Environmental Health Engineering and Management Journal. 2026;13:1587
http://ehemj.com
doi 10.34172/EHEM.1587
Environmental Health Engineering and Management Journal
Original Article
Environmental Health Engineering and Management
Open Access Publish Free

Assessing the Effects of Air Pollution on All-Cause, Respiratory, and Heart-Related Mortality Using Generalized Additive Models in Mashhad, Iran

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Abstract

Background: Air pollution is a major public health concern associated with increased respiratory and cardiovascular mortality. This study investigates the effects of air pollution and meteorological factors on respiratory, cardiovascular, and all-cause mortality in Mashhad, Iran, using generalized additive models with cumulative lag structures.

Methods: Daily mortality data from February 18, 2017, to March 19, 2020, were classified by cause. Air pollutants (PM_{10}, $PM_{2.5}$, NO_2, SO_2, and CO) and meteorological data (temperature and humidity) were analyzed using quasi-Poisson GAMs, adjusting for temporal trends, weather, and day of the week. Lag effects (0–10, 0–20, and 0–30 days) were assessed for pollutant impacts on mortality.

Results: Higher $PM_{2.5}$, PM_{10}, and NO_2 levels were significantly associated with increased risks of all-cause, respiratory, and cardiovascular mortality. A 10-unit increase in $PM_{2.5}$ was associated with the highest risk for all-cause mortality at Lag 0–30 (RR = 1.184, P = 0.012). $PM_{2.5}$ and NO_2 showed the strongest associations with respiratory mortality over 30-day cumulative exposure, while $PM_{2.5}$ (RR = 1.132, 95% CI: 1.012–1.267) and NO_2 (RR = 1.074, 95% CI: 1.006–1.147) also impacted cardiovascular deaths. Shorter lags revealed more immediate impacts, particularly for NO_2 and $PM_{2.5}$ on all-cause mortality.

Conclusion: These findings underscore the urgent need for strategies to reduce air pollution in Mashhad, addressing both short- and long-term health effects, particularly respiratory and cardiovascular outcomes. The results support policy interventions for improved air quality management in urban Iran.

Keywords: Air pollution, Cardiovascular diseases, Respiratory tract diseases, Mortality

Citation: Akbari Sharak N, Rastaghi S, Salari M, Shakeri MT, Esmaili R. Assessing the effects of air pollution on all-cause, respiratory, and heart-related mortality using generalized additive models in Mashhad, Iran. Environmental Health Engineering and Management Journal. 2026;13:1587. doi: 10.34172/EHEM.1587.

Article History:
Received: 7 April 2025
Revised: 1 June 2025
Accepted: 31 July 2025
ePublished: 20 January 2026

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Introduction

Air pollution remains a critical global public health issue. According to the World Health Organization (WHO, 2021), 99% of the global population lived in areas where air quality did not meet WHO guidelines in 2019 (1). Numerous studies have established a strong link between air pollution and adverse health effects, including increased rates of respiratory and cardiovascular diseases and higher mortality associated with pollutant exposure. The WHO reports that air pollution is a significant contributor to deaths from cancer, lower respiratory infections, stroke, ischemic heart disease, and chronic obstructive pulmonary disease, highlighting the urgent need for effective preventive measures (2-6).

Mashhad, the second-largest city in Iran, faces severe air pollution challenges. Contributing factors include its large population, extensive motor vehicle fleet, numerous industrial centers, pilgrimage and tourism, and unique climatic conditions, making it one of the most polluted cities in the country. Despite the critical need to address air pollution in Mashhad, research in this area is limited. Existing studies often fail to account simultaneously for meteorological variables and air pollution, and they do not adequately explore the delayed effects of pollutants on mortality.

