Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Air pollution impact on the Covid-19 mortality in Iran considering the comorbidity (obesity, diabetes, and hypertension) correlations

Nima Norouzi a,*, Zahra Asadi b

a Bournemouth University, Fern Barrow, Poole, Dorset, BH12 5BB, UK
b Al-Ameen College of Pharmacy, Rajiv Gandhi University of Health Science (RGUHS), Bangalore, India

A R T I C L E   I N F O
Keywords:
SARS-CoV-2
Nitrogen oxides
Particulate matter
Air quality
Meteorological parameters

A B S T R A C T
Since the rise of the Covid-19 pandemic, several researchers stated the possibility of a positive relationship between Covid-19 spread and climatic parameters. An ecological study in 12 Iranian cities using the report of daily deaths from Covid-19 (March to August 2020) and validated data on air pollutants, considering average concentrations in each city in the last year used to analyze the association between chronic exposure to air pollutants and the death rate from Covid-19 in Iran. Poisson regression models were used, with generalized additive models and adjustment variables. A significant increase of 2.7% (CI95% 2.6–4.4) was found in the mortality rate due to Covid-19 due to an increase of 1 μg/m³ of NO₂. The results suggest an association between Covid-19 mortality and NO₂ exposure. As a risk approximation associated with air pollution, more precise analysis is done. The results also show a good consistency with studies from other regions; this paper’s results can be useful for the public health policymakers and decision-making to control the Covid-19 spread.

1. Introduction

On Dec 31, 2019, cases of pneumonia with unknown etiology were presented in the municipality of Wuhan, in the province of Hubei in China, and on Jan 9, 2020, the SARS-CoV-2 virus was identified as the causal agent of the Severe Acute Respiratory Syndrome (SARS) (Ken i et al., 2020). This virus belonging to the coronavirus family causes a new infectious disease (Covid-19), with rhinorrhea, sore throat, cough, fever, diarrhea, anosmia, and myalgia. Its most severe form manifests as pneumonia with dyspnea, disseminated coagulation, and eventually death (Adams, 2020). The virus is transmitted by respiratory droplets when an infected person coughs, speaks, sneezes, or directly contacts people carrying the virus or contaminated surfaces (Bashir et al., 2020).

Due to its potential for transmissibility, the SARS-CoV-2 virus managed to spread worldwide until reaching Iran, where the first case was confirmed on Mar 2, 2020; 180 days later, by Aug 31, 2020, the figure of 375,212 confirmed cases was reached (Iranian Statistics Organization). In Iran, the fatality rate for Covid-19 up to that date was 6.3%, almost 1.5 times higher than that registered in the rest of the world, of 4.2% with groups of greater vulnerability made up of people with some comorbidity such as hypertension, diabetes, cardiovascular diseases and diseases of the respiratory system (Bell et al., 2004), as well as the population over 60 years of age (Bontempi, 2020).

