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Death from Respiratory Diseases and Air Pollutants in Shiraz, Iran (2006-2012)

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Abstract Air pollution has been associated with modern life. The respiratory system is the first point of contact with air pollutants. This research was carried out about the relationship between air pollution and respiratory deaths in Shiraz, Iran. In this ecological study the number of respiratory deaths sorted by gender and age and air pollutants including NO, CO, NO_2, NO_X, PM_{10}, SO_2, O_3, CH_4, THC, and NMHC were inquired from 2006 to 2011. The relationship between respiratory mortality and air pollutants were studied simultaneously and with one month delay by negative binomial regression with adjustment for confounding variables and correlation coefficients. The analysis was done through MINITAB16 and STATA11. During this time 2598 respiratory deaths occurred in Shiraz. Respiratory mortality in total, male, female, and individuals aged between 18 to 60 years was positively related to CO and for individuals over 60 were related to ozone. NO and NO_X showed positive correlations in females and people under 18. NO_2 had a positive correlation with 18 to 60 year old respiratory deaths in the next month. The results show that air pollution is possibly contributing to respiratory mortality in Shiraz. This evidence reinforces policies for reducing air pollution.

Keywords: *air pollution, respiratory death, shiraz*

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1. Introduction

Human health is largely affected by the environmental [1]. The mechanization of human life has never been without complications. Amongst these consequences air pollution is an increasing concern. The rising levels of air pollution in large cities seriously threatens the health of their residents [2]. Death and human diseases are largely linked to air pollution patterns [3]. Air pollution is nowadays intertwined with modern life [4]. Today the severity of global air pollution in major world cities has reached a point that can be potentially hazardous. One of the first disasters of this kind happened in London in 1952 with more than 4,000 deaths due to photochemical smog and acid rains [5].

Air pollution is a problem in many countries, and has increased through high population growth, urban development and expansion of urban traffic, rapid economic development, inappropriate use of industrial systems and devices, increased energy consumption and non-compliance with environmental regulations [1]. Not only Western Europe, and North America but also developing countries are now facing health problems from air pollution [6,7]. According to a report by the Yale Center for Environmental Law & Policy many developing countries in Latin America and Asia are exposed to serious air pollution risks and based on the indicators from Environmental Performance Index in 2006, Iran held the 117th position among 133 countries in air pollution indicators [8]. According to the World Bank annual report the damages of air pollution in Iran is 14,420 billion Rials equivalent to 1.6 percent of gross domestic product (GDP) [9]. This loss includes the costs of death and diseases caused by urban air pollution, the cost of education in this field, the damage caused by air pollution to the city's recreation centers, and other effects of air pollution on health [10]. In the newest ranking of the Environmental Performance Index (EPI) in 2014 this country took the 83th place from 178 countries [11].

Air pollutants have huge effects on human health [12]. The main effects of air pollution in addition to acute and long-term effects are diseases such as increased respiratory symptoms [13], measurable decrease in lung function [14], and increased mortality [15]. Several studies have shown the relationship between pollutants and respiratory disease exacerbations and respiratory mortality [2,16,17]. Research shows chronic obstructive pulmonary disease patients are at higher risk of dying on days with higher levels of air pollution [18]. Today, in the industrialized countries and even countries with low and middle income; respiratory diseases and environmental pollution represents a social

and health problem; however, further research in both human and animal studies are required to understand the details of the relationship between air pollution and morbidity and mortality in humans [16].

Most epidemiological studies about the association between air pollution and non-accidental mortality were conducted in Northern America and European cities [19]. A study from Rome, showed a link between NO and respiratory mortality [20]. Khanjani et al's study in Kerman, Iran found a significant relationship between respiratory mortality in men with increased dust, ozone and sulfur disulfide [21]. In a study from Taiwan, ozone and sulfur dioxide were significantly associated with death from respiratory diseases [22]. A study estimates that the central areas of Tehran have the highest levels of air pollution. More studies are required from regions with different climates and cultures to understand the effects of air pollution on death [23]. Despite numerous studies over the past few decades, about the effects of air pollution on human health, so far none have comprehensively examined its effects [24].