Recent epidemiological research has utilized advanced analytical methods, such as generalized additive models (GAMs), to analyze time series data and identify associations between air pollution and health outcomes, including increased mortality rates, morbidity, hospital

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admissions, and outpatient visits. GAMs allow for the simultaneous analysis of linear and non-linear variables, offering a more comprehensive understanding of ecological processes. For instance, GAMs have been employed to link PM_{10} with hospital admissions for chronic obstructive pulmonary disease and pneumonia (7) and to correlate elevated ozone concentrations with increased respiratory disease admissions (8). In Asian cities, GAMs have shown significant associations between air pollutants and respiratory hospital admissions (9) and increased hospitalization risks for respiratory diseases linked to PM_{10} and NO_2 among children (10). Additionally, studies in Seoul and Tehran (11,12) and in Indian cities such as Delhi and Chennai (13-15) have demonstrated the utility of GAMs in elucidating complex relationships between air pollution and health.

This study aims to address research gaps by examining the simultaneous effects of meteorological variables and air pollution on respiratory, cardiovascular, and overall mortality in Mashhad. By employing GAMs and considering the delayed effects of pollutants, the research seeks to provide valuable insights for public health officials and policymakers, supporting the development of more effective strategies to mitigate the health impacts of air pollution and guiding future research in this field.

Materials and methods

Mortality, air pollution, and meteorological data

The Mashhad district of Khorasan Razavi was chosen as the research site due to its status as one of Iran's most polluted cities, attributed to the high density of industrial facilities and heavy urban traffic. The substandard air quality in Mashhad poses significant risks to residents' health. Daily mortality data, covering February 18, 2017, to March 19, 2020, were obtained from the death registration system of the Deputy of Health. Fatalities were classified using the 10th edition of the *International Statistical Classification of Diseases* (ICD-10), including overall mortality (A00-R99), circulatory disease-related mortality (I00-I99), and respiratory disease-related mortality (J00-J99).

Key ambient air pollutants—particulate matter (PM), sulfur dioxide (SO_2), nitrogen oxides (NO_2), ozone (O_3), and carbon monoxide (CO)—were examined for their health impacts. Hourly concentration data for NO_2, SO_2, CO, PM_{10}, and $PM_{2.5}$ were systematically collected from February 18, 2017, to March 19, 2020, across 11 monitoring stations in Mashhad, and average daily pollutant levels were used for analysis.

Temperature and relative humidity, identified as potential confounding variables, were sourced from Mashhad Meteorological Organization, and their daily averages were incorporated into the analytical framework. All datasets used in this study were complete, ensuring the reliability of the analysis.

Statistical analysis

Descriptive statistics, including the mean, standard deviation, 25th, 50th (median), 75th, and 98th percentiles, and minimum and maximum values, were calculated for air pollutants, meteorological variables, and mortality counts. Seasonal variations were visualized using box plots for four major air pollutants (PM_{10}, $PM_{2.5}$, CO, and NO_2), two meteorological variables (temperature and relative humidity), and total mortality across the four seasons (winter, spring, summer, and autumn). We calculated Pearson correlation coefficients between daily air pollutant concentrations and meteorological parameters to assess potential multicollinearity and identify relationships among variables. Correlations were interpreted using a significance level of $P<0.01$.

The relationship between daily mortality and air pollution was assessed using quasi-Poisson regression models within overdispersed generalized additive models (GAMs). Quasi-Poisson distribution was used to account for overdispersion in the mortality count data where the variance exceeded the mean. GAMs extend generalized linear models by accommodating both linear and non-linear associations between the response variable and its predictors (16,17). This approach allows for greater flexibility, as GAMs describe the response variable through smooth functions rather than relying solely on fixed parametric relationships with the covariates (18). To control for potential confounding effects, non-parametric smoothing splines were applied in the model. We used 10 degrees of freedom for calendar time to account for long-term trends and seasonality, 3 degrees of freedom for mean temperature, and 1 degree of freedom for mean relative humidity. Degrees of freedom for the natural spline functions were selected based on the lowest Akaike information criterion (AIC). The day of the week (DOW) was included as a categorical variable to adjust for weekday effects. The final model was formulated as follows:

$$Log\left[E\left(Y_i\right)\right]=\alpha+\beta\times X_i+ns\left(time,df_1\right)+ns\left(temperature,df_2\right)+s\left(humidity,df_3\right)+DOW$$