Several diverse pieces of research have been done to investigate essential parameters impacting the spread of SARS-CoV-2 disease to control the transmission of the COVID-19 pandemic. Many premier pieces of research have determined that person-to-person contact could enhance the danger of infection (Chen et al., 2020; Gilbert et al., 2020; Lu et al., 2020; Sohrabi et al., 2020; Kraemer et al., 2020). Besides these human-based factors mentioned by Kraemer (Xie and Zhu, 2020), Xie and Zhu (Ali et al., 2021) mentioned that the climate condition could also be a very important parameter in the Covid-19 spread. They mentioned that mean temperature increase was positively associated with newly confirmed Covid-19 cases. Also, in their results, they mentioned a 4.861% increase in the daily covid cases for each 1 °C rise in the mean temperature. Similarly, the World Health Organization (WHO) reported that in European and North American cities with high concentrations of nitrogen dioxide (NO₂), there is a decrease in lung function (Hendryx and Luo, 2020). All these results opened a discussion to the field of climatic parameters such as air quality impacts on the Covid-19 pandemic aspects. Several significant papers studied association between air quality and covid-19 pandemic. Conticini et al. (2020) investigated the correlation between the high level of Severe Acute Respiratory Syndrome CoronaVirus 2 (SARS-CoV-2) lethality and the
atmospheric pollution in Northern Italy. They concluded that the high level of pollution in Northern Italy should be considered an additional co-factor of the high level of lethality recorded in that area. Cole et al. (2020) estimated the relationship between long term air pollution exposure and Covid-19 in 355 municipalities in the Netherlands. Using detailed data they found compelling evidence of a positive relationship between air pollution, and particularly PM$_{2.5}$ concentrations, and Covid-19 cases, hospital admissions and deaths. Setti et al. (2020) presented a position paper proposing a research hypothesis concerning the association between higher mortality rates due to COVID-19 observed in Northern Italy and average concentrations of PM$_{10}$ exceeding a daily limit of 50 µg/m$^3$. Barnett-Izhaki and Levi (2021) examined the association between populations’ exposure to air pollution and the morbidity and mortality rates from COVID-19. According to their results and comparison with previously published studies, it appears that long-term exposure to air pollutants concentrations exceeding WHO guidelines, such as PM$_{2.5}$ and NO$_x$, might exaggerate morbidity and mortality rates from COVID-19. These results should raise a red flag globally among decision makers about the urgent need to reduce air pollution and its harmful effects. Jiang and Xu (2020) used the Pearson and Poisson regression models accordingly to understand the association between COVID-19 deaths and each risk factor. The results suggested that PM$_{2.5}$ and diurnal temperature range are tightly associated with increased COVID-19 deaths. Also Stieb et al. (2020) observed a positive association between COVID-19 incidence and long-term PM$_{2.5}$ exposure in Canadian health regions. Another study by Wu et al. (2020) also found that higher historical PM$_{2.5}$ exposures are positively associated with higher county-level COVID-19 mortality rates after accounting for many area-level confounders. Yao et al., 2020a, 2020b explored the temporal correlation between the case fatality rate (CFR) of COVID-19 and particulate matter (PM) in Wuhan. They observed a higher CFR of COVID-19 with increasing concentrations of inhalable particulate matter (PM) with an aerodynamic diameter of 10 µm or less (PM10) and fine PM with an aerodynamic diameter of 2.5 µm or less (PM2.5) in the temporal scale. Zoran et al., 2020a, 2020b investigates the correlation between the high level of coronavirus SARS-CoV-2 infection accelerated transmission and lethality, and surface air pollution in Milan metropolitan area, Lombardy region in Italy. The results show positive correlation of daily averaged O3, PM2.5 and PM10 with air temperature and inversely correlations with relative humidity and precipitation rates. Nearly all these paper concluded a significant association between air pollution and Covid-19 pandemic transition or mortality rate. This conclusion is also considered by two important reviews done by Marquès et al. (Marquès and Domingo, 2021; Marquès et al., 2021) in which they state: “Taking together the previous results and those of most investigations now reviewed, we have concluded that there is a significant association between chronic exposure to various outdoor air pollutants: PM$_{2.5}$, PM$_{10}$, O$_3$, NO$_2$, SO$_2$ and CO, and the incidence/risk of COVID-19 cases, as well as the severity/mortality of the disease” and with this statement concluded from a literature review of hundreds of papers in this field a firm confirmation of this theory is made in this papers. Considering the previous studies have found a relationship between exposure to air pollutants and increased mortality and morbidity from Covid-19 (Coker et al., 2020). However, it is unknown whether these impacts are similar in the different regions of the world, making it necessary to carry out specific analyses by country and city (Iqair ranking (2021) and ava, 2021). Iranian cities have higher levels of pollutants than other cities, such as Europe and North America (Safar-i-Faramani et al., 2019). On the other hand, the Iranian population has high prevalences of comorbidities such as diabetes and hypertension that should be considered in studies on exposure to pollutants and Covid-19 (Contini and Costabile, 2020). The role that chronic exposure to air pollutants plays in increasing the risk of bacterial and respiratory infections is known. The chronic inflammation they produce, added to the immune response effect, explains this effect. During the influenza pandemic, it was observed that the most polluted cities had higher incidence rates (Deek, 2020). However, no large-scale and reliable study on this field was done in Iran; a limited number of researchers considered this issue. Ali & Islam (Ali and Islam, 2020) stated that available data also indicate that exposure to air pollution may influence COVID-19 transmission. Faridi et al. (2020) found a significant association between Coronavirus disease (COVID-19) lethality and exposure to ambient air pollution, the rise in airborne PM2.5 during this outbreak may increase the mortality rate of SARS-CoV-2 in the city of Tehran. Khorsandi et al., 2021a, 2021b concluded that the short-term exposure to air pollution (especially O3) may increase the population’s susceptibility infected with COVID-19 and, therefore, increase hospital admissions and mortality rates even during the warm seasons.