Few studies have been done about the relationship between air pollution and mortality in Asia [12,22]. Every country and city has its own geographical, social, political and health situation, therefore more studies can assist in better understanding the effects of air pollution on health [25]. Comparing studies about the relationship between exposure to air pollution and mortality is difficult and the reason for this extensive heterogeneity has not yet been demonstrated. It may be due to different sensitivity in exposure to contaminants [26], differences in situations, scales, study designs and exposure assessment methods [27], differences in particle composition, relative toxicity, the health status of the population or measurement and control of potential confounding factors [28].

This study focuses on respiratory death. The respiratory system is the first point of contact with air pollutants [29]. Also identifying population subgroups that are susceptible to the effects of air pollution is a research priority [30], and has been considered in this study. Shiraz is one of the crowded cosmopolitan cities of Iran, and has had a relatively high population growth. The lack of modern city transportation such as subway lines, the dominant use of private vehicles, the large number of vehicles, heavy traffic in some parts of the city, the existence of factories and industrial workshops, are the factors that have increased the amount and variety of pollutants in this city. Also Shiraz is located between mountains which block air flow and is one of the 8 polluted cities in Iran. In most Iranian cities including Shiraz the main source of air pollution are motor vehicles [31]. This study was conducted to study the association between air pollution and respiratory deaths in different sub populations in Shiraz city.

2. Materials and Methods

This study is a population-based and ecological study. The data used includes respiratory deaths from March 2006 until March 2012 (6 years), the recorded levels of air pollutants, temperature and other climate variables.

Respiratory mortality data was inquired from the Shiraz University of Medical Sciences, Deputy of Health. The data were obtained anonymously. Respiratory mortalities were classified by sex (male, female) and age (under 18 years, 18 to 60 years, over 60 years). Registered respiratory deaths included deaths from reasons such as asthma, chronic diseases of the lung and bronchi, pneumonia, pyothorax, other respiratory diseases, other acute lower respiratory tract infections, tuberculosis, lung abscess, respiratory malformations, lung cancer, and influenza.

The air pollutants recorded in the Environmental Protection Agency (EPA) of Shiraz included 10 pollutants which were carbon monoxide (CO), nitrogen oxides (NOX), nitric oxide (NO), nitrogen dioxide (NO2), particles with a diameter less than 10 micrometers (PM10), sulfur dioxide (SO2), ozone (O3), methane (CH4), non-methane hydrocarbons (NMHC) and total hydrocarbons (THC). Daily data from the same period were obtained.

The daily mean values of temperature, relative humidity, rainfall, wind speed and direction of the same time frame was taken from the Meteorological Office of Shiraz.

The number of deaths in Shiraz per day was low and we encountered many days with zero counts and on some days of the year due to machinery trouble air pollution measurements were not performed. Therefore all data (mortality, pollution, climate factors) were converted to monthly data.

In order to determine the relationship between respiratory mortality and pollutants negative binomial regression analysis was used and the Incidence Rate Ratio (IRR) was calculated in univariate and multivariate models. Due to over dispersion (variance greater than mean), the negative binomial regression model was used instead of Poisson regression for analyzing data. Multivariate models included independent contaminants and confounding variables (temperature and humidity, rainfall, wind direction and speed). The NO_X variable is a sum of NO and NO_2, and the THC variable is a sum of CH_4 and NMHC. These correlated variables were not placed into the same multivariate analyzes. The size of population groups studied was obtained from the Statistical Center of Iran and were entered into the negative binomial regression analysis model as the exposed population.

Using statistical methods, one month lags were calculated for the independent variables (air pollutants) and their associations with respiratory mortality was determined with Pearson or Spearman Correlation Coefficients. All analysis was done in 6 subpopulations which included men, women, and people less than 18 years, between 18 to 60 years and above 60 years.

Most studies that examined the health effects of contaminants observed effects in delays of just a few days [32,33,34,35]. Therefore, in this study we examined only one month delays and its correlation with respiratory mortality.

The best model for prediction of respiratory mortality was found by time series analysis. Descriptive analysis, time series and negative binomial regression were computed through MINITAB 16, STATA 11 and R version Rx64 2.15.2.