In this model, α represents the intercept, $E(Y_i)$ represents the expected number of daily mortalities, β denotes the regression coefficient, and X_i refers to the daily mean concentration of pollutants. The term ns signifies the natural cubic splines used to account for non-linear relationships. After adjusting for the confounding effects of temperature, time, and relative humidity, daily concentrations of pollutants such as $PM_{2.5}$, PM_{10}, NO_2, SO_2, and CO were incorporated into the base model. Following the estimation of β, we calculated the relative risk (RR) and the 95% confidence interval (CI) as follows:

$$RR=\exp\left(\beta\right)$$

$$95\%\ \mathrm{CI} = \exp\left(\beta \pm 1.96\ SE\right)$$

Given the delayed and lingering effects of air pollution (19), we examined cumulative exposure effects by constructing moving average lag structures over 0–10, 0–20, and 0–30 days. This approach involved averaging pollutant concentrations across the specified lag periods to capture the total exposure burden. Statistical analyses were performed using the "mgcv" and "splines" packages in R software (version 4.0.2).

Results

During the 3-year study period (1126 days), a total of 45,686 deaths occurred in Mashhad, including 17,239 cardiovascular and 6,579 respiratory deaths. The deaths were distributed across seasons as follows: 10,617 in spring, 10,480 in summer, 11,932 in autumn, and 12,657 in winter. The frequency of deaths from 2017 to 2020 is detailed in Table 1.

The means, standard deviations, ranges, and percentiles of the daily air pollution, meteorological data, and death counts are shown in Table 2. The study found that the daily average concentrations of $PM_{2.5}$ and PM_{10} were 29.19 μg/m³ and 45.84 μg/m³, respectively, exceeding the WHO 2021 annual thresholds of 15 μg/m³ for $PM_{2.5}$ and 45 μg/m³ for PM_{10}. In contrast, the daily average concentrations of CO and SO_2 were below the WHO thresholds. The mean relative humidity (RH) value of 46.60% in Mashhad aligns with the optimal RH range for health and comfort, which is between 30% and 50%. The three-year average temperature of 16.19 ± 9.5 shows a mild temperature. The analysis of the death data reveals significant variability in the number of cardiovascular, respiratory, and all-cause deaths over the study period. The all-cause death count exhibited a mean of 40.57 with substantial variability (SD = 8.27). Cardiovascular deaths had a mean of 15.31, while respiratory deaths displayed the lower mean of 5.84.

A strong positive correlation was observed between $PM_{2.5}$ and PM_{10} ($r = 0.980$). PM_{10} also exhibited notable positive correlations with SO_2 ($r = 0.118$) and NO_2 ($r = 0.302$). Similarly, $PM_{2.5}$ showed positive correlations with SO_2 ($r = 0.132$) and NO_2 ($r = 0.340$). CO was weakly negatively correlated with $PM_{2.5}$ ($r = -0.092$) and PM_{10} ($r = -0.051$). Among meteorological variables, SO_2 had a moderate negative correlation with temperature ($r = -0.387$) and a weak positive correlation with relative humidity ($r = 0.072$). PM_{10}, $PM_{2.5}$, and NO_2 generally showed weak negative correlations with relative humidity, indicating that as these pollutants increase, relative humidity might decrease slightly (Table 3).

Figure 1 shows the box plot of some pollutants and mortalities. According to the plots, spring and fall are the seasons with the highest variability and pollution levels, particularly for $PM_{2.5}$, PM_{10}, and CO. These seasons also correlate with higher median respiratory and heart-related mortality. Summer tends to have the lowest pollution levels and associated mortality rates, while winter shows more consistent environmental conditions but slightly elevated mortality rates.