It is estimated that outdoor air pollution, mainly by fine particulate matter (PM$_{2.5}$), leads to 3.3 million premature deaths per year globally (Domingo and Bosira, 2020). Furthermore, it is recognized that the potential of these particles to generate a toxic effect depends on factors such as frequency and duration of exposure, in addition to their composition (Fattorini and Regoli, 2020). Various epidemiological studies, systematic reviews, and meta-analyses have associated chronic exposure to PM$_{2.5}$ and PM$_{10}$ with conditions such as ischemic heart disease (Frontera et al., 2020), cerebrovascular disease (Nouri et al., 2021), lower respiratory tract infections, chronic obstructive pulmonary disease, lung cancer (Cole et al., 2020), and type 2 diabetes in the case of PM$_{2.5}$. In the same way, the acute effects of these particles have been reported (Khorsandi et al., 2021a; Iranian meteorological organization). As the review of the early literature shows, no comprehensive research is done for the Iranian case. This study is aimed to study the relationship between concentrations of three pollutants with major healthcare impacts (PM$_{2.5}$, PM$_{10}$, and NO2) and daily confirmed COVID-19 cases and mortality in 12 Iranian cities to supply useful implications for the control and prevention of this novel coronavirus disease. These cities were selected to cover all minor climate conditions of the country, which can be a main solidification point for the results of this paper with correcting the climate impact on the results, which is not considered in the previous researches.

2. Material and methods

An ecological study with retrospective analysis was carried out from Mar 1, 2019 to Aug 31, 2020, in 12 Iranian cities: Tehran, Tabriz, Isfahan, Shiraz, Mashhad, Ahvaz, Karaj, Yazd, Kermanshah, Bandar-Abbas, Zahedan, and Rasht. The inclusion criteria were that these cities had a continuous air quality monitoring system and sufficient and validated data to estimate exposure and confirmed mortality cases from SARS-CoV-2 in the period study. Also, one of the other main reasons was their diverse climate characteristics to validate the research samples. And the study period was only limited to access to reliable data (see Fig. 1).

Data collection, processing Air quality, the data on suspended particles (PM$_{10}$ and PM$_{2.5}$) and nitrogen dioxide (NO2) were obtained from the National Air Quality Information System (Iranian meteorological organization). Also, the results of monitoring stations in all cities were only included in the processing data after being validated under sufficiency (data of at least two of the pollutants be available) and consistency (data be gathered in at least two-thirds of each month) standards. After validating the gathered data, the data preparation process was implemented and prepared for further study stages.
The daily data of cases and the percentage of them with some comorbidity (obesity, diabetes, and hypertension) were obtained from the database of the official coronavirus site enabled by the Ministry of Health (Food and Drug association). Next, the cumulative confirmed cases and mortality rates per 100,000 inhabitants for the analysis period were estimated to be used in the data analysis.

The information on the prevalence of comorbidities in the general population was obtained from the National Survey of Nutrition and Health databases in the reports of the years 2020 and 2021 (Bajgain et al., 2021). The report’s number of people classified with diabetes and hypertension was divided by the total number of respondents for each city for the prevalence of comorbidities. For the prevalence of obesity, the body mass index (BMI) was used, and the population was classified according to international standards, considering the value of BMI $\geq 30$ as obesity.

The investigation resolution for all parameters is on a daily scale. However, the air quality and comorbidities investigation period is 365 days longer (545 days) than the Covid-19 data investigation period (180 days). The difference between observations of covid-19 cases and the other cases and data observations is due to studying the historical trend of other parameters. This extended investigation period shows the natural trend of air pollution in comorbidity cases, which by neutralizing this natural trend from the post-Covid-19 trend, more accurate results can be obtained.

This study consists of three main stages (as shown in Fig. 2). The first stage is data gathering, in which the needed data is gathered from accessible sources in the Iranian health system and Air quality control datasets. Then a data preparation and classification process are done. In this process, the data is made ready for processing and analysis. Also, age classification and then a Comorbidity classification is done in this stage. Four age categories are used in this paper, Children (Under 18), Adulthood (18–35), Middle Age (35–55), and Elderly (Above 55). Considering these categories, observations are first classified under each class, and then the comorbidity classification is implemented (with three classes of Hypertension, Diabetes, and Obesity) (Bajgain et al., 2021; Asadi and Norouzi, 2021). A correlative analysis is implemented on the results of these classifications to determine the impact of each parameter on the Covid-19 and air pollution impact on each of these parameters. This strategy estimates the indirect impact of the air quality on the Covid-19 mortality and infected cases (see Table 1 and Table 1A).

