease in this city.

**Methods**

This was a time series and population-based study conducted in Tehran, Iran. Tehran is geographically located in a valley and surrounded by medium to high mountains on its north, northwest, east, and southeast.

**Air pollution, meteorological and death data**

Data on ambient air pollutants (CO, O₃, NO₂, SO₂, and PM₁₀) from 2005 to 2014 were collected from the Tehran Department of Environment and Tehran Air Quality Control Company. Tehran has 22 municipality districts and there are one or more air pollution monitoring stations in each district (36 in total). In all monitoring stations, the concentrations of air pollutants are registered hourly. In this study, the outlier observations were identified with spatio-temporal screening tools. In this method the mean and standard deviation of each observation in a specific hour, and 1 and 2 h before and after it, in each station and the neighboring stations were computed. Then observation which were more than ±3 SD away from the mean were recognized as outliers (Shamsipour et al. 2014, Dehghan et al. 2018).

Missing air pollution data was estimated using the Expectation-Maximization (EM) algorithm in SPSS20 software. This approach was proposed by Dempster et al. (1977). This method is an algorithm for nonlinear optimization and is appropriate for time series applications involving unknown components (Anava et al. 2015). EM is a repetitive and effective process that uses maximum likelihood estimation in estimating missing data. Each repetition of the algorithm consists of two steps: the mathematical expectation stage (E-Step) and the maximization step (M-Step). In the mathematical expectation step, missing data is estimated based on observed data and the current estimation of the model parameters. In the maximization step, the likelihood function is maximized with the assumption that the missing data is known. Here, the estimates of missing data from the E-step are placed instead of missing values. By repeating the algorithm, the missing value is corrected at each step, and convergence can be assured (Afshari Safavi et al. 2015).

After missing imputation was done, the daily averages of pollutants in selected stations were computed. Then the average of included stations was computed and one value was generated for the whole city in all days. The included stations were the Aghdasieh, Azadi, Poonak, Pardisan, Razi, Park-e-roz and Shahr-e-rey stations.

The data of cardiovascular deaths were collected from the Tehran’s Cemetery (Behesht-e Zahra) Organization. Cardiovascular deaths included deaths from heart attacks, strokes, heart diseases related to blood pressure, kidney diseases related to blood pressure, pulmonary embolism, embolism and arterial thrombosis, aortic aneurysm, other vascular diseases, other heart diseases, other cardiovascular diseases, non-rheumatic disorders in the mitral and aortic valves, acute and sub-acute endocarditis, acute peri-carditis, acute myocarditis, cardiomyopathy, cardiac failure, and congenital abnormality of the cardiovascular system. The daily count of cardiovascular deaths was entered in the GAM model as the outcome variable.

The daily average of meteorological data (temperature and relative humidity), were inquired from the Tehran Meteorological Organization as potential confounder variables; because some studies have reported that cardiovascular disease mortality may change with fluctuations in temperature (Khanjani and Bahrampour 2013), although other studies have denied a relation (Dadbakhsh et al. 2018).

**Data analysis**

The mean, standard deviation, median, 25th and 75th percentiles of air pollutants, meteorological variables
and the frequency of cardiovascular deaths were computed.

A time-series regression analysis was used to assess the short-term association between air pollutant exposures and count of cardiovascular deaths. Generalized Additive Models (GAM) were used to estimate Rate Ratio (RR). GAM models have been widely used in studies about air pollution and health outcomes; because they are able to adjust for the effect of non-linear confounding variables such as seasonal changes, trends and meteorological variables (Dominici et al. 2002, Guisan et al. 2002, Dehghan et al. 2018).

The degree of freedom for the smoothers was determined by Generalized Cross Validation (GCV) using the "mgcv" package in R 136 3.2.2 software.

Multivariate GAM models were also run for the same outcome and in subgroups. Relative humidity, temperature, season and weekdays were entered into the model as potential confounding variables. Then the strongest lag for pollutants was reported.