The general fit of the base GAM model is illustrated in Figure 2. The residuals follow a normal distribution and appear randomly dispersed without a discernible pattern. Additionally, the response aligns closely with the fitted values, indicating that the model is likely performing well.

The results of the multi-pollutant generalized additive model (GAM) analysis, which included $PM_{2.5}$, PM_{10}, NO_2, SO_2, and CO as predictors over cumulative lag periods of 0–10, 0–20, and 0–30 days, are presented in Tables 4-6. According to Table 4, a 10-unit increase in $PM_{2.5}$ is associated with a statistically significant increase

Table 1. Frequency of respiratory death, cardiovascular death, and all-cause death from 2017 to 2022

Cause of death	2017 (*n* = 317)	2018 (*n* = 365)	2019 (*n* = 365)	2020 (*n* = 79)
Respiratory death	4803	5701	5528	1207
Cardiovascular death	1534	2313	2224	508
All-cause death	12679	15183	14738	3086

Table 2. Descriptive statistics of daily air pollution, meteorological data, and mortality

variable	Mean	SD	Min	25%	50%	75%	Max.
$PM_{2.5}$	29.19	15.99	4.75	19.23	26.56	35.21	213.03
PM_{10}	45.84	22.93	8.83	31.88	42.14	53.83	311.50
SO_2	10.40	8.83	1.25	4.93	7.81	12.66	96.33
NO_2	52.86	15.2	22.17	42.64	50.67	61.13	157.04
CO	1.77	0.82	0.24	1.06	1.65	2.39	5.78
Temperature	16.19	9.5	−6.66	7.82	15.71	24.83	34.35
Cardio. death	15.31	4.67	5	12	15	18	32
Resp. death	5.84	2.94	0	4	6	8	18
All-cause death	40.57	8.27	19	35	40	45	75

Table 3. Pearson correlation coefficients between daily meteorological factors and air pollutants for Mashhad (2017–2020)

	$PM_{2.5}$	PM_{10}	SO_2	NO_2	CO	Temperature	Relative humidity
$PM_{2.5}$	1.000						
PM_{10}	0.980**	1.000					
SO_2	0.132**	0.118**	1.000				
NO_2	0.340**	0.302**	0.179**	1.000			
CO	−0.092**	−0.051	0.195**	0.071*	1.000		
Temperature	0.029	0.093**	−0.387**	−0.147**	−0.080**	1.000	
Relative humidity	−0.127**	−0.184**	0.072*	−0.096**	0.075*	−0.078**	1.000