3. Results and Discussion

Table 1 contains descriptive information about ambient air pollutants in Shiraz city from March 2006 to March 2012.

Table 1. Status of air pollutants in Shiraz from March 2006 to March 2012

Pollutant	Mean	Median	Minimum	Maximum	SD
CO (ppb)	3034.758	2866.15	1205.63	5864	1290.237
PM_{10} (ug/m³)	86.143	80.372	28.341	212.007	35.751
NO (ppb)	57.598	48.105	22.79	181.43	30.336
NO_2 (ppb)	30.996	28.722	22.11	55.08	7.133
NO_x (ppb)	88.235	82.078	44.85	223.53	34.4333
O_3 (ppb)	17.49	16.289	4.48	40.18	8.368
SO_2 (ppb)	101.531	82.734	3.1	292.74	94.238
CH_4 (ppmc)	2.416	2.506	0.832	4.449	0.753
NMHC (ppmc)	1.535	1.374	0.538	4.098	0.635
THC (ppmc)	3.989	3.95	1.663	7.887	1.149

The numbers of respiratory deaths in different subgroups during March 2006 to March 2012 are shown in Table 2.

Table 2. The number of respiratory deaths in Shiraz city during March 2006 to March 2012

	Total	Male	Female	Under18 years	18 to 60years	over 60 years
number of respiratory deaths	2598	1699	899	188	680	1730

The total number of respiratory deaths in Shiraz during March 2006 to March 2012 was 2598.

The results of crude and multivariable negative binomial regression of respiratory mortality in different subgroups and the effect of monthly air pollution levels adjusted for temperature, humidity, rainfall, and wind speed and direction are shown in Table 3 and Table 4.

Table 3. Results of crude and adjusted negative binomial regression, and the effect of pollutants on respiratory deaths (ratio of increase in death in month per unit of increase in pollutants monthly average) in men and women.

Group of respiratory deaths	Pollutant	Crude IRR* and 95% CI	P	Adjusted IRR* and 95% CI	P
Total people	CO	1.00005 (1.00000–1.00010)	0.042†	1.00009 (1.00001–1.00016)	0.014†
	PM_{10}	0.99819 (0.9963–1.00000)	0.050†	1.00208 (0.99940–1.00476)	0.127
	NO	1.00262 (1.00052–1.00472)	0.014†	1.00058 (0.99799–1.00318)	0.660
	NO_2	1.00083 (0.99150-1.01024)	0.862	1.00429 (0.99637–1.01228)	0.289
	NOx	1.00209 (1.00022–1.00395)	0.028†	1.00021 (0.99796–1.00247)	0.851
	O_3	0.99228 (0.98465–0.99996)	0.049†	1.00690 (0.99392–1.02005)	0.299
	SO_2	0.99988 (0.99917–1.00060)	0.756	0.99959 (0.99866–1.00051)	0.385
	CH_4	1.01316 (0.92540–1.10924)	0.770	1.02661 (0.93951–1.12180)	0.561
	NMHC	1.05456 (0.94729–1.17397)	0.332	1.04069 (0.90985–1.19035)	0.561
	THC	1.01653 (0.95820–1.07841)	0.586	1.01794 (0.96131–1.07791)	0.542
Men	CO	1.00004 (0.99998–1.00009)	0.152	1.00008 (1.000002–1.00016)	0.045†
	PM_{10}	0.99904 (0.99708–1.00101)	0.341	1.00214 (0.99922–1.00507)	0.150
	NO	1.00189 (0.99965–1.00414)	0.098	1.00000 (0.99709–1.00292)	0.999
	NO_2	0.99872 (0.98886–1.00867)	0.801	1.00630 (0.99873–1.01393)	0.103
	NOx	1.00140 (0.99945–1.00344)	0.154	0.99977 (0.99726–1.00230)	0.863
	O_3	0.99291 (0.98466–1.00122)	0.094	1.00582 (0.99112–1.02074)	0.440
	SO_2	1.00002 (0.99926–1.00077)	0.954	0.99973 (0.99871–1.00075)	0.609
	CH_4	1.00786 (0.91300–1.10911)	0.873	1.00628 (0.90828–1.11486)	0.905
	NMHC	1.03979 (0.92784–1.16525)	0.502	1.02292 (0.87238–1.19943)	0.780
	THC	1.01235 (0.95078–1.07791)	0.701	1.00925 (0.94346–1.07963)	0.789
Women	CO	1.00006 (1.00000–1.00013)	0.045†	1.00012 (1.00003–1.00022)	0.010†
	PM_{10}	0.99661 (0.99417–0.99905)	0.007†	1.00168 (0.99807–1.00530)	0.362
	NO	1.00370 (1.00104–1.00647)	0.007†	1.00123 (0.99797–1.00451)	0.457
	NO_2	1.00401 (0.99164–1.01653)	0.527	1.00197 (0.99253–1.01150)	0.683
	NOx	1.00308 (1.00067–1.00550)	0.012†	1.00072 (0.99785–1.00360)	0.620
	O_3	0.99170 (0.98146–1.00206)	0.116	1.01321 (0.99615–1.03055)	0.130
	SO_2	0.99954 (0.99859 –1.00050)	0.353	0.99934 (0.99810–1.00058)	0.298
	CH_4	1.02956 (0.91153–1.16288)	0.639	1.04223 (0.92781–1.17077)	0.486
	NMHC	1.07335 (0.93190–1.23628)	0.326	1.05501 (0.88649–1.25555)	0.546
	THC	1.02478 (0.94701–1.10895)	0.543	1.02067 (0.94703–1.10004)	0.592