The formula of the GAM model is as follows (Wang and Pham 2011).

$$Y_t \sim \text{Poisson} \left( \mu_t \right)$$

$$\log \mu_t = \alpha + \beta_i(X_i) + \sum S_j(X_j) + yS(\text{season}) + \eta D(\text{dow})$$

In this formula $Y_t$ is the frequency of the incidence of cardiovascular deaths. $\beta_i$ is the coefficient for air pollutants ($X_i$) and indicates the logarithm of Risk Ratio (RR) for 10 unit increase in all pollutants (10 $\mu g/m^3$ for PM$_{10}$ and 10 ppb for O$_3$, S O$_2$ and NO$_2$), except CO which it is for 1 ppm increase. Furthermore, $S_j(X_j)$ is a smoothing function for meteorological variables (relative humidity and temperature) and trend. S(Season) are indicator variables for Spring, Summer, Autumn and Winter. D(Dow) are indicator variables for weekdays. Season and weekdays were added to the model as categorical variables.

In this study, due to the correlation between pollutants, one pollutant models were performed. But, we also used two pollutant models to assess the stability of the results from the one pollutant models.

**Result**

During the 10-year study period, 215,373 cardiovascular deaths occurred in Tehran which included 122,911 (57.07%) male and 92,462 (42.93%) female deaths. The frequencies of cardiovascular deaths are shown in Table 1 by year and gender. Figure 1 shows the trend of cardiovascular deaths.

The descriptive statistics of air pollutants, humidity, temperature and death during 2005–2014 in Tehran are showed in Table 2. These results show the annual average of PM$_{10}$ was over the WHO 2014 annual thresholds guidelines (20 $\mu g/m^3$). The average of SO$_2$ concentrations was higher than the standard values as well.

Table 3 shows the Mean±SD of pollutants and number of cardiovascular deaths by season in Tehran, during 2005–2014. The highest concentration of O$_3$ was in summer, CO and PM$_{10}$ was in fall, and NO$_2$ and SO$_2$ was in winter and spring respectively. Also most cardiovascular deaths occurred in winter (29.03%) and the lowest number of deaths was in summer (21.34%).

Table 4 shows the correlation between different pollutants. All pollutants had a significant correlation with each other; except O$_3$ that showed a direct correlation only with PM$_{10}$ and an inverse correlation with CO. The highest correlation was found between nitrogen dioxide and sulfur dioxide ($r = 0.696$, $p = <.001$).
Table 5 shows the GAM results of air pollutants and total cardiovascular death. After adjusting for confounders including temperature, relative humidity, trend, season and DOW; total deaths were significantly associated with NO2 in lag 0 to lag 4 in the one pollutant model and lag 0 to 3 in the two pollutant model. But the strongest relation was seen in lag 3 in the one pollutant and lag 1 in the two pollutant model. SO2 in the one pollutant model showed significant associations with total death in lag 0 and 1. But in the two pollutant model no significant relation was seen. PM10 showed a significant association with total death in lag 0 to 3 in both models (one and two pollutant). But the strongest relation was seen in lag 0.

Table 6 shows the RR of air pollutants and cardiovascular deaths in men. In men, NO2, SO2 and PM10 had the strongest direct relation with cardiovascular death in lag 3, 0 and 0 respectively, in the one pollutant model. But in the two pollutant model, the strongest relation for NO2 and PM10 was seen in lag 0; and SO2 did not show a significant relation with death.

Table 7 shows the RR of air pollutants and cardiovascular deaths in women. In women, O3 showed a significant direct relation with deaths, in lag 0–3 in the one pollutant and lag 0–4 in the two pollutant models. NO2 in lag 6 (one pollutant model) and lag 5 (two pollutant model) had a significant relation with death. PM10 had a relation with cardiovascular deaths in lag 0–2 in the one and two pollutant models.

No pollutant was related to cardiovascular deaths in people under 18 years old (Table 8). In people 18–60 years, NO2, SO2 and PM10 showed a strong relation with death in lag 1, 0 and 0 (day) respectively, in the one pollutant model. But in the two pollutant model, NO2 and PM10 showed the strongest relation in lag 3 (Table 9).

NO2 and PM10 in people over 60 years had the strongest relation with cardiovascular deaths in 1, and 0 day lags respectively in the one and two pollutant models. SO2 showed a direct relation only in the one pollutant model (Table 10).

Discussion

This study showed a probable association between high levels of NO2, SO2, and PM10 with cardiovascular mortality.

