scientific reports

Check for updates

OPEN

# Association between exposure to air pollutants and cardiovascular mortality in Iran: a case-crossover study

Nadia Mohammadi Dashtaki[1], Mohammad Fararouei[2]✉, Alireza Mirahmadizadeh[3] & Mohammad Hoseini[4]

**This space-time-stratified case-crossover study examined the association between short-term exposure to satellite-derived air pollutants and cardiovascular disease (CVD) mortality in eight Iranian cities from 2018 to 2022. Using quasi-Poisson regression and distributed lag non-linear models (DLNM), we estimated the effects of air pollutant exposure on cumulative lags (0–6, 0–14, 0–21, and 0–28 days) before mortality. The simultaneous effects of multiple air pollutants on CVD were also examined. This association was adjusted for potential confounders, including meteorological factors. Finally, we conducted a stratified analysis based on gender, age, and season to evaluate possible effect modification in the study. During the study period, 115,193 CVD deaths were reported across eight large cities in Iran. In single-pollutant models, CO, $PM_{2.5}$, and $O_3$ showed the strongest significant associations with CVD mortality during the cumulative lag of 0–28 days, while no significant association was observed for $O_3$. In the two-pollutant models, the association between CVD mortality and $NO_2$ was weakened when $PM_{2.5}$ was added, whereas the associations with CO and $O_3$ slightly strengthened. Adding CO to the model containing $NO_2$ led to a significant reduction in the association with CO, while the association with $NO_2$ remained unchanged. Similar patterns to the single-pollutant models were observed for the combination of $NO_2$ and $O_3$, as well as CO and $O_3$. The association with $PM_{2.5}$ remained unchanged in all two-pollutant models, preserving its lag structure and statistical significance. The findings indicate that estimates varied based on gender, age groups, and season. Men, individuals aged 40 or older, and winter seasons showed higher sensitivity to pollutants. Our findings highlight the importance of investigating the health-related multidimensional impact of air pollutants, particularly in more polluted developing countries like Iran. The results should warn national policy makers to set guided resource allocations for environmental health monitoring, and support the implementation of targeted interventions to reduce its impact on public health. Meanwhile, future research should explore the effectiveness of pollution mitigation strategies and investigate the long-term health impacts of sustained air pollutants.**

**Keywords** Air pollution, Environmental pollutants, Cardiovascular mortality, Satellite data, Case-crossover study

Cardiovascular diseases (CVDs), as classified by the World Health Organization (WHO), include a broad group of disorders of the heart and blood vessels such as coronary artery disease, cerebrovascular disease, rheumatic heart disease, and congenital heart defects[1]. These conditions are the leading cause of death and disability globally, despite major advancements in prevention and treatment strategies[2]. According to WHO estimates, CVDs are responsible for approximately 17.9 million deaths per year, accounting for 32% of all global deaths, and 38% of premature deaths resulting from non-communicable diseases[3,4]. Cardiovascular diseases also constitute the primary cause of mortality and years of life lost (YLL) in Iran[5]. Statistics underscore the importance of identifying modifiable risk factors contributing to CVDs both globally and locally[2,6].

[1]Student Research Committee, Shiraz University of Medical Sciences, Shiraz, Iran. [2]Department of Epidemiology, School of Public Health, Shiraz University of Medical Sciences, Shiraz, Iran. [3]Non-communicable Diseases Research Center, Shiraz University of Medical Sciences, Shiraz, Iran. [4]Department of Environmental Health Engineering, School of Health, Shiraz University of Medical Sciences, Shiraz, Iran. ✉email: Fararooei@gmail.com

Ambient air pollution has been identified as one of the most significant environmental risk factors contributing to global morbidity and mortality[6–8]. It is composed of a complex mixture of harmful substances, including particulate matter (PM10 and $PM_{2.5}$), sulfur dioxide ($SO_2$), nitrogen dioxide ($NO_2$), carbon monoxide (CO), and ozone ($O_3$). Exposure to these pollutants is estimated to cause approximately 6.7 million premature deaths globally each year[9]. The WHO reported in 2019 that 99% of the world's population lived in areas where air quality levels exceeded recommended limits[10]. This widespread exposure underscores the global urgency of addressing air pollution as a critical determinant of health. Numerous epidemiological studies have linked both short- and long-term exposure to air pollution with a wide range of adverse health outcomes, including all-cause mortality, respiratory diseases, decreased lung function, cardiovascular diseases, cancer, diabetes, COVID-19, and adverse birth outcomes[2,11–13]. The burden of air pollution-related cardiovascular mortality is particularly concerning in aging populations, especially where baseline pollution exposure is high[14].

While extensive global research has explored the association between air pollution and CVD mortality[14–16]. Results remain inconsistent due to variations in exposure levels, methodological approaches, and socio-demographic differences across study populations[17]. This concern is particularly pressing in low- and middle-income countries where research on air pollution and cardiovascular health remains limited despite rising mortality[6,14,18]. In Iran, air pollution is a critical public health issue, especially in major industrial cities where pollutant concentrations regularly exceed WHO standards. Several factors contribute to this ongoing problem, including widespread use of fossil fuels, aging vehicle fleets, insufficient emission regulations, and unique topographical and climatic conditions. Although national reports have highlighted the health implications of air pollution, particularly for respiratory diseases, peer-reviewed studies[19,20] examining its effects on cardiovascular mortality in Iran remains limited.

The lack of robust evidence hinders the development of effective policies and targeted interventions to mitigate health risks[21]. This time-stratified case-crossover study was conducted across eight large Iranian cities to assess the effects of short-term exposure to major air pollutants (CO, $NO_2$, $O_3$, and $PM_{2.5}$) on cardiovascular mortality. Stratified analyses were used to assess the potential modification of this association based on individual characteristics (gender, age) and the season of death. The inclusion of cities with varying levels of air pollution aimed to enhance exposure diversity and statistical power. This study aims to conduct a spatiotemporal analysis of the relationship between exposure to air pollutants and cardiovascular mortality, considering time lags and meteorological variations in Iran from 2018 to 2022 using satellite data.

## Methods

### Settings

This space-time-stratified case-crossover study was used to evaluate the association between short-term exposure to air pollution and mortality due to cardiovascular diseases in the period between September 26, 2018, and March 20, 2022. We selected eight large and evenly distributed metropolitan areas of Iran inhabited by about 23% of the country's total population. These cities included, Tehran (the capital), Mashhad (the capital of Khorasan province), Tabriz (the capital of Azerbaijan province), Shiraz (the capital of Fars province), Kerman (the capital of Kerman province), Hamedan (the capital of Hamedan province), Arak (the capital of Markazi province), and Yazd (the capital of Yazd province). The selection of these eight cities was based on a combination of criteria, including high population density, availability of consistent mortality data, variation in geographic and climatic conditions, and significant differences in air pollution levels, which together enhance exposure variability and statistical power. The selected time range (September 26, 2018, to March 20, 2022) corresponds to the period during which high-quality and consistent satellite data (from Sentinel-5P and CAMS) were available for all pollutants of interest.