**$P<0.01$
*$P<0.05$

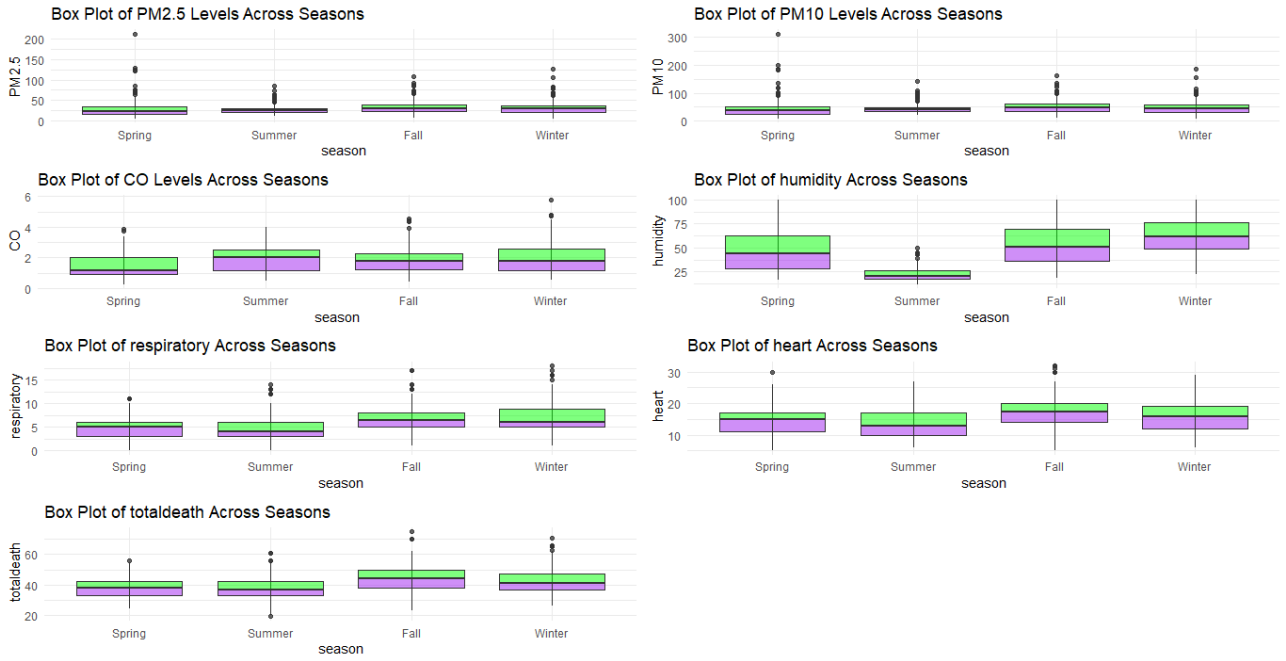

Figure 1. Box plots of three air pollutants, two meteorological variables, and mortalities in four seasons

in all-cause mortality across all lag periods, with the highest relative risk (RR) observed at Lag 0-30 (RR = 1.184, $P = 0.012$). Conversely, PM_{10} is associated with a statistically significant decrease in all-cause mortality across all lag periods, with the lowest relative risk observed at Lag 0–30 (RR = 0.893, $P = 0.014$). The relationship between SO_2 and all-cause mortality shows an increasing trend over time, reaching statistical significance at Lag 0–30 (RR = 1.066, $P = 0.024$). NO_2 is significantly associated with increased mortality at Lag 0–10 (RR = 1.025, $P = 0.027$), but this association is not statistically significant at Lag 0-20 or Lag 0–30. A 1-unit increase in CO is consistently associated with a significant reduction in all-cause mortality across all lag periods, with the most substantial effect observed at Lag 0–30 (RR = 0.866, $P < 0.001$).

Table 5 outlines the associations between pollutants and respiratory mortality. The most pronounced effect is observed for SO_2 during Lag 0–10, with an RR of 1.096 (95% CI: 1.015, 1.184) and a P value of 0.019, suggesting a potential immediate impact of this pollutant on respiratory deaths. Other pollutants do not exhibit consistent or statistically significant effects across the different lag periods.

Table 6 indicates that $PM_{2.5}$ (RR: 1.132, 95% CI: 1.012, 1.267) and CO (RR: 0.927, 95% CI: 0.877, 0.981) significantly impact heart-related deaths, particularly in the short term (Lag 0–10). NO_2 demonstrates statistical significance only in the long term (Lag 0–30), with an RR of 1.074 (95% CI: 1.006, 1.147), while PM_{10} exhibits borderline significance in the short term (Lag 0–10, RR: 0.919, 95% CI: 0.852, 0.991) and mid-term (Lag 0–20, RR: 0.903, 95% CI: 0.813, 1.002).