In this study, with a 10 mg/m³ increase in PM10 on the same day, total cardiovascular deaths increased 0.57% (95% CI: 0.34–0.79%) in the one pollutant model and 0.59% (95% CI: 0.28–0.84%) in the two pollutant model. PM10 was also related with cardiovascular death.
in men, women, and in the 18–60 and over 60 years old age groups. Similar to these results, in Wuhan, China, the maximum effect of PM$_{10}$ on cardiovascular deaths occurred on the same day, and was a 0.51% increase for every 10 µg/m$^3$ increase in PM$_{10}$ (95% CI 0.28–0.75%) (Qian et al. 2007). In a meta-analysis, the
pooled results of studies analyzed by the GAM method showed that PM$_{10}$ was associated with increased mortality from cardiovascular diseases, and for each 1 μg/m$^3$ increase in the concentration of PM$_{10}$, cardiovascular death increased by 2.2% (CI 95%: 1.6 to 2.8%), but the pooled results of another study that did not use the GAM model, showed the increase in cardiovascular death was 1.3% (CI 95%: 0.8–1.9%) (Stieb et al. 2003). In a study done by Dastoorpoor et al. in Ahvaz, Iran; 10 μg/m$^3$ increase in PM$_{10}$ increased cardiovascular deaths by 1.012% (95% CI:1.001–1.023%) (Dastoorpoor et al. 2018). In a study done by Middleton et al. in Nicosia, Cyprus, every 10 mg/m$^3$ increase in PM$_{10}$ concentration increased hospital admissions because of cardiovascular diseases by 1.2% (95%CI: –0.0%, 2.4%) (Middleton et al. 2008). In Vahedian et al.’s study conducted in Arak, Iran; for every 10 μg/m$^3$ increase in PM$_{10}$, hospital admissions for cardiovascular diseases increased 0.7% (95% CI: 0.02–1.2%) (Vahedian et al. 2017).

However, in some studies, the results were inconsistent with our results, for example in studies from Mashhad, Iran (Ghorbani et al. 2017), Shiraz, Iran (Dadbakhsh et al. 2016), and Kerman, Iran (Hashemi et al. 2014), PM$_{10}$ did not have a significant direct relation with cardiovascular mortality; although, in these three studies the concentration of PM$_{10}$ was more than the PM$_{10}$ concentration in Tehran. One reason for these different results may be that negative binomial regression models were used in these previous studies, which are different and less advanced than the GAM models. Also the time unit in the Kerman (Hashemi et al. 2014) and Shiraz (Dadbakhsh et al. 2016) study was month, and in the Mashhad study (Ghorbani et al. 2017) no confounder variable was used in the model.
Ambient particulate matter may cause heart disease and cardiovascular death through increase in blood clotting, impaired heart function, increased blood viscosity and changes in heart rate (Qian et al. 2007).

The World Health Organization guidelines state that reduction of particulate matter (PM$_{10}$) from 70 to 20 $\mu g/m^3$ can decrease air pollution-related deaths by around 15%. In this study, the annual average of PM$_{10}$ was higher than the WHO recommended 2014 guideline.

Another pollutant that showed a significant relation with cardiovascular deaths in this study was Nitrogen dioxide. NO$_2$ was associated with all cardiovascular deaths, and with each 10 ppb increase in NO$_2$, total cardiovascular deaths increased (0.88%, 95% CI: 0.3–0.99%) in lag 3 in the one pollutant; and (0.57%, 95% CI: 0.23–0.92%) in lag 1, in two pollutant models. In this study, NO$_2$ showed relations with cardiovascular death in men, women and elder age groups, as well. Ghorbani et al. study’s in Mashhad, Iran, also showed that by 1 ppb increase in NO$_2$, all cardiovascular deaths increased by 1% (95% CI:0.6 to 1.4) (Ghorbani et al. 2017). In one study in 8 Chinese cities, each 10 $\mu g/m^3$ increase in NO$_2$, related to 1.3% (95% CI:0.45–2.14) increase in coronary heart disease mortality after 2 days lag (Li et al. 2015). In a study from Shiraz NO (RR = 1.00229, 95% CI: 1.00031–1.00426) and NO$_x$ (RR = 1.00187, 95% CI: 1.00016–1.003) were related to cardiovascular disease mortality, but NO$_2$ had no relation with cardiovascular deaths (RR = 1.00429, 95% CI: 0.99637–1.01228) (Dadbakhsh et al. 2016).