### Air pollution and meteorology data

To monitor air pollutants, including CO, O3, and NO2, Sentinel-5P satellite data were obtained using the Google Earth Engine (GEE) (https://developers.google.com/earth-engine/datasets/catalog/sentinel-5p). Sentinel-5 Precursor (S5P) is a satellite launched on 13 October 2017 by the European Space Agency to monitor air pollution and has a spatial resolution of $7 \times 3.5$ km2[22,23]. The task of this satellite is to monitor air pollutants such as Nitrogen dioxide (NO2), Carbon monoxide (CO), sulfur dioxide (SO2), ozone (O3), formaldehyde (CH2O), methane (CH4), and aerosol. All S5P datasets, except CH4, have two versions: Near Real-Time (NRTI) and Offline (OFFL). The NRTI products are generated faster but cover smaller areas and may have limited spatial accuracy due to preliminary calibration. In contrast, the OFFL products contain data from a full orbital pass and offer higher spatial consistency and reliability, though they are provided with some delay. This version was preferred due to its better suitability for retrospective environmental epidemiology studies requiring spatial completeness and data stability[22,24]. For this study, the Offline (OFFL) version of the dataset was used due to its higher data quality and greater consistency, as it undergoes additional calibration and validation processes compared to the Near Real-Time (NRTI) version (ESA, 2023)[25].

The $PM_{2.5}$ concentrations were collected from the Copernicus Atmosphere Monitoring Service (CAMS) using the Google Earth Engine platform (https://developers.google.com/earth-engine). CAMS can continuously monitor the composition of the Earth's atmosphere at global and regional scales. Unlike Sentinel-5P, which does not directly provide $PM_{2.5}$ values, CAMS estimates $PM_{2.5}$ using assimilation of satellite and ground-based observations through a global atmospheric composition forecasting system. The main global near-real-time production system is a data assimilation and forecasting system providing two 5-day forecasts per day for aerosols and chemical compounds that are part of the chemical scheme.

Also, daily meteorological data such as temperature (°C), relative humidity (%), and wind speed (m/s) were collected from the Iranian Meteorological Organization. These variables were used as potential confounders in the models. The meteorological data were obtained at the city level, with a temporal resolution of daily averages.

## Study outcome

For this study, daily cardiovascular mortality data were collected from the Iranian Ministry of Health and Medical Education for the years 2018–2022. We identified deaths from cardiovascular diseases based on the International Classification of Diseases, 10th Edition (ICD-10) codes (I00–I99).

## Statistical analysis

Spearman correlation analysis was conducted to assess the linear relationships between air pollutant concentrations (PM2.5, NO2, O3, etc.) and meteorological variables (temperature, relative humidity, wind speed). Spearman correlation coefficient was calculated to determine the strength and direction of the associations between these variables, which allowed for the identification of potential confounders and multicollinearity before incorporating them into the statistical models. The Spearman correlation coefficient (r) ranges from − 1 to 1, where values closer to 1 or -1 indicate a strong positive or negative linear relationship, respectively, and values near 0 suggest little to no linear relationship. The significance of the correlation was assessed with a p-value threshold of 0.05. This correlation analysis was performed using Stata software (version 17).

The relationship between short-term exposure to air pollutants and mortality due to cardiovascular disease was assessed using a space-time stratified case-crossover design. This method considers each individual as her or his control. For each case, it introduces a stratum combining two dimensions of time and space. So, within each stratum, the case day and control days are matched by day of the week in the same month, in the same year, and in the same City. Thus, each case has 3 or 4 control days (before and/or after the case day in the same month)[26,27]. With this method, one can adjust individual characteristics (e.g., sex, race, education, weight, etc.) that are unlikely to change within the small-time window[27]. In addition, this method enables simultaneous control for the long-term trends and seasonality of unmeasured time-varying confounders and the influence of the day of the week[26]. Generally, a case-time-stratified crossover design compares the exposure on the case day with their own control days from a different time period (i.e., day-of-week within a month and year)[26].

We combined distributed lag nonlinear models (DLNM) with conditional quasi-Poisson regression to investigate the cumulative lagged and potentially nonlinear effects of air pollutant exposures on cardiovascular disease mortality. Conditional quasi-Poisson regression can be used to perform the space-time-stratified case-crossover study. Under its design, conditional Poisson (quasi-Poisson) regression allows researchers to adjust for overdispersion and autocorrelation in the count data. DLNM was implemented using a cross-basis function that allows for simultaneous modeling of both the nonlinear exposure–response relationship and the distributed lag effects over time[28]. Given that pollutant effects may extend over several days, using a cumulative lag model provides a more accurate measure of exposure than a one-day lag model in air pollution epidemiological studies[29–31]. Therefore, to capture the delayed effects of exposure, we selected multiple lag structures: 0–6, 0–14, 0–21, and 0–28 days, based on findings from previous studies[31]. The selection of the degrees of freedom (df) for pollutants and lag days was based on the minimization of the Akaike Information Criterion (AIC) among different combinations. Accordingly, we selected 3 degrees of freedom for the pollutants and lags. A sensitivity analysis was also conducted by varying the lags and degrees of freedom to assess the robustness of the model estimates. The results of sensitivity analyses confirmed the consistency of the main findings. To control for potential confounding effects of meteorological conditions, we included daily mean temperature, relative humidity, and wind speed with the same lag structure as the pollutants as covariates in all models.

The following formula can represent the general model:

$$\log\left(\mathrm{E}(\mathrm{Y}\,\mathrm{t}\,)=\alpha\,+\mathrm{cb}(\text{Air Pollutant})+\mathrm{cb}\,(\text{Temperature})+\mathrm{cb}(\text{Humidity})+\mathrm{cb}(\text{Wind Speed}),\ \text{eliminate}\ =\ \text{factor}\,(\text{stratum})\right.$$

Where Yt denotes the daily count of cardiovascular deaths at day t; α is the intercept, and cb() represents the cross-basis function applied to each variable. Cross-basis functions were used for all variables to simultaneously model their nonlinear effects and lagged impacts. Stratum variable was defined by the combination of the day of week, month, year, and city. We conditioned on the stratum through the "eliminate" function in the "gnm" package to include adjusted factors that are required in the model but are not of direct interest[30].

In addition, to identify potential effect modification, stratified analyses were conducted by sex (male and female), age (under 40, between 40 and 65, and over 65 years old), and season. the data was stratified into four distinct seasons: winter (from December to February), spring (from March to May), summer (from June to August), and autumn (from September to November).

Finally, we examined two pollutant models to assess the association between air pollutants and CVD deaths, accounting for the potential confounding effects of co-pollutants.

All statistical analyses were performed in R (Version 4.4.0) with the "(gnm)" package for fitting the conditional quasi-Poisson regression, and the "dlnm" package for fitting DLNM. Effects were estimated as Relative Risk (RR) in the model. In this study, a p-value < 0.05 was considered statistically significant.

## Ethical approval and consent to participate

This study was performed according to the ethical guidelines expressed in the Declaration of Helsinki. This study was approved by the Shiraz University of Medical Sciences (SUMS) Local Ethics Committee code: IR.SUMS.SCHEANUT.REC.1402.108. Informed consent was also waived by the Research Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.SCHEANUT.REC.1402.108).