Discussion

The generalized additive model (GAM) has been widely employed to assess the relationship between air pollution and mortality, given its ability to handle both linear and non-linear relationships effectively. However, the use of GAM to investigate air pollution-related mortality in Iranian cities remains limited. Our analysis found that a

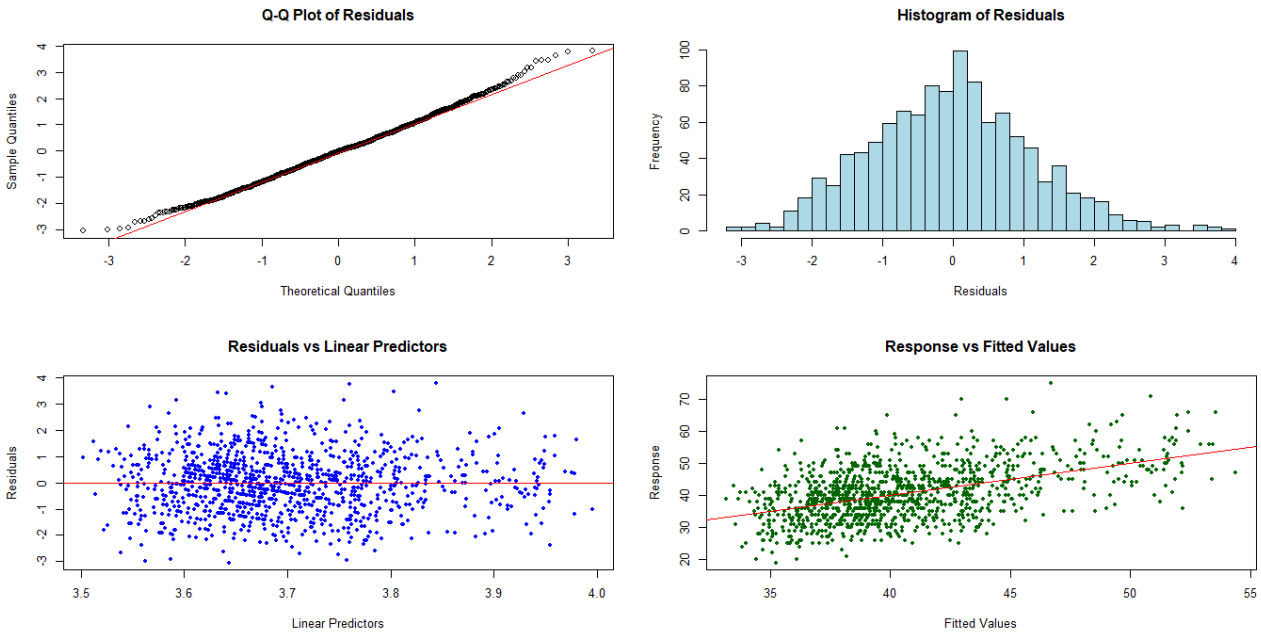

Figure 2. GAM base model performance

Table 4. Results of the adjusted generalized additive model about the effect of air pollutants on all-cause deaths (for a 1 unit increase in CO and a 10 unit increase in all other pollutants)

	Pollutant	RR	95% CI for RR	*P* value
	$PM_{2.5}$	1.086	(1.011, 1.166)	0.024*
	PM_{10}	0.946	(0.901, 0.99)	0.024*
Lag 0–10	SO_2	1.028	(0.995, 1.061)	0.097
	NO_2	1.025	(1.003, 1.047)	0.027*
	CO	0.931	(0.899, 0.96)	<0.001*
	$PM_{2.5}$	1.136	(1.030, 1.253)	0.011*
	PM_{10}	0.921	(0.862, 0.985)	0.016*
Lag 0–20	SO_2	1.043	(0.999, 1.089)	0.055
	NO_2	1.017	(0.987, 1.047)	0.277
	CO	0.897	(0.859, 0.936)	<0.001*
	$PM_{2.5}$	1.184	(1.038, 1.350)	0.012*
	PM_{10}	0.893	(0.817, 0.97)	0.014*
Lag 0–30	SO_2	1.066	(1.008, 1.126)	0.024*
	NO_2	1.004	(0.966, 1.043)	0.842
	CO	0.866	(0.823, 0.912)	<0.001*

* $P<0.05$

Table 5. Results of adjusted generalized additive model, about the effect of air pollutants on respiratory deaths (for a 1-unit increase in CO and a 10-unit increase in all other pollutants)