NO$_2$ is a gas with a red-orange (almost brown) color. It has a boiling point of 21.2°C. The toxicity of NO$_2$ is several times higher than NO in humans. NO$_2$
at 15 ppm concentration can damage human kidney, liver and heart tissues after just 2 h contact (Bahrami Asl et al. 2014). The main mechanism of toxicity of NO₂ is intervening with the peroxidation of lipids in cell membranes. Its free radicals have various adverse effects on structural and functional molecules (Kelly et al. 1996). According to the World Health Organization's guideline the mean annual threshold for NO₂ is 40 μg/m³.

In this study, sulfur dioxide showed a significant relation with cardiovascular deaths in the one pollutant model, and for 10 ppb increase in SO₂, total death increased by 0.89% (95% CI: 0.36–1.62%). According to a study done by Hong et al. in Korea, sulfur dioxide showed a relation with ischemic stroke as well; and the Rate Ratio was 1.04 (95% CI, 1.01 to 1.08) (Hong et al. 2002). In a study from Shiraz, a relation was observed between SO₂ and cardiovascular mortality in women, and the IRR was 1.00089 (95% CI: 1.00008–1.00171) for each 1 ppb increase in SO₂ (Dadbakhsh et al. 2016). In a study done in Brazil, the 7-day moving average of SO₂ was significantly related with mortality due to circulatory diseases and the RR was 1.04 (95% CI = 1.01–1.06), after adjusting for ozone (Amancio and Nascimento, 2012). Zeng et al showed that SO₂ per 10 μg/m³ increase and after one day lag, increased cardiovascular deaths by 0.48% (95% CI: 0.11–0.85%) (Zeng et al. 2015).

Researchers think sulfur dioxide exacerbates cardiovascular complications and causes death. But many questions about the effects of sulfur dioxide on human health remain unanswered. Sulfur oxides

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### Table 8. Results of Adjusted Generalized Additive Model, about the effect of air pollutants on under 18 years old cardiovascular death, for 1 unit increase in CO and 10 units increase in all other pollutants (adjusted for relative humidity, temperature, trend, season and day of week).

<table>
<thead>
<tr>
<th></th>
<th>One pollutant</th>
<th>Two pollutant</th>
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<tbody>
<tr>
<td></td>
<td>RR (95% CI)</td>
<td>p</td>
</tr>
<tr>
<td></td>
<td>df</td>
<td>p</td>
</tr>
<tr>
<td>CO (ppm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1</td>
<td>1.013 (0.957–1.072)</td>
</tr>
<tr>
<td>1</td>
<td>1.35</td>
<td>1.027 (0.971–1.086)</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>1.009 (0.953–1.069)</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>1.027 (0.971–1.088)</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>1.029 (0.969–1.076)</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>1.039 (0.982–1.100)</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>1.049 (0.992–1.109)</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>1.014 (0.958–1.074)</td>
</tr>
<tr>
<td>O₃ (ppb)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.75</td>
<td>1</td>
<td>0.985 (0.937–1.036)</td>
</tr>
<tr>
<td>1</td>
<td>1.33</td>
<td>0.995 (0.949–1.044)</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>0.971 (0.923–1.022)</td>
</tr>
<tr>
<td>3</td>
<td>1.36</td>
<td>0.967 (0.921–1.015)</td>
</tr>
<tr>
<td>NO₂ (ppb)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1.01</td>
<td>1.026 (0.998–1.054)</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>1.011 (0.983–1.039)</td>
</tr>
<tr>
<td>3</td>
<td>2.57</td>
<td>1.014 (0.986–1.043)</td>
</tr>
<tr>
<td>4</td>
<td>2.02</td>
<td>1.004 (0.977–1.032)</td>
</tr>
<tr>
<td>5</td>
<td>2.07</td>
<td>1.007 (0.979–1.035)</td>
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<tr>
<td>6</td>
<td>1</td>
<td>1.015 (0.987–1.044)</td>
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<tr>
<td>7</td>
<td>1.46</td>
<td>1.007 (0.979–1.035)</td>
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<tr>
<td>SO₂ (ppb)</td>
<td></td>
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<tr>
<td>1.67</td>
<td>1</td>
<td>1.029 (0.987–1.074)</td>
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<tr>
<td>1</td>
<td>1.20</td>
<td>1.041 (0.998–1.085)</td>
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<td>2</td>
<td>1.02</td>
<td>1.025 (0.999–1.114)</td>
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<tr>
<td>3</td>
<td>1</td>
<td>1.049 (0.982–1.123)</td>
</tr>
<tr>
<td>PM₁₀ (μg/m³)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>0.994 (0.975–1.012)</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>0.999 (0.981–1.017)</td>
</tr>
<tr>
<td>3</td>
<td>1.01</td>
<td>1.000 (0.982–1.019)</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>0.994 (0.976–1.013)</td>
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<tr>
<td>5</td>
<td>1</td>
<td>0.995 (0.973–1.017)</td>
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<tr>
<td>6</td>
<td>1</td>
<td>1.002 (0.985–1.021)</td>
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<tr>
<td>7</td>
<td>1</td>
<td>1.003 (0.985–1.021)</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
<td>1.011 (0.993–1.029)</td>
</tr>
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tends to be present in polluted air containing suspended solids and severe moisture and as a result, few epidemiologic studies are able to distinguish the effects of these pollutants separately (Goudarzi et al. 2014).