Then in the third stage, an ecological analysis was carried out in three steps. First, the distribution, measures of central tendency, and correlation of the information in each city were estimated and observed. Then, using simple bivariate Poisson regression, the implicit risk of the association between mortality and air quality (PM and NO$_2$) was independently explored. Finally, a Poisson multivariate association model was developed, with robust variance adjustment, including available adjustment covariates (prevalence of hypertension, diabetes, obesity, and days elapsed after the first case); the statistical model assumes that the data of the dependent variable Y (cases) follows a Poisson distribution of the form (Coker et al., 2020):

$$Pr(y|\mu) = \frac{e^{-\mu} \mu^y}{y!} \text{ for } y = 0, 1, 2, \ldots$$

where $\mu$ is the occurrence rate or the expected number of times, an event will occur in a period, and $y$ is a random variable indicating the number of times an event occurred (cases). Sometimes the event will occur fewer times than the average rate or will not occur at all, and other times it will occur more frequently. The relationship between the expected count ($\mu$) and the probability of examining any observed count ($y$) is specified by the Poisson distribution (Ali and Islam, 2020). The Wald test was used to measure the level of significance of each coefficient, and both in simple and multivariate regressions were with a significance level of 5% in the described model. The analysis was performed with Eviews software version 10.1.
3. Results and discussion

3.1. Analysis and results

During the period considered, the average of PM$_{10}$ was 45.4 μg/m$^3$ and that of PM$_{2.5}$ was 19.5 μg/m$^3$ in the 12 cities included; Kermanshah presented the minimum concentration of PM$_{2.5}$ (7.5 μg/m$^3$) and Tehran the maximum with 38.4 μg/m$^3$. Concerning NO$_2$, a minimum concentration of 7.9 μg/m$^3$ were recorded in Zahedan, a maximum of 45.3 μg/m$^3$ in Tehran, and an average of 26.03 μg/m$^3$ (Tables 1 and 2).

In the cities considered, the estimated prevalence of hypertensive patients was 24.3% of the general population and 18.44% in the confirmed cases of Covid-19. The prevalence of diabetes was 13.17% in the general population and 16.12% in the cases of Covid-19. Likewise, the prevalence of obesity in the general population of these cities was 51.02% and 27.3% in the cases of Covid-19 (Table 1).

Tehran presented the highest number of confirmed cases (73,080) and deaths (5,580) from Covid-19. The lowest mortality and fatality rates were registered in Kermanshah in this same period, while the highest mortality rate was registered in Ahvaz. In that period, the national mortality rate ratio was 1.29. The mortality rate ratio shows that Isfahan, Karaj, Tehran, and Mashhad present a mortality rate higher than the national average (Table 2).

The statistical model results indicate an association between NO$_2$ concentrations and an increase with the IRR$_{NO2}$ mortality rate in which the incidence risk rate of NO$_2$ (IRR$_{NO2}$) impact on the Covid-19 mortality rate is estimated at 1.051 (IC(95%) 1.031–1.068). Furthermore, the comorbidities of diabetes and obesity were also significant. The results of PM$_{2.5}$ indicate an incidence risk rate for mortality of 1.024; however, it is classified as not significant according to results (IC(95%) 0.992–1.045) (Table 3). Also, the PM$_{10}$ was excluded from the models due to an insignificant direct association with the mortality rate from Covid-19.

3.2. Discussion

In this study, it was found that there is an association between chronic concentrations of air pollutants and an increase in mortality rates from Covid-19. According to the results presented, NO$_2$ concentrations are those that contribute most significantly to this association. These results are similar to those found in other studies (Zoran et al., 2020b; Marques and Domingo, 2021). In studies of chronic exposure and controlled by covariates, a significant association similar to that of the present study, between mortality due to Covid-19 and levels of NO$_2$ were found; and reported an increase of 1 μg/m$^3$ in the long-term average of NO$_2$ is significantly associated with a 2.5% increase in mortality from Covid-19 (Zoran et al., 2020a). As in this study, these authors found that the increase in PM$_{2.5}$ was not a significant predictor of Covid-19 mortality, although it was a significant predictor of the number of cases (12% increase in cases per 1 μg/m$^3$ increase) (Yao et al., 2020b). Similarly, other researchers found a significant association between NO$_2$ levels and fatality and mortality rates from Covid-19, as well as a marginal association between exposure to PM$_{2.5}$ and the mortality rate; they report an increase of 11.3 and 16%, respectively, due to an increase in...
Mean concentration of air pollution and mortality rate by city, from Mar 1, 2019 to Aug 31, 2020 (for 12 mentioned cities).