# Results

## Descriptive statistics of cardiovascular disease (CVD) mortality and ambient air pollutants

During the study period from 26 September 2018 to 20 March 2022, a total number of 115,193 cardiovascular disease (CVD) deaths were recorded in 8 provinces in Iran, including 63,317 deaths (55%) from male patients

| Variable | Characteristics | Number of Deaths (%) |
|---|---|---|
| City | Tehran | 49,764 (43.2) |
| | Mashhad | 20,113 (17.5) |
| | Tabriz | 16,491 (14.3) |
| | Arak | 3986 (3.5) |
| | Hamedan | 5175 (4.5) |
| | Kerman | 4824 (4.2) |
| | Yazd | 2852 (2.5) |
| | Shiraz | 11,988 (10.4) |
| Season | Spring | 25,464 (22.1) |
| | Summer | 24,972 (21.7) |
| | Autumn | 31,172 (27.1) |
| | Winter | 33,585 (29.1) |
| Sex | Male | 63,317 (55.0) |
| | Female | 51,876 (45.0) |
| Age of Death | < 40 | 2312 (2.0) |
| | 40–65 | 22,431 (19.5) |
| | ≥ 65 | 90,450 (78.5) |

**Table 1**. Demographic characteristics of the study population ($N = 115193$).

| Variables | Mean | SD | Min | Max |
|---|---|---|---|---|
| $PM_{2.5}$ (μg/m$^3$) | 20.79 | 16.64 | 2.00 | 83.00 |
| CO (mmol/m$^2$) | 27.50 | 3.87 | 15.41 | 58.35 |
| $O_3$ (mmol/m$^2$) | 130.01 | 11.96 | 24.49 | 200.23 |
| $NO_2$ (mmol/m$^2$) | 0.15 | 0.24 | 0.03 | 4.48 |
| Temperature (Â°C) | 15.77 | 9.55 | -12.4 | 38.30 |
| Relative humidity (%) | 41.65 | 22.39 | 4.25 | 100.00 |
| Wind speed (m/s) | 2.58 | 1.35 | 0.00 | 10.12 |

**Table 2**. Daily average air pollutant concentration data and meteorological data in Iran, 2018–2022.

| Pollutants | Cardiovascular death | CO | $O_3$ | $NO_2$ | $PM_{2.5}$ | Temperature | Relative Humidity | Wind speed |
|---|---|---|---|---|---|---|---|---|
| Cardiovascular death | **1** | | | | | | | |
| CO | 0.271* | **1** | | | | | | |
| $O_3$ | 0.136* | 0.143* | **1** | | | | | |
| $NO_2$ | 0.460* | 0.224* | 0.072* | **1** | | | | |
| $PM_{2.5}$ | 0.179* | 0.175* | -0.034* | 0.184* | **1** | | | |
| Temperature | -0.018* | 0.278* | -0.354* | -0.001 | 0.110* | **1** | | |
| Relative humidity | 0.134* | -0.308* | 0.346* | -0.004 | -0.001 | -0.768* | **1** | |
| Wind speed | 0.156* | 0.262* | 0.170* | -0.167* | 0.057* | 0.268* | -0.181* | **1** |

**Table 3**. Association analysis for cardiovascular death, air pollutants, and meteorological variables. * $p < 0.05$.

and 51,876 deaths (45%) from female patients. The stratification of CVD mortality according to gender, age group, city of residence, and season is shown in Table 1. In addition, the distribution of air pollution and meteorological indicators is presented in Table 2. Accordingly, for the study period, the average $PM_{2.5}$, CO, $O_3$, and $NO_2$ were reported to be 20.79 μg/m$^3$, 27.50 mmol/m$^2$, 130.01 mmol/m$^2$, 0.15 mmol/m$^2$, respectively. Also, Wind speed, temperature, and relative humidity had daily mean values of 2.58 m/s, 15.77 °C, and 41.65% recorded, respectively.

## Association analysis between environmental factors

The Spearman correlation coefficients between cardiovascular death, air pollutants, and meteorological parameters are presented in Table 3. The results show that the number of cardiovascular deaths with all air pollutants and meteorological parameters exhibited significant positive correlations, except for Temperature, which had an inverse correlation. Also, correlation analysis suggested a positive correlation between all air pollutants (except for O3 and PM2.5, with a negative correlation). Furthermore, all air pollutants' association

(except PM2.5 with relative humidity and NO2 with Temperature and relative humidity) showed significant correlations with meteorological variables.

## Associations between air pollutant exposure and CVD mortality with different lag times

The adjusted relationships between exposure to air pollutants and CVD mortality for lag and acute effects are shown in Fig. 1. Estimates of the associations between exposure to air pollutants at each lag and CVD mortality are adjusted for temperature, relative humidity, and wind speed.

Overall, increases in $NO_2$, CO, and $PM_{2.5}$ were positively and significantly associated with CVD mortality when examined overall and at different lags. The greatest effects for $NO_2$, CO, and $PM_{2.5}$ were observed during the 4-week cumulative lag before the mortality date. The estimated RRs are 1.716(95%CI = 1.527–1.930), 1.023(95%CI = 1.014–1.031), and 1.010(95%CI = 1.008–1.012) respectively. In contrast, no significant association was observed between $O_3$ and CVD mortality (Fig. 1).

Effects of $NO_2$, CO, and $PM_{2.5}$ were significantly stronger during the winter season with the strongest associations observed during the 4-week cumulative lag before the mortality date, The estimated RR are 2.656(95%CI = 2.253–3.130), 1.064(95%CI = 1.050–1.078), and 1.017(95%CI = 1.014–1.020) respectively. only the effect of $O_3$ was statistically significant during the winter season at a 0-day lag (RR: 1.002, 95% CI: 1.001–1.003) (Fig. 1).

Overall, an increase in ozone levels showed the weakest association with CVD deaths than that observed with the other pollutants. In contrast, increased $NO_2$ relative to other pollutants showed the strongest association with CVD deaths.