* IRR=Incidence Rate Ratio

† Statistically Significant.

Results of multivariate analysis of the relationship between air pollutants and respiratory mortality showed a statistically significant and positive relationship for carbon monoxide in all individuals and men and women subgroups.

Multivariate analysis of the relationship between pollutants and respiratory mortality showed a significant positive association with carbon monoxide in persons 18 to 60 years. Also the number of respiratory deaths in persons over 60 years was significantly related to ozone

pollution. Respiratory deaths under 18 were not significantly associated with any pollutant.

Table 4. Results of crude and adjusted negative binomial regression and the effect of pollutants on respiratory deaths under 18 years, 18 to 60 years and over 60 years (ratio of increase in death in month per unit of increase in pollutants monthly average) in different age groups

Group of respiratory deaths	Pollutant	Crude IRR* and 95% CI	P	Adjusted IRR and 95% CI	P
Under 18 years	CO	1.00000 (0.99987–1.00014)	0.894	1.00000 (0.99980–1.00019)	0.997
	PM_{10}	0.99702 (0.99193–1.00213)	0.253	1.00383 (0.99660–1.01111)	0.299
	NO	1.00609 (1.00100–1.01117)	0.018†	1.00264 (0.99628–1.00903)	0.416
	NO_2	1.00443 (0.98108–1.02833)	0.712	1.00639 (0.97381–1.04005)	0.704
	NOx	1.00479 (1.00032–1.00929)	0.036†	1.00216 (0.99667–1.00768)	0.441
	O_3	0.97511 (0.95438–0.99630)	0.022†	0.98095 (0.94408–1.01925)	0.325
	SO_2	0.99952 (0.99765–1.00140)	0.619	0.99901 (0.99642–1.00161)	0.458
	CH_4	0.91599 (0.72482–1.15757)	0.462	0.88019 (0.68730–1.12722)	0.312
	NMHC	0.86491 (0.63740–1.17361)	0.351	0.76206 (0.50887–1.14122)	0.187
	THC	0.91626 (0.77844–1.07847)	0.293	0.91762 (0.77877–1.08123)	0.304
18 to 60 years	CO	1.00014 (1.00006–1.00022)	<0.001†	1.00014 (1.00002–1.00026)	0.022†
	PM_{10}	0.99888 (0.99584–1.00192)	0.471	1.00310 (0.99872–1.00751)	0.165
	NO	1.00206 (0.99833–1.00581)	0.278	1.00017 (0.99583–1.00453)	0.997
	NO_2	1.00490 (0.98947-1.02058)	0.535	1.00527 (0.99568–1.01496)	0.282
	NOx	1.00173 (0.99849–1.00497)	0.295	0.99976 (0.99611–1.00342)	0.899
	O_3	0.98359(0.97074–0.99661)	0.014†	0.99336 (0.97231–1.01488)	0.543
	SO_2	1.00094 (0.99974–1.00213)	0.122	0.99933 (0.99777–1.00089)	0.403
	CH_4	1.02035 (0.87891–1.18455)	0.791	1.07279 (0.92522–1.24389)	0.352
	NMHC	1.25035 (1.06073–1.47386)	0.008†	1.14154 (0.91807–1.41939)	0.234
	THC	1.07099 (0.97477–1.17671)	0.153	1.05631 (0.96159–1.16036)	0.252
over 60 years	CO	1.00011 (0.99998–1.00024)	0.074	1.00013 (0.99992–1.00035)	0.200
	PM_{10}	0.99366 (0.98872–0.99863)	0.012†	0.99601 (0.98831–1.00377)	0.313
	NO	0.99890 (0.99226–1.00559)	0.748	0.99560 (0.98829–1.00298)	0. 242
	NO_2	1.00356 (0.97782-1.02997)	0.788	1.01247 (0.98723–1.03836)	0.336
	NOx	0.99966 (0.99375–1.00559)	0.911	0.99751 (0.99126-1.00380)	0.437