	Pollutant	RR	95% CI for RR	*P* value
	$PM_{2.5}$	0.940	(0.780, 1.132)	0.514
	PM_{10}	1.025	(0.904, 1.162)	0.698
Lag 0–10	SO_2	1.096	(1.015, 1.184)	0.019*
	NO_2	1.012	(0.958, 1.069)	0.666
	CO	0.964	(0.882, 1.052)	0.414
	$PM_{2.5}$	1.039	(0.807, 1.337)	0.768
	PM_{10}	0.953	(0.803, 1.132)	0.585
Lag 0–20	SO_2	1.103	(0.994, 1.225)	0.065
	NO_2	0.959	(0.889, 1.035)	0.284
	CO	0.923	(0.829, 1.027)	0.140
	$PM_{2.5}$	1.076	(0.758, 1.529)	0.681
	PM_{10}	0.890	(0.700, 1.133)	0.346
Lag 0–30	SO_2	1.120	(0.963, 1.300)	0.143
	NO_2	1.018	(0.913, 1.136)	0.747
	CO	0.988	(0.844, 1.158)	0.886

* $P<0.05$

10-unit increase in $PM_{2.5}$ was associated with a significant rise in all-cause mortality across all lag periods, while PM_{10} was linked to a decrease in mortality. The association of SO_2 with all-cause mortality strengthened over time, becoming statistically significant, and CO consistently showed a negative correlation with mortality. NO_2 had significant effects at shorter lags (0–10) but showed no statistical significance over extended lags (0–20, 0–30).

Regarding respiratory mortality, SO_2 was the only pollutant with a statistically significant effect at Lag 0–10, while other pollutants showed inconsistent or non-significant results. For heart-related mortality, $PM_{2.5}$ had a significant short-term impact, NO_2 was significant over more extended periods, and PM_{10} showed borderline significance in the short and medium terms.

These findings align with and contrast with studies both locally and globally. One study used a spatial heteroscedastic generalized additive distributed lag model and found significant short-term associations between $PM_{2.5}$ exposure and cardiovascular hospitalizations, especially in the central and southeastern districts of the city, highlighting both temporal and spatial variability

Table 6. Results of the adjusted generalized additive model about the effect of air pollutants on cardiovascular-related deaths (for a 1-unit increase in CO and a 10-unit increase in all other pollutants)

	Pollutant	RR	95% CI for RR	*P* value
	$PM_{2.5}$	1.132	(1.012,1.267)	0.030*
	PM_{10}	0.919	(0.852, 0.991)	0.028*
Lag 0–10	SO_2	0.988	(0.939, 1.038)	0.624
	NO_2	1.011	(0.977, 1.046)	0.516
	CO	0.927	(0.877, 0.981)	0.008*
	$PM_{2.5}$	1.162	(0.997, 1.354)	0.055
	PM_{10}	0.903	(0.813, 1.002)	0.055
Lag 0–20	SO_2	0.994	(0.929, 1.064)	0.869
	NO_2	1.008	(0.963, 1.056)	0.724
	CO	0.889	(0.831, 0.951)	<0.001*
	$PM_{2.5}$	1.046	(0.848, 1.289)	0.675
	PM_{10}	0.934	(0.809,1.079)	0.352
Lag 0–30	SO_2	0.958	(0.872, 1.052)	0.368
	NO_2	1.074	(1.006, 1.147)	0.032*
	CO	0.872	(0.792, 0.962)	<0.001*

* $P<0.05$

in risk (20). Another study identified $PM_{2.5}$ as having the most significant health impact, increasing the risk of all-cause mortality by 1.5% per 10 μg/m³ (21). However, our findings on PM_{10} diverge from those that reported an increase in mortality associated with PM_{10} exposure, especially for older populations (22). Similarly, studies in Tehran indicated associations between NO_2, PM_{10}, and respiratory deaths, findings that partially align with our results, where NO_2 showed significant effects in the short term but not over extended lags. More recent research further confirmed the high mortality rates attributed to $PM_{2.5}$ pollution across Iranian cities, including Mashhad (23).