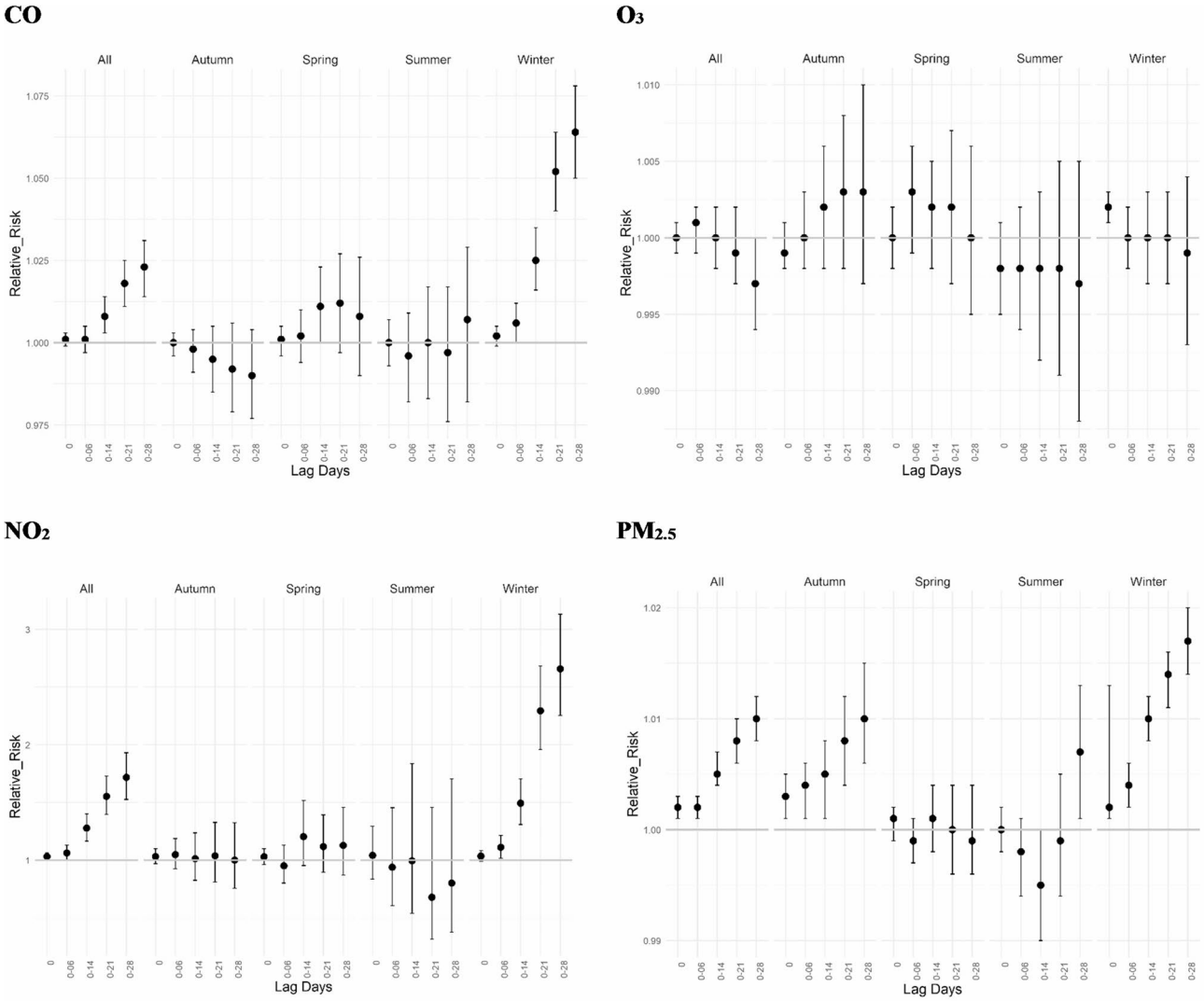


**Fig. 1**. Lagged effects of the associations between exposure to air pollutants and CVD mortality by season, in Iran, 2018–2022. Note: Estimates of the associations between exposure to air pollutants at each lag and CVD mortality are adjusted for temperature, relative humidity, and wind speed.

## Stratification analyses by sex and age groups

When stratified by gender, statistically significant associations were found between both genders (males and females) and CVD mortality at different lags.

As shown in Fig. 2, an increased risk of CVD mortality in the male population demonstrated a stronger association with increased $NO_2$, CO, and $PM_{2.5}$ concentrations particularly in the 4-week cumulative lag before the mortality date. The estimated RRs are 1.790(95%CI = 1.541–2.079), 1.023(95%CI = 1.013–1.034), and 1.011(95%CI = 1.008–1.013) respectively.

By age group, for those aged < 40 years, only the effect of $O_3$ was statistically significant at a 0-day lag (RR: 1.005, 95% CI: 1.001–1.009).

Expectedly, the result also indicated that the effects of $NO_2$, CO, and $PM_{2.5}$ were statistically significant and stronger in the elderly population, especially in the population aged 40 years or above. Among adults over 40 years, higher associations were observed for the group between 40 and 65 years in cumulative lags 0–28 days. The estimated RR are 1.983(95%CI = 1.566–2.512), 1.023(95%CI = 1.006–1.039), and 1.011(95%CI = 1.007–1.015) respectively.

In contrast, no significant association was detected between $O_3$ and CVD mortality in the adults aged above 40 years.

## Results for the combined effect of twopollutant models

The association between air pollutants and CVD deaths showed slight changes when a second pollutant was added to the models (Table 4). Specifically, the association of CVD deaths with $NO_2$ weakened when $PM_{2.5}$ was included. Conversely, in the two-pollutant model with $PM_{2.5}$ and CO, the association with CO slightly increased.

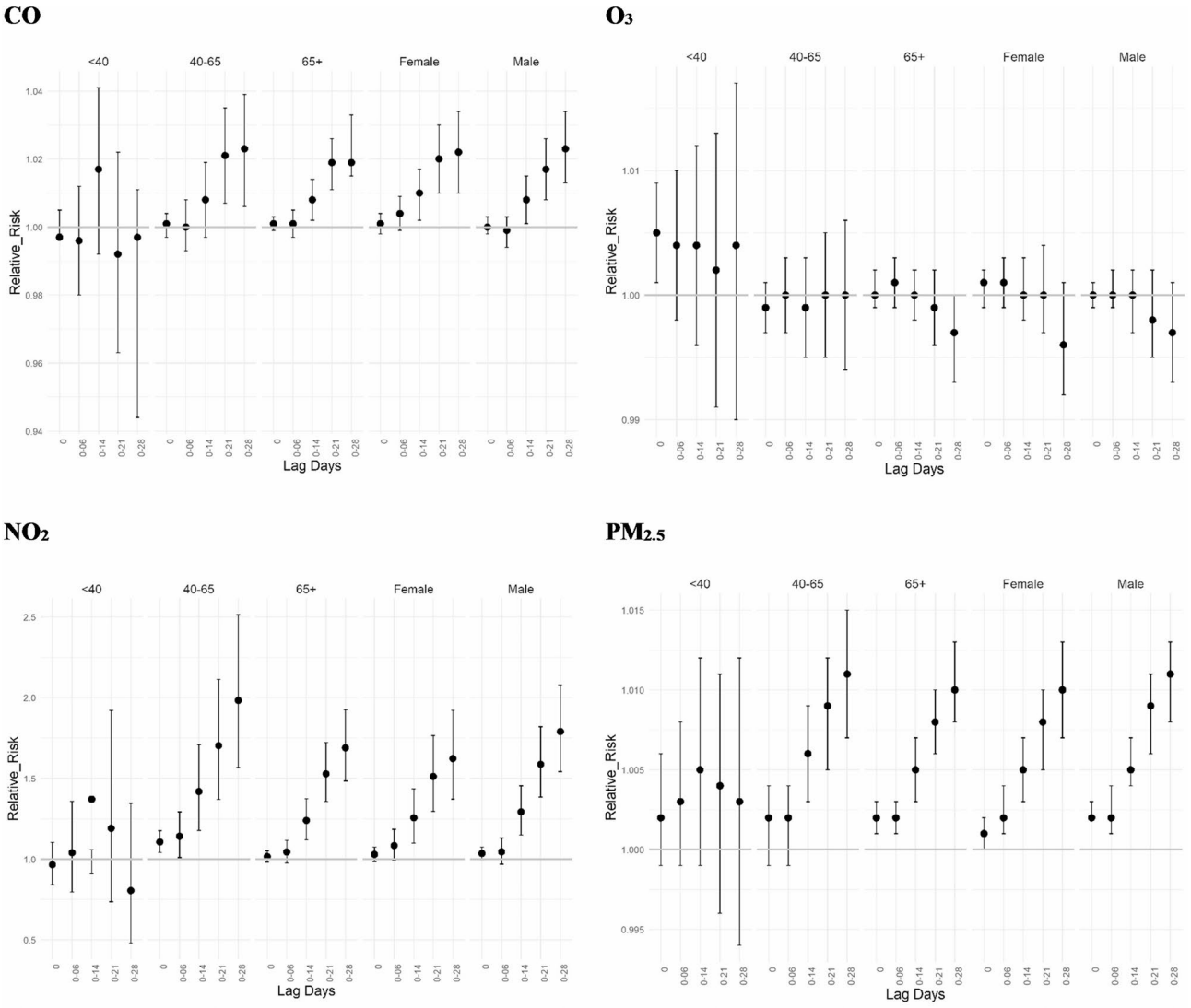


**Fig. 2**. Lagged effects of the associations between exposure to air pollutants and CVD mortality by sex and age group, Iran, 2018–2022. Note: Estimates of the associations between exposure to air pollutants at each lag and CVD mortality are adjusted for temperature, relative humidity, and wind speed.