	O_3	0.99487 (0.97537–1.01475)	0.610	1.04156 (1.00213–1.08254)	0.039†
	SO_2	1.00087 (0.99902–1.00270)	0.354	1.00113 (0.99849–1.00378)	0.401
	CH_4	0.96108 (0.75700–1.22003)	0.744	1.12258 (0.86592–1.45532)	0.383
	NMHC	1.30644 (0.95186–1.79311)	0.098	1.24487 (0.84525–1.83344)	0.267
	THC	1.05386 (0.89951–1.23470)	0.516	1.07908 (0.91651-1.27050)	0.361

* IRR=Incidence Rate Ratio
† Statistically Significant.

In order to investigate the relationship between the one month delays in death from respiratory pollutants initially delays were calculated, then Spearman or Pearson were performed depending on non-normal or normal distribution of variables. The results have been shown in Table 5.

Results showed a significant positive association between delayed respiratory mortality in women with NO and NO_X. Respiratory deaths in people under 18 had a positive and significant relationship with NO and NO_X, but a significant negative correlation with O_3. Respiratory mortality in individuals over 60 years had a significant negative correlation with mean SO_2 levels in the previous month. There was a significant positive correlation between NO_2 and respiratory mortality of 18 to 60 year olds in the next month.

In order to suggest a time-series model for the number of respiratory deaths, difference conversion was performed and autocorrelation function (ACF) and partial autocorrelation function (PACF) were plotted. The appropriate suggested model for the prediction of death from respiratory diseases in Shiraz between March 2006 to March 2012 was ARIMA (3, 1, 2) with MS=97.96.

In this study, the relation between ambient air pollutants with respiratory mortality was investigated. Ambient air pollutants can cause respiratory mortality by directly acting on the respiratory system through acute mechanisms. For this reason, the effect of air pollutants on respiratory mortality is more acute than other deaths. Particles can damage lung tissue and can trigger inflammatory responses [36]. Inhalation of dust may cause oxidative stress and inflammatory responses in the lungs [37]. Carbon monoxide is one of the main components of diesel exhaust and mainly originates from traffic. Carbon monoxide also triggers complex inflammatory responses in the airways and can have harmful adverse effects on people exposed to these pollutants [38]. Inhalation of airborne pollutants can also cause alveolar inflammation

and activation of cellular and molecular mechanisms which aggravate lung disease [39]. Exposure to ozone for several hours, causes damage to the airway epithelium [40]. Sulfur dioxide is an irritant that affects the mucosa of the eyes, nose, throat, and respiratory tract and causes coughing and increased bronchial reactivity, and facilitates bronchoconstriction [40].