In this study, O₃ showed no significant relation with cardiovascular deaths in males and in total. In some other studies, similar results have been seen (Wong et al. 2002, Hashemi et al. 2002, Kan et al. 2016). But in women, after a 1 day lag, with 10 ppb increase of O₃, cardiovascular deaths increased 1.66% (95% CI: 0.73–2.61%) in the one pollutant and 1.65% (0.71–2.61%) in the two pollutant model. Some other studies have shown a relation between O₃ with cardiovascular death as well. Zhang et al. showed that for each 10 μg/m³ increase in O₃ concentration, cardiovascular deaths increased by 0.45% (CI 95%: 0.16–0.73) in Shanghai (Zhang et al. 2006). In a meta-analysis done in 2005, the short-term effects of exposure to ozone and cardiovascular and respiratory mortality were analyzed. The pooled results showed that a 10 ppb increase in daily ozone, in lags 0, 1, or 2 days was associated with a 0.87% (95% CI = 0.55–1.18) increase in overall (male and female) mortality. But in some studies ozone had no significant relation with cardiovascular deaths (Dadbakhsh et al. 2016). Kan et al. reported that the effect of O₃ on total mortality in females was higher than males; and gender was an effect modifier in Shanghai, China (Kan et al. 2008). However, the mechanism of effect of ozone on cardiovascular deaths is still not known and requires further investigation (Ghanbari Ghozikki et al. 2014).
CO was not related with cardiovascular deaths in this study, and Dastoorpoor et al. did not see a relation between CO and cardiovascular deaths in Ahwaz either (Dastoorpoor et al. 2018). But some studies have shown a relation between this pollutant and cardiovascular deaths. In Hong et al.’s study in Korea, carbon monoxide was related to ischemic stroke and the Rate Ratio was 1.04 (95% CI = 1.01–1.07) (Hong et al. 2002). One of the reasons for these controversial results may be that in our study and in the Ahwaz study, all cardiovascular deaths have been included, but Hong et al. only included deaths from ischemic stroke. More investigation is needed about the effects of air pollutants on specific cardiovascular diseases.

In this present study, NO₂, SO₂ and PM₁₀ in people over 60 years had a stronger relation with cardiovascular deaths than the younger age group. This finding shows the stronger effects of NO₂, SO₂ and PM₁₀ pollutants on the elderly people. Maheswaran et al. in south London also showed a higher risk of ischemic stroke in the 65 to 79-year old age group, and the RR for NO₂ and PM₁₀ were respectively 1.86 (95% CI: 1.10–3.13) and 1.23 (95% CI: 0.99–1.53) (Maheswaran et al. 2012). The elderly are probably more susceptible to air pollution due to the consequences of natural aging (Bentayeb et al. 2012).

In some cases air pollutants may show significant negative relations with cardiovascular deaths. But this is usually due to the harvesting effect. In this study the RR for the effect of pollutants on cardiovascular deaths in percentiles above the 95th percentile were compared to the 5th percentile. Result showed that the ratio of count of deaths in the above the 95th percentile range on the count of deaths in the under the 5th percentile range were greater than 1. And this shows that the harvesting effect has probably

Table 10. Results of Adjusted Generalized Additive Model, about the effect of air pollutants on over 60 years old cardiovascular death, for 1 unit increase in CO and 10 units increase in all other pollutants (Adjusted for relative humidity, temperature, trend, season and day of week).