| Lag days | RR (95% CI) | |
|---|---|---|
| **$PM_{2.5}$+$NO_2$** | **$PM_{2.5}$** | **$NO_2$** |
| Lag 0 | 1.001 (1.001–1.002) * | 1.013 (0.981–1.046) |
| Lag 0 to 6 | 1.002 (1.001–1.003) * | 1.015 (0.949–1.086) |
| Lag 0 to 14 | 1.004 (1.003–1.006) * | 1.135 (1.025–1.257) * |
| Lag 0 to 21 | 1.006 (1.004–1.008) * | 1.310 (1.163–1.474) * |
| Lag 0 to 28 | 1.006 (1.004–1.008) * | 1.336 (1.173–1.523) * |
| **$PM_{2.5}$+CO** | **$PM_{2.5}$** | **CO** |
| Lag 0 | 1.002 (1.001–1.003) * | 1.000 (0.998–1.002) |
| Lag 0 to 6 | 1.002 (1.001–1.003) * | 0.998 (0.995–1.002) |
| Lag 0 to 14 | 1.005 (1.003–1.007) * | 1.002 (0.996–1.008) |
| Lag 0 to 21 | 1.007 (1.006–1.009) * | 1.010 (1.002–1.017) * |
| Lag 0 to 28 | 1.008 (1.006–1.010) * | 1.012 (1.004–1.021) * |
| **$PM_{2.5}$+$O_3$** | **$PM_{2.5}$** | **$O_3$** |
| Lag 0 | 1.002 (1.001–1.002) * | 1.001 (1.000-1.002) |
| Lag 0 to 6 | 1.002 (1.001–1.003) * | 1.001 (1.000-1.003) |
| Lag 0 to 14 | 1.005 (1.004–1.007) * | 1.001 (0.999–1.003) |
| Lag 0 to 21 | 1.009 (1.007–1.010) * | 1.003 (1.001–1.005) * |
| Lag 0 to 28 | 1.009 (1.007–1.011) * | 1.003 (1.001–1.006) * |
| **$NO_2$ + CO** | **$NO_2$** | **CO** |
| Lag 0 | 1.036 (1.001–1.072) * | 1.000 (0.997–1.002) |
| Lag 0 to 6 | 1.080 (1.001–1.164) * | 0.998 (0.994–1.003) |
| Lag 0 to 14 | 1.276 (1.138–1.430) * | 1.000 (0.993–1.007) |
| Lag 0 to 21 | 1.545 (1.344–1.776) * | 1.001 (0.992–1.009) |
| Lag 0 to 28 | 1.642 (1.406–1.918) * | 0.998 (0.987–1.009) |
| **$NO_2$ + $O_3$** | **$NO_2$** | **$O_3$** |
| Lag 0 | 1.033 (1.002–1.065) * | 1.001 (1.000-1.002) |
| Lag 0 to 6 | 1.066 (1.003–1.133) * | 1.001 (1.000-1.002) |
| Lag 0 to 14 | 1.279 (1.166–1.403) * | 1.000 (0.999–1.002) |
| Lag 0 to 21 | 1.558 (1.398–1.735) * | 1.000 (0.998–1.003) |
| Lag 0 to 28 | 1.616 (1.439–1.815) * | 1.000 (0.998–1.003) |
| **CO + $O_3$** | **CO** | **$O_3$** |
| Lag 0 | 1.001 (0.999–1.003) | 1.000 (0.999–1.001) |
| Lag 0 to 6 | 1.001 (0.997–1.005) | 1.001 (0.999–1.002) |
| Lag 0 to 14 | 1.008 (1.003–1.014) * | 1.000 (0.998–1.002) |
| Lag 0 to 21 | 1.019 (1.012–1.026) * | 0.999 (0.996–1.001) |
| Lag 0 to 28 | 1.022 (1.014–1.030) * | 0.998 (0.995–1.001) |

**Table 4**. Associations between concentrations of two air pollutants and CVD deaths, Iran, 2018–2022. Estimates of the associations between exposure to air pollutants at each lag and CVD mortality are adjusted for temperature, relative humidity, and wind speed. * $p < 0.05$.

Additionally, the association of CVD deaths with $O_3$ strengthened when $PM_{2.5}$ was included. In the two-pollutant model for $NO_2$ and CO, the association with CO significantly decreased compared to the single-pollutant model and lost its statistical significance. However, the association with $NO_2$ remained unchanged, preserving its lag structure and statistical significance. In the two-pollutant model incorporating $NO_2$ and $O_3$, the associations of $NO_2$ and $O_3$ remained consistent with those observed in the single-pollutant models, preserving their lagged and statistical structure patterns. Similarly, in the two-pollutant model involving CO and $O_3$, the associations of CO and $O_3$ showed no changes compared to the single-pollutant models, maintaining their lagged and statistical structure patterns. In all two-pollutant models, the associations with $PM_{2.5}$ were unchanged compared to the single-pollutant models, retaining their lag structure and statistical significance.

## Discussion

This space-time stratified case-crossover study investigated the potential impact of exposure to major air pollutants ($PM_{2.5}$, $NO_2$, $O_3$, CO) on cardiovascular mortality up to 28 days before death in 8 large Iranian cities. To account for the delayed effects of air pollution, we applied a Distributed Lag Non-linear Model (DLNM) framework within the case-crossover design. The DLNM allows us to simultaneously estimate both the non-linear exposure-response relationship and the lag structure over multiple days. This approach is particularly powerful in identifying how the effects of pollutants unfold over time[32]. The space-time stratified case-crossover design controls for time-invariant individual characteristics and adjusts for long-term and seasonal trends by

using each case as its control. When integrated with the DLNM, this combination offers a robust methodology for capturing short-term associations and complex lag patterns while minimizing confounding effects.