Table 5. Correlation between respiratory deaths happening one month later in the whole population, men, women, under 18 years, 18 to 60 years and over 60

	Respiratory Death					
	Total people		Women		Men	
Pollutant	Pearson correlation coefficient(r)	P	Pearson correlation coefficient(r)	P	Pearson correlation coefficient(r)	P
CO	0.011	0.929	0.068	0.579	- 0.039	0.750
PM_{10}	- 0.134	0.265	- 0.181	0.130	- 0.068	0.575
NO_2	0.118	0.328	0.169	0.158	0.058	0.632
O_3	- 0.123	0.308	- 0.153	0.204	- 0.073	0.548
CH_4	0.005	0.966	- 0.016	0.894	0.024	0.840
THC	- 0.032	0.794	- 0.036	0.765	- 0.019	0.872
Pollutant	Spearman correlation coefficients(ρ)	P	Spearman correlation coefficients(ρ)	P	Spearman correlation coefficients(ρ)	P
NO	0.202	0.091	0.293	0.013†	0.140	0.244
NO_x	0.173	0.148	0.250	0.035†	0.117	0.331
SO_2	- 0.150	0.213	- 0.198	0.098	- 0.117	0.333
NMHC	- 0.040	0.738	- 0.069	0.568	- 0.048	0.688
	over 60 years		18 to 60 years		Under 18 years	
Pollutant	Pearson correlation coefficient(r)	P	Pearson correlation coefficient(r)	P	Spearman correlation coefficients(ρ)	P
CO	- 0.079	0.511	0.195	0.104	0.042	0.730
PM_{10}	- 0.092	0.444	- 0.108	0.370	- 0.137	0.255
NO_2	- 0.030	0.802	0.278	0.019†	0.128	0.287
O_3	- 0.019	0.878	- 0.167	0.116	- 0.272	0.022†
CH_4	- 0.011	0.925	0.044	0.715	- 0.113	0.350
THC	- 0.092	0.446	0.121	0.316	- 0.068	0.572
Pollutant	Spearman correlation coefficients(ρ)	P	Spearman correlation coefficients(ρ)	P	Spearman correlation coefficients(ρ)	P
NO	0.143	0.235	0.077	0.522	0.298	0.012†
NO_x	0.120	0.320	0.073	0.545	0.285	0.016†
SO_2	- 0.302	0.010†	0.181	0.131	0.021	0.859
NMHC	- 0.161	0.180	0.132	0.272	- 0.043	0.723

† Statistically Significant.

In a study in China a strong relationship was observed between sudden cardio-respiratory death and ambient PM_{10} concentrations, and these effects were more prominent on people between 45 to 65 years than younger people [12]. A cohort study done by Cesaroni et al's in Rome showed that exposure to $PM_{2.5}$ is associated with death due to lung cancer [20]. In a study done in New Zealand the adjusted odds ratio between PM_{10} and respiratory mortality (excluding lung cancer) was 1.013 (1.005-1.021) and the relation was significantly stronger in respiratory deaths than any other death [26]. Joneidi Jafari et al's study showed a significant positive but weak correlation between particles and cardio - respiratory deaths in Tehran [41]. In another study in California, PM_{10} showed a strong correlation with benign respiratory mortality in both genders [42]. In a study using data from the American Cancer Society (ACS) the hazard rate (HR) from exposure to particles in lower respiratory tract infections among non –smokers was 1.20 (1.02–1.41) [43]. A study in Wuhan, China revealed every 10 $\mu g/m^3$ increase in PM_{10} concentrations was related to 71 % (95% CI 0.20–1.23%) increase in respiratory deaths [12].