<table>
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<tr>
<th>Pollutant</th>
<th>lag</th>
<th>CO (ppm)</th>
<th>RR (95% CI)</th>
<th>p</th>
<th>NO₂ (ppb)</th>
<th>RR (95% CI)</th>
<th>p</th>
<th>SO₂ (ppb)</th>
<th>RR (95% CI)</th>
<th>p</th>
<th>PM₁₀ (μg/m³)</th>
<th>RR (95% CI)</th>
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<td>0.998 (0.989–1.007)</td>
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<td>2.28</td>
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<td>.388</td>
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<td>.460</td>
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<td>0.993 (0.988–1.003)</td>
<td>.623</td>
<td>1.88</td>
<td>1.002 (0.993–1.011)</td>
<td>.709</td>
<td>1.000</td>
<td>0.998 (0.997–1.001)</td>
<td>.709</td>
<td>1.000</td>
<td>0.997 (0.995–0.999)</td>
<td>.709</td>
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<td>0.993 (0.988–1.003)</td>
<td>.623</td>
<td>1.88</td>
<td>1.002 (0.993–1.011)</td>
<td>.709</td>
<td>1.000</td>
<td>0.998 (0.997–1.001)</td>
<td>.709</td>
<td>1.000</td>
<td>0.997 (0.995–0.999)</td>
<td>.709</td>
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<td>0.993 (0.988–1.003)</td>
<td>.623</td>
<td>1.88</td>
<td>1.002 (0.993–1.011)</td>
<td>.709</td>
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happened. Spix et al. have introduced methods for identifying the harvesting effect (Spix et al. 1993).

Ambient air pollutants may cause cardiovascular death through numerous mechanisms, such as accelerated atherosclerosis, changes in heart function, increased inflammatory cytokines in the heart, increased blood clotting, increased blood viscosity, increased plasma fibrinogen and changes in heart rate, lung inflammation and aggravation of lung disease (Brook et al. 2010).

Several studies have shown that ambient air pollutants are related to cardiovascular deaths. But, the different results between studies may be related to differences in the concentration of pollutants in different parts of the world, the statistical models use for data analysis, and adjusting for different confounders.

Mobile and stationary sources are both responsible for the air pollution crisis in Tehran. Motor vehicles are the main source for especially CO, NO₂ and PM₁₀ in Tehran. Tehran also has a lot of factories and is an industrial hub. According to Mazaheri et al, mobile sources of air pollution are more important than stationary sources in making and emitting NO₂ and CO in Tehran (Mazaheri Tehrani et al. 2015). Therefore, efforts to reduce pollutants released from mobile resources are essential.

**Strengths and limitations**

The strength of this study was that air pollution and cardiovascular death data from a ten-year period was used; and air pollution and meteorological data were obtained from reliable sources. Also as studies have shown that meteorological data, do not have a linear relation with health outcomes (Bhaskaran et al. 2009), in this study, we used Generalized Additive Models (GAM) for nonlinear confounder variables.

A limitation of this study was that about 8% of the air pollution data was missing. However, they were estimated using the EM algorithm method. Analysis was done separately for completed cases and imputed cases and the results were almost the same. But, in most cases analysis by EM imputed data produced higher precision.

Another limitation was that the impact of other potential confounding variables such as the concentrations of other pollutants, and wind direction were not investigated. We did not do variable interactions in this study either, but it can be an interesting topic for future researchers.

**Conclusion**

The results of this study showed that air pollution in Tehran may be responsible for some part of the cardiovascular deaths that happen in this city. Further efforts to control air pollutants, especially PM₁₀, and NO₂ in Tehran are essential. These efforts can include reducing emissions in the industrial and transport sector and strict regulations for using low sulfur gasoline or diesel filters. It is also recommended that elderly people with cardiovascular diseases avoid outdoor work and activity and use approved masks on days when air pollution is higher than the WHO standard guidelines.

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**Ethical approval**

This project was approved by the Standing Committee of Ethics in Research of Kerman University of Medical Sciences (Ethics code: IR.KMU.REC.1395.267).

**Disclosure statement**

No potential conflict of interest was reported by the authors.

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