The results showed that after controlling for the effects of confounding factors (such as temperature, relative humidity, and wind speed), there was a positive and significant relationship between cardiovascular mortality and $PM_{2.5}$, CO, $NO_2$, and $O_3$. The results from the single pollutant models in this study showed that $PM_{2.5}$, $NO_2$, and CO are consistently associated with cardiovascular mortality, with $NO_2$ showing the strongest association compared to the other pollutants examined. Additionally, a positive relationship was observed between various exposure delays, with the strongest estimates identified at 0–28 day cumulative lag for all pollutants. These findings suggest that the effects of air pollution on mortality are observed over several days and provide strong evidence regarding the importance of the timing of exposure to air pollution. Furthermore, no significant association between $O_3$ and cardiovascular mortality was observed. In the subgroup analyses, the effect of $NO_2$ on cardiovascular mortality was slightly higher in men than in women. However, previous research has yielded different results[2]. The gender differences in sensitivity may be related to factors such as lifestyle or cultural and social, and even exposure differences. Specifically, men tend to participate more in outdoor activities and are more exposed to ambient air pollution, while women may be more exposed to indoor pollution, such as cooking smoke. Additionally, this discrepancy may stem from biological or hormonal differences between women and men. A better understanding of these differences could help formulate more effective policies to reduce the negative health effects of air pollution[14]. Another important finding was that exposure to air pollutants has a greater impact on the adult population in the age groups 40–65 years and above 65 years. This is likely due to the reduced efficiency of the organs, including the lungs, with age, as well as the presence of underlying chronic conditions. Therefore, older adults are more vulnerable than other groups to the negative health effects of air pollution[14,31,33]. Findings suggest that effect modifiers should be considered when interpreting the impact of air pollutants on CVD mortality. Previous studies have shown that the impact of air pollutants on cardiovascular mortality varies across different seasons of the year[15,34]. Similarly, in this study, it was observed that the effect of pollutants depends on the season. Accordingly, the greatest impact of $PM_{2.5}$, CO, $NO_2$, and $O_3$ on cardiovascular mortality was observed in winter. During the summer, due to a greater tendency of people to stay indoors, exposure to environmental pollutants decreases[34]. In addition, in winter, due to low humidity and low wind speed, pollutants disperse slowly and remain in the air for a longer period. This leads to an increased duration of exposure to air pollution for residents of polluted areas, ultimately raising the likelihood of higher mortality[29,31]. This suggests that lower temperatures may facilitate the spread of pollutants[35]. In addition to general seasonal trends, several region-specific environmental and geographical factors in Iran may intensify the effects of air pollution on cardiovascular mortality. A prominent contributor is transboundary dust storms initiated particularly from neighboring countries (e.g., Iraq and Saudi Arabia), which affect more or less all provinces of Iran. The dust significantly increases PM2.5 and PM10 levels[36]. Furthermore, many studied cities are located in basins or mountain-surrounded terrains, where intensified inversions are common during colder months, trapping pollutants near the surface.

Additionally, urban features such as high traffic density, insufficient green infrastructure, and widespread use of inefficient heating and cooling systems contribute to elevated pollutant concentrations and uneven dispersion, especially in densely populated districts. These region-specific conditions might potentially explain the observed feature of associations in our study when compared to others[37]. In addition, these differences may also stem from diverse methodological approaches, variations in population sensitivity, and pollutant measurement methods.

In the two-pollutant models, the association between $PM_{2.5}$ and cardiovascular mortality remained strong after adjustment for gaseous pollutants ($NO_2$, $O_3$, and CO), indicating an independent effect of $PM_{2.5}$ on cardiovascular mortality. Although all associations remained positive after adjustment for other pollutants, we observed some attenuated associations: adjusting for $PM_{2.5}$ reduced the relationship between mortality and $NO_2$, and the association between CO and mortality decreased after adjusting for both $PM_{2.5}$ and $NO_2$. On the other hand, the association between $O_3$ and cardiovascular mortality increased when adjusted for $PM_{2.5}$. Ultimately, our analyses revealed that the direction and effects of temporal delay structures in two-pollutant models remained consistent with those observed in single-pollutant models.

The above findings are generally consistent with previous literature that reported individually measured associations between exposure to $PM_{2.5}$, $O_3$, $NO_2$, and CO and cardiovascular mortality. A meta-analysis performed in China identified a positive association between air pollutant concentrations ($PM_{2.5}$, $PM_{10}$, $NO_2$, $SO_2$, and $O_3$) and cardiovascular mortality[2]. A study in Korea demonstrated that exposure to $PM_{2.5}$, $PM_{10}$, CO, $SO_2$, and $NO_2$ elevates the risk of cardiovascular events and mortality, while no significant link was found with $O_3$[38]. Another study by Demoury in Belgium linked an increased mortality due to all causes with PM, NO2, and BC pollutants during colder months[17]. Similarly, a few studies reported greater risks of cardiovascular death associated with these pollutants during warmer seasons[39–41]. A study in Singapore applied time series analysis and a 0–5 days lag model to report an increase in cardiovascular mortality with higher concentrations of PM10 and $PM_{2.5}$. However, this association was significant only in older adults (≥65 years), and the effects of other pollutants, such as carbon monoxide (CO), nitrogen dioxide ($NO_2$), ozone ($O_3$), and sulfur dioxide ($SO_2$), were minimal[33]. In addition to the previously discussed explanations, these discrepancies may be attributed to factors such as differences in the composition and toxicity of pollutants[34,42], geographical variations[34], population sensitivity[34], differences in demographic characteristics[43], different study designs and statistical analysis methods[2], variations in pollutant measurement and recording methods[2], differences in confounding factors or effect modifiers[34,42], diverse lifestyle patterns[44], and the difference in considered lags[29].

The impact of air pollution on cardiovascular health has garnered significant attention due to its multifaceted effects on the cardiovascular system. Research indicates that air pollutants contribute to an elevated risk of cardiovascular events through various mechanisms, including oxidative stress, systemic inflammation, autonomic nervous imbalance, and direct particle translocation. These pathways often activate secondary

mechanisms, such as thrombotic pathways, endothelial dysfunction, hypothalamic-pituitary-adrenal (HPA) axis activation, and epigenetic changes, which collectively exacerbate cardiovascular risks[8,33]. The mechanisms triggered by air pollution are diverse and may activate at different times and in various parts of the body. Despite their distinct nature, these pathways are interconnected, often converging to the elevated risk of cardiovascular disease (CVD). Many of these mechanisms share common intermediate outcomes, such as arrhythmias, elevated blood pressure, arterial stiffness, and atherosclerosis. These factors collectively increase the likelihood of severe cardiovascular events, including cardiac arrest, ischemic heart disease (IHD), heart failure, stroke, and ultimately, CVD-related mortality. The activation of these pathways depends on the timing and duration of exposure to air pollution. Short-term exposures might primarily trigger autonomic imbalances, while long-term exposures are more likely to drive chronic conditions such as atherosclerosis. Additionally, the type of pollutant, its concentration, duration of exposure, and the individual's health profile all influence how these pathways operate and their eventual outcomes[8,45].

In general, air pollutants act through different interconnected pathways, creating a cascade of physiological and molecular events that significantly elevate the risk of cardiovascular events. This underscores the critical need for mitigating air pollution to protect cardiovascular health.

Given that a large portion of the global population, especially in middle- and low-income countries like Iran, is exposed to high levels of air pollution in urban areas, and pollutant concentrations continue to rise, Using advanced measures like of high-resolution satellite data can play a crucial role in accurately assessing exposure to air pollution. This data can help identify health risks associated with air pollution and enable the development of effective strategies for managing and reducing these risks.