However, some studies reported no significant relation between particles and respiratory deaths. For example, a study in France indicates the adjusted relative risk of sudden cardio-respiratory death in adults for each 10 $\mu g/m^3$ increase in total suspended particles (TSP) was 1.06 and insignificant [44]. In another study in Taiwan PM_{10} was not significantly associated with respiratory deaths [45]. In a study done in California, there was not a significant correlation between concentrations of suspended ambient particles and cardiac - pulmonary death [42]. In Lipsett et al's study in California the estimates for HRs (Hazard Ratios) for each 10 $\mu g/m^3$ increase in concentration of $PM_{2.5}$ and nonmalignant respiratory mortality was larger than one, [HR: 1.21 (95% CI: 0.97, 1.52)] but was not significant [28]. In a study in Kerman there was a positive and significant correlation between increased respiratory mortality among men and increased dust, but this relationship was not observed among women [21]. In a study in Taiwan in the adjusted model PM_{10} particles were not associated with increased respiratory mortality [22]. In the present study, a significant relationship between respiratory mortality and PM_{10} were not observed, but this result might be due to low levels of PM_{10} in Shiraz. In the 2190 days under study (in 6 years) only 370 days (17 % of all days) had PM_{10} values exceeding the 24 hours threshold which is 150 $\mu g/m^3$ [4]. The mean daily PM_{10} concentration in Qian et al's study was 141.8 $\mu g/m^3$ and was significantly related to respiratory mortality, but in our study it was 86.143 ug/m^3. This association was not observed in our study which is

similar Wong et al's study [22]. In Wong et al's study the average daily concentration of dust was 51.53 μg/m^3.

Researchers found a statistically significant and positive relationship between respiratory deaths with NO_2 [20,46]. In a study in Norway adjusted risk ratios between respiratory death and exposure to NO_X was 1.16 (95% CI, 1.06–1.26) and significant [27]. However, some studies showed insignificant results. In a study in France mortality from heart-lung disease and NO_2 was insignificant [44]. In another in Taiwan NO_2 had no significant relationship with respiratory deaths [45]. The results of the present study were in line with the two recent studies and no significant correlation was found between respiratory deaths and NO, NO_2, NO_X pollutants in the subgroups. In Liang et al's study the concentration of NO_2 was 28.04 ppb [45] and similar to our study (30.99 ppb) and in both studies non-significant effects were found between NO_2 and respiratory deaths.

In a study in Tehran positive significant correlations (r =0.70) were observed between carbon monoxide and respiratory mortality [17]. Another study from Tehran indicated that when the levels of carbon monoxide increased, mortality due to respiratory diseases in children less than 12 years increased as well [9]. In Italy a significant relationship between carbon monoxide and exacerbation of chronic obstructive pulmonary diseases was reported [16]. However, other studies found insignificant results between CO and respiratory deaths [45]. In the present study results showed a significant relationship between respiratory death and carbon monoxide in the entire population, men, women, and individuals between 18 to 60 years. As noted in the study of Liang et al the mean daily concentrations of carbon monoxide was 1.10 ppm and there was no significant association between CO and respiratory mortality [45]. However the mean daily concentrations of carbon monoxide in our study were 3.03 ppm and higher than Liang's study. Therefore it seems logical to find an association considering the higher amount of carbon monoxide in Shiraz. Carbon monoxide is one of the main traffic emissions and triggers a complex inflammatory response in the airways [38]. The affinity of hemoglobin with carbon monoxide is approximately 200 times greater than oxygen. CO in breathing air causes the formation of a stable compound (COHb) and reduces oxygen delivery to tissues, affects the central nervous system, changes cardiac performance, and can cause fatigue, drowsiness, coma, and death [47]. The human sources of CO are forest fires and incomplete combustion of fossil fuels or other organic materials, transport and urban areas with heavy traffic [40]. In Shiraz heavy traffic is probably the main source of CO.