Internationally, various studies provide additional context. Research in Singapore found that increased air pollution, measured by PSI, was associated with all-cause mortality, although the effects were not always statistically significant (24). In Paris, wavelet analysis combined with GAM demonstrated non-linear time-dependent effects between air pollution and mortality, with distinct short- and medium-term patterns (25). In Mexico City, a study highlighted the importance of considering seasonality and temperature when assessing the effect of air pollution on cardiovascular and respiratory mortality (26). Similar to our findings, Kan et al found that short-term exposure to pollutants like PM_{10}, SO_2, and NO_2 increased daily mortality in Shanghai (27).

Furthermore, studies in Canada demonstrated increased risks of respiratory mortality due to O_3, NO_2, and $PM_{2.5}$ exposure (1). In the Netherlands, trends in mortality associated with air pollution were assessed over different time periods, revealing upward trends in relative risk estimates, although these trends varied by cause of death (28). Research in Kathmandu Valley also highlighted the lag effect of PM_{10}, showing a 2.57% increase in all-cause mortality for a 10 μg/m³ rise in concentrations, with effects persisting beyond 20 days (29).

The comparison between our findings and these studies underscores the complex and variable associations between air pollutants and mortality. The mixed evidence on the impact of NO_2, as seen in our study and elsewhere, reflects the pollutant's inconsistent effects over different time frames and populations. Importantly, our findings reinforce the significant role of $PM_{2.5}$ in contributing to all-cause and heart-related mortality in both short- and long-term exposures.

Regarding socioeconomic status (SES), we acknowledge this as an important confounder. However, due to the unavailability of reliable daily SES data across the study period and at the city-wide level, we were unable to include it in the time-series analysis. We have now clarified this limitation and highlighted it as an area for improvement in future studies, where individual- or neighborhood-level SES data may become accessible.

Despite the strength of our results, several limitations must be acknowledged. The use of environmental monitoring data introduces measurement errors, likely underestimating associations between air pollutants and mortality. The reliance on death certificates also carries the risk of misclassification, affecting the accuracy of mortality causes. Furthermore, separating the individual effects of specific pollutants remains challenging due to the complex nature of air pollution mixtures.

Conclusion

In conclusion, our study reveals a significant association between long-term exposure to $PM_{2.5}$ and all-cause mortality in Mashhad from 2017 to 2020, with short-term effects also observed on cardiovascular mortality. These results emphasize the critical need for interventions to reduce $PM_{2.5}$ concentrations, alongside continued health monitoring. Moreover, this research highlights the importance of addressing broader socioeconomic and environmental factors in future studies.

Acknowledgments

We would like to thank the National Institutes for Medical Research Development (NIMAD) for their financial support of this study (grant number: 4000191).

Authors' contributions

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Funding acquisition: Mohammad Taghi Shakeri.
Investigation: Nooshin Akbari Sharak, Sedighe Rastaghi.
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Resources: Nooshin Akbari Sharak.

Software: Nooshin Akbari Sharak.
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Validation: Mohammad Taghi Shakeri, Maryam Salari, Raza Esmaili.
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Writing – review& editing: Mohammad Taghi Shakeri, Maryam Salari, and Raza Esmaili.

Competing Interests

The authors declare no competing interests.

Ethical issues

All information was collected as aggregated and without individual identity. The research proposal was approved by the Ethics Committee of the National Institute for Medical Research Development (NIMAD), Iran (ethics code: IR.NIMAD.REC.1400.097).. Informed consent was obtained from all subjects and/or their legal guardian (s).

Funding

This study was financially supported by the National Institute for Medical Research Development (NIMAD), Iran, under grant/award number 4000191. Mohammad Taghi Shakeri has received research support from NIMAD.

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