### Strengths and limitations

We employed a space-time stratified case-crossover design at an individual level, which effectively controls for a wide range of potential unknown confounders that do not change over short periods (e.g., age, gender, health status, socioeconomic status, genetics). This approach enhanced causal inference due to its robust design. We utilized high-resolution spatiotemporal data from Sentinel-5 satellite measurements to estimate air pollutant levels, significantly improving exposure assessment accuracy and reducing exposure measurement errors. To the best of our knowledge, this is the first study to utilize air pollution data provided by the Sentinel-5 satellite to examine the effects of pollutant exposure on mortality in Iran. Given the limited coverage of air quality monitoring stations in the cities and the absence of stations in some areas, satellite data allowed us to assess large population groups lacking sufficient exposure information. Studies have confirmed that these satellite data have a strong correlation with ground-level data[22,46], making them a valuable tool for health research in regions where air quality monitoring stations are limited or unavailable. Additionally, we conducted stratified analyses to evaluate potential effect modifications by age, gender, and season. Given that the association between cardiovascular mortality and ambient air pollution observed in this study was likely due to interactions between air pollutants, we assessed the simultaneous effect of multiple air pollutants on cardiovascular mortality. Moreover, we accounted for the potential confounding effects of meteorological factors such as temperature, humidity, and wind speed. Finally, we examined multiple lags in the relationships of interest using distributed lag models, providing a comprehensive evaluation of temporal dynamics.

Our study has several limitations that should be acknowledged. First, the lack of detailed diagnostic information on cardiovascular disease subtypes prevented us from exploring associations between short-term environmental exposures and cause-specific cardiovascular mortality, thereby limiting the granularity and interpretability of our findings. Second, we were unable to account for indoor air pollution exposures, which may contribute significantly to total exposure but were not measurable due to data unavailability. Third, although the use of satellite-based air pollutant data enhanced spatial resolution and coverage, these measurements are reported in units such as $mol/m^2$ rather than the conventional $\mu g/m^3$ used in health-based standards. This unit discrepancy may hinder direct comparability with regulatory guidelines, although prior studies have demonstrated strong correlations between satellite-derived and ground-level pollutant concentrations[22]. In this study, we examined the joint effects of multiple air pollutants on cardiovascular mortality. Among them, nitrogen dioxide ($NO_2$) consistently exhibited a strong and statistically significant association across all model specifications. However, this persistent association may, in part, be influenced by potential collinearity with other unmeasured pollutants, which could confound the observed estimates.

## Conclusion

This time-stratified case-crossover study conducted in large cities in Iran showed robust evidence of a statistically significant association between short-term exposure to ambient air pollution and an increased risk of cardiovascular mortality, identifying sensitive subpopulations. Our findings revealed that the cumulative effects of air pollution, particularly $NO_2$, CO, and $PM_{2.5,}$ are stronger than single-day effects. Moreover, the impact of air pollution on cardiovascular mortality was slightly more pronounced in men than women. Among different age groups, middle-aged and elderly individuals, especially those over 40 years old, were found to be at higher risk. Additionally, the risk of cardiovascular mortality due to air pollution increases during colder seasons. Therefore, it is recommended to pay special attention to the elderly and individuals with cardiovascular diseases, particularly during the cold seasons. also, health authorities should provide targeted health recommendations to vulnerable populations to mitigate the adverse effects of air pollution. These findings expand our knowledge of the acute effects of air pollution on cardiovascular mortality and can guide policymakers in establishing stricter regulations and developing effective strategies for air pollution control.

### Competing interests

The authors declare no competing interests.

## Data availability

The datasets generated during and analyzed during the current study are available from the corresponding author on reasonable request.