The other pollutant under investigation in this study was ozone. Ozone itself is a greenhouse gas with short-term survival and varies with climate changes [48]. Tropospheric ozone is created from photochemical reactions in the lower layers and is a strong oxidizing agent and can damage plants and animals and is considered a pollutant [4]. In a study from Taiwan there was a significant correlation between daily respiratory death and ozone in all ages in winter. But, this relationship was positive only for over 65 year-olds in summer [49]. In Lipsett et al's study in California the HRs (Hazard Ratios) relationship between ozone and benign respiratory disease mortality was insignificant [1.07 (0.97-1.19)] [28]. In Khanjani et al's study in Kerman after adjustment for temperature and humidity significant relation was revealed between respiratory deaths in men and ozone pollution, but this relationship was not significant in women [21]. Santus et al's study in Milan after adjusting for weather variables showed that increase in ozone levels, especially during the warm season, increases the number of emergency admissions for asthma by 78% [16]. Some studies however found insignificant relationships between respiratory mortality and ozone [22, 50]. In the present study, multivariate analysis of the associated between respiratory mortality and ozone was significant in people over 60. This was similar to the Taiwan study that showed a relation between ozone and respiratory death in people over 65. Probably this age group is more susceptible to ozone pollution, yet these findings require further investigation. Future studies should better identify susceptible populations to the effects of air pollution [51]. There are biological explanations for the effects of ozone pollution on respiratory deaths and more severe effects are expected in people with a history of respiratory disease [52]. Ozone may contribute to airway inflammation or injury [53] and may cause acute respiratory effects by direct oxidation of cells, inflammatory and neurological reflexes especially in people with asthma and chronic obstructive pulmonary disease [54]. High levels of ozone are associated with increased admissions for asthma during the hot season [16]. Higher ozone concentrations cause increased airway resistance, decreased lung functioning, nose and throat irritation, chest tightness, and severe coughing [4].

A study in the US showed the toxic effects of SO_2 on the respiratory system and it seems that SO_2 has a crucial role in hospital admissions and exacerbation of chronic obstructive pulmonary disease (COPD) [55]. Wong et al's study in China indicated a positive and significant relationship between respiratory deaths and sulfur dioxide [22]. Another study from California shows sulfur dioxide has a strong relationship with lung cancer in both genders [42]. In a study in Kerman after adjustment for temperature and humidity, ambient sulfur disulfide showed a significant relationship with male, but not female respiratory deaths [21]. But other studies showed no significant association between sulfur dioxide and respiratory mortality [44,45,56]. In the present study no significant relationship was found between respiratory deaths and ambient SO_2. This insignificant result was probably due to low levels of SO2 (0.10 ppm) that were less than the standard daily threshold for this pollutant (0.14 ppm).

In the existing study correlations between pollutants and respiratory mortality in the next month were also evaluated. Evaluating the effects of air pollution on death with delays of more than 1 day may provide more insights for mechanisms that may contribute to the effects of air pollutants on mortality [33]. Braga et al's study in 12 US cities indicated that after 7 days delay; for each 10 μg/m^3 increase in PM_{10} death due to pneumonia increased by 2.7% (95% CI: 1.5, 3.9) and death due to chronic obstructive pulmonary disease increased by 1.7%, (95% CI: 0.1, 3.3) [33]. In Zanobetti et al's study in 30 European cities and in all age groups after 40 days delay the effect of PM_{10} on respiratory mortality increased about 4 times

[4.2% (95% CI 1.08% to 7.42%)] [57]. Over the past decade, air pollution effects were estimated on the same day or within one or two days after. Then the best delay was chosen. But, this approach has been criticized due to overestimation of the results [57]. In the present study some significant relationship was detected for NO, NO_X and NO_2. The reverse effect between SO2 and O_3 and respiratory deaths in the next month requires more investigation, and is possibly due to the harvesting effect [58].

The limitations of this study include the limitations of ecological studies, which are using aggregated data that cannot be directly inferred to the individual level. Also we were not able to adjust for migrations or other population changes [59].

4. Conclusions

This study shows evidence about an association between respiratory deaths and ambient air pollution. Although the results of this study showed some populations are more susceptible to the adverse effects of air pollution, the results should be interpreted with caution and further studies are needed. Interventions and policies to reduce ambient air pollution, and protect people at risk especially on days with high pollution levels are emphasized.

Since the most important source of air pollution in Shiraz is vehicles, interventions such as prohibiting the commuting of polluting cars, phasing-out old cars, routine vehicle technical examination, use of extruders in car exhausts, use of low sulfur diesel fuel for urban bus fleet, CNG using taxis and cars, implementation of urban train in big cities and replacing old buses and taxis is recommended.

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Statement of Competing Interests

Authors have no competing interests.

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