Received: 27 January 2025; Accepted: 26 May 2025
Published online: 28 May 2025

## References

1. (WHO) WHO. Cardiovascular diseases [Available from:https://www.who.int/europe/news-room/fact-sheets/item/cardiovascular-diseases 17 July 2024] Access date: 06 September 2025.
2. Zhao, L. et al. Association between air pollution and cardiovascular mortality in China: a systematic review and meta-analysis. *Oncotarget* **8** (39), 66438 (2017).
3. Chagahi, M. H., Dashtaki, S. M., Moshiri, B. & Piran, M. J. Cardiovascular disease detection using a novel stack-based ensemble classifier with aggregation layer, DOWA operator, and feature transformation. *Computers Biology Med.* **173**, 108345 (2024).
4. (WHO) WHO. Cardiovascular diseases (CVDs) [Available from: https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds) -11 June 2021.] Access date: 29 September 2023.
5. Sharifi, M. H., Mirahmadizadeh, A., Hassanzadeh, J., Drissi, H. B. & Azarbakhsh, H. Mortality rate and years of life lost due to ischemic heart disease in Southern Iran between 2004 and 2019: A Population-Based study. *Arch. Iran. Med.* **27** (9), 494 (2024).
6. Sokoty, L., Rimaz, S., Hassanlouei, B., Kermani, M. & Janani, L. Short-term effects of air pollutants on hospitalization rate in patients with cardiovascular disease: a case-crossover study. *Environ. Sci. Pollution Res.* **28**, 26124–26131 (2021).
7. Niu, Z., Liu, F., Yu, H., Wu, S. & Xiang, H. Association between exposure to ambient air pollution and hospital admission, incidence, and mortality of stroke: an updated systematic review and meta-analysis of more than 23 million participants. *Environ. Health Prev. Med.* **26**, 1–14 (2021).
8. de Bont, J. et al. Ambient air pollution and cardiovascular diseases: an umbrella review of systematic reviews and meta-analyses. *J. Intern. Med.* **291** (6), 779–800 (2022).
9. Abbasi, M. T., Alesheikh, A. A., Jafari, A. & Lotfata, A. Spatial and Temporal patterns of urban air pollution in Tehran with a focus on PM2. 5 and associated pollutants. *Sci. Rep.* **14** (1), 25150 (2024).
10. Huang, G., Brown, P. & Shin, H. H. Multi-pollutant case-crossover models of all-cause and cause-specific mortality and hospital admissions by age group in 47 Canadian cities. *Environ. Res.* **225**, 115598 (2023).
11. de Bont, J., Krishna, B. & Stafoggia, M. Ambient air pollution and daily mortality in ten cities of India: a causal modelling study. *Lancet Planet. Health*. **8** (7), e433–e440 (2024).
12. Dashtaki, N. M. et al. The Lag-Effects of air pollutants and meteorological factors on COVID-19 infection transmission and severity: using machine learning techniques. *J. Res. Health Sci.* **24** (3), e00622 (2024).
13. Mohammadi Dashtaki, N., Fararouei, M., Mirahmadizadeh, A., Hoseini, M. & Heidarzadeh, M. A case-crossover study of air pollution exposure during pregnancy and the risk of stillbirth in Tehran, Iran. *Sci. Rep.* **15** (1), 257 (2025).
14. Gouveia, N. et al. Short-term associations between fine particulate air pollution and cardiovascular and respiratory mortality in 337 cities in Latin America. *Sci. Total Environ.* **920**, 171073 (2024).
15. Mahakalkar, A. U., Gianquintieri, L., Amici, L., Brovelli, M. A. & Caiani, E. G. Geospatial analysis of short-term exposure to air pollution and risk of cardiovascular diseases and mortality–A systematic review. *Chemosphere* :141495. (2024).
16. Saucy, A. et al. Mutual effects of fine particulate matter, nitrogen dioxide, and fireworks on cause-specific acute cardiovascular mortality: a case-crossover study in communities affected by aircraft noise. *Environ. Pollut.* **291**, 118066 (2021).
17. Demoury, C. et al. Impact of short-term exposure to air pollution on natural mortality and vulnerable populations: a multi-city case-crossover analysis in Belgium. *Environ. Health.* **23** (1), 11 (2024).
18. Fuller, R. et al. Pollution and health: a progress update. *Lancet Planet. Health*. **6** (6), e535–e47 (2022).
19. Dehghan, A., Khanjani, N., Bahrampour, A., Goudarzi, G. & Yunesian, M. The relation between air pollution and respiratory deaths in Tehran, Iran-using generalized additive models. *BMC Pulm. Med.* **18**, 1–9 (2018).
20. Karimi, B. & Shokrinezhad, B. Air pollution and the number of daily deaths due to respiratory causes in Tehran. *Atmos. Environ.* **246**, 118161 (2021).
21. Hosseini, V. & Shahbazi, H. Urban air pollution in Iran. *Iran. Stud.* **49** (6), 1029–1046 (2016).
22. Kawano, A., Kim, Y., Meas, M. & Sokal-Gutierrez, K. Association between satellite-detected tropospheric nitrogen dioxide and acute respiratory infections in children under age five in Senegal: spatio-temporal analysis. *BMC Public. Health*. **22** (1), 178 (2022).
23. Veefkind, J. P. et al. TROPOMI on the ESA Sentinel-5 precursor: A GMES mission for global observations of the atmospheric composition for climate, air quality and Ozone layer applications. *Remote Sens. Environ.* **120**, 70–83 (2012).
24. Filippini, T. et al. Satellite-detected tropospheric nitrogen dioxide and spread of SARS-CoV-2 infection in Northern Italy. *Sci. Total Environ.* **739**, 140278 (2020).
25. Ghasempour, F., Sekertekin, A. & Kutoglu, S. H. Google Earth engine based spatio-temporal analysis of air pollutants before and during the first wave COVID-19 outbreak over Turkey via remote sensing. *J. Clean. Prod.* **319**, 128599 (2021).
26. Wu, Y., Li, S. & Guo, Y. Space-time-stratified case-crossover design in environmental epidemiology study. *Health Data Sci.* **2021**, 9870798 (2021).
27. Tobias, A., Kim, Y. & Madaniyazi, L. Time-stratified case-crossover studies for aggregated data in environmental epidemiology: a tutorial. *Int. J. Epidemiol.* **53** (2), dyae020 (2024).
28. Hou, W. Effect and prediction of long-term weather and pollutant exposure on hemorrhagic fever with renal syndrome: based on statistical models. *Front. Public. Health*. **13**, 1393763 (2025).
29. Ren, Z. et al. Effect of ambient fine particulates (PM2. 5) on hospital admissions for respiratory and cardiovascular diseases in Wuhan, China. *Respir. Res.* **22** (1), 128 (2021).
30. Nyadanu, S. D., Tessema, G. A., Mullins, B. & Pereira, G. Maternal acute thermophysiological stress and stillbirth in Western Australia, 2000–2015: A space-time-stratified case-crossover analysis. *Sci. Total Environ.* **836**, 155750 (2022).
31. Chung, C. Y. et al. An investigation into the impact of variations of ambient air pollution and meteorological factors on lung cancer mortality in Yangtze river Delta. *Sci. Total Environ.* **779**, 146427 (2021).
32. Chen, Y., Hou, W. & Dong, J. Time series analyses based on the joint lagged effect analysis of pollution and meteorological factors of hemorrhagic fever with renal syndrome and the construction of prediction model. *PLoS Negl. Trop. Dis.* **17** (7), e0010806 (2023).
33. Yap, J. et al. Particulate air pollution on cardiovascular mortality in the tropics: impact on the elderly. *Environ. Health*. **18**, 1–9 (2019).
34. Nhung, N. T. T. et al. Exposure to air pollution and risk of hospitalization for cardiovascular diseases amongst Vietnamese adults: Case-crossover study. *Sci. Total Environ.* **703**, 134637 (2020).
35. Chen, Y., Hou, W., Hou, W. & Dong, J. Lagging effects and prediction of pollutants and their interaction modifiers on influenza in Northeastern China. *BMC Public. Health*. **23** (1), 1826 (2023).
36. Rashki, A., Middleton, N. J. & Goudie, A. S. Dust storms in Iran–Distribution, causes, frequencies and impacts. *Aeolian Res.* **48**, 100655 (2021).

37. Ghahremanlou, A. & Ghahremanlou, D. Identifying the causes of air pollution in the Tehran Metropolis-Iran and policy recommendations for sustainability. *Aerosol Sci. Eng.* :1–15. (2025).
38. Kim, H. et al. Cardiovascular effects of long-term exposure to air pollution: a population-based study with 900 845 person-years of follow-up. *J. Am. Heart Association.* **6** (11), e007170 (2017).
39. Liu, C. et al. Coarse particulate air pollution and daily mortality: a global study in 205 cities. *Am. J. Respiratory Crit. Care Med.* **206** (8), 999–1007 (2022).
40. Carugno, M. et al. Air pollution exposure, cause-specific deaths and hospitalizations in a highly polluted Italian region. *Environ. Res.* **147**, 415–424 (2016).
41. Guo, Y. et al. Time series analysis of ambient air pollution effects on daily mortality. *Environ. Sci. Pollution Res.* **24**, 20261–20272 (2017).
42. Dehbi, H-M. et al. Air pollution and cardiovascular mortality with over 25 years follow-up: A combined analysis of two British cohorts. *Environ. Int.* **99**, 275–281 (2017).
43. Hu, S. et al. Association of short-term exposure to ambient air pollution and temperature with bronchiectasis mortality: a nationwide time-stratified case-crossover study. *EBioMedicine* ;**110**. (2024).
44. Ma, Y. et al. Estimation of health risk and economic loss attributable to PM2. 5 and O3 pollution in Jilin Province, China. *Sci. Rep.* **13** (1), 17717 (2023).
45. Brook, R. D. et al. Particulate matter air pollution and cardiovascular disease: an update to the scientific statement from the American heart association. *Circulation* **121** (21), 2331–2378 (2010).
46. Van Donkelaar, A. et al. Global estimates of fine particulate matter using a combined geophysical-statistical method with information from satellites, models, and monitors. *Environ. Sci. Technol.* **50** (7), 3762–3772 (2016).



## Acknowledgements
We highly appreciate the contribution of the Ministry of Health to providing Mortality data. We also thank the National Meteorological Organization for providing us with meteorology data.


## Author contributions
N.MD: Conceptualization, Data Curation, Formal analysis, Investigation, Methodology, Software, Visualization, Writing - Original Draft, Writing - Review & EditingM.F: Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Validation, Writing - Review & EditingA.M: Conceptualization, Review & EditingM.H: Conceptualization, Review & Editing All authors reviewed the manuscript.

## Declarations

## Competing interests
The authors declare no competing interests.

## Additional information
**Correspondence** and requests for materials should be addressed to M.F.

**Reprints and permissions information** is available at www.nature.com/reprints.

**Publisher's note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.