| Variable | Observations | Mean | Std.Dev. | Min | Max |
|----------|--------------|------|----------|-----|-----|
| X1 PM2.5 (µg/m³) | 6540 | 45.4 | 10.7 | 26.9 | 65.1 |
| X2 PM10 (µg/m³) | 6540 | 19.5 | 7.0 | 7.4 | 38.4 |
| X3 NO₂ (µg/m³) | 6540 | 26.3 | 11.7 | 8.0 | 47.8 |
| X4 NO₂ (ppm) | 6540 | – | – | 0.004 | 0.144 |
| X5 Covid-19 Confirmed Cases | 2160 | 1953.0 | 352.9 | 584.0 | 3574.0 |
| X6 Covid-19 Death Cases | 2160 | 143.0 | 11.7 | 126.0 | 179.0 |
| X7 Hypertension (%) | 6540 | 24.3 | 9.7 | 11.8 | 52.8 |
| X8 Diabetes (%) | 6540 | 13.2 | 5.1 | 5.1 | 24.1 |
| X9 Obesity (%) | 6540 | 51.0 | 10.8 | 42.9 | 63.2 |
| X10 Hypertension in confirmed cases of Covid-19 (%) | 2160 | 18.4 | 6.0 | 7.1 | 35.0 |
| X11 Diabetes in Covid-19 cases (%) | 2160 | 18.4 | 6.0 | 7.1 | 35.0 |
| X12 Obesity in Covid-19 cases (%) | 2160 | 273.3 | 5.9 | 17.8 | 37.5 |
| X13 Elderly with diabetes (%) | 6540 | 54.1 | 1.3 | 45.3 | 60.3 |
| X14 Adults with diabetes (%) | 6540 | 4.2 | 1.9 | 4.0 | 11.0 |
| X15 Middle ages with diabetes (%) | 6540 | 40.6 | 2.8 | 39.9 | 46.9 |
| X16 Children with diabetes (%) | 6540 | 1.1 | 0.7 | 1.0 | 1.8 |
| X17 Elderly with obesity (%) | 6540 | 33.2 | 1.9 | 24.3 | 38.7 |
| X18 Adults with obesity (%) | 6540 | 37.8 | 1.5 | 29.4 | 42.6 |
| X19 Middle ages with obesity (%) | 6540 | 45.2 | 2.8 | 37.1 | 48.6 |
| X20 Children with obesity (%) | 6540 | 19.1 | 1.9 | 7.3 | 21.2 |
| X21 Elderly with hypertension (%) | 6540 | 42.2 | 3.5 | 33.5 | 42.5 |
| X22 Adults with hypertension (%) | 6540 | 4.3 | 1.3 | 2.4 | 5.4 |
| X23 Middle ages with hypertension (%) | 6540 | 22.3 | 2.3 | 14.0 | 23.4 |
| X24 Children with hypertension (%) | 6540 | 1.1 | 0.9 | 0.6 | 3.4 |
| X25 Elderly Covid cases (%) | 2160 | 22.2 | 3.4 | 21.8 | 25.5 |
| X26 Adults Covid cases (%) | 2160 | 29.9 | 3.6 | 29.4 | 35.1 |
| X27 Middle ages Covid cases (%) | 2160 | 17.6 | 3.5 | 17.3 | 22.7 |
| X28 Children Covid cases (%) | 2160 | 4.8 | 1.1 | 4.4 | 7.4 |
| X29 Elderly Covid mortality (%) | 6540 | 13.1 | 2.8 | 12.5 | 16.2 |
| X30 Adults Covid mortality (%) | 6540 | 0.5 | 0.1 | 0.4 | 0.6 |
| X31 Middle ages Covid mortality (%) | 6540 | 1.4 | 0.5 | 0.9 | 1.9 |
| X32 Children Covid mortality (%) | 2160 | 0.4 | 0.3 | 0.3 | 1.0 |

* Observations are reported based on the total data for each parameter. As an example, 2160 data in Covid-19 confirmed cases is equal to covid cases of 12 cities × 180 days of the investigation period (=2160) or 6540 data in hypertension is equal to hypertension cases in 12 cities × 545 days (a year before first Covid-19 case and start of covid-19 investigation period) of the investigation period (=6540).

* The difference between observations of covid-19 cases and the other cases and data observations is due to studying the historical trend of other parameters. This extended investigation period shows the natural trend of air pollution in comorbidity cases, which by neutralizing this natural trend from the post-Covid-19 trend, more accurate results can be obtained.

Our results also indicate an increase (although not significant) in mortality from Covid-19 per unit increase in the concentration of PM₁₀ and PM₂.₅. In other studies, this association was significant, and an 8% increase in the mortality rate for each µg/m³ of PM₂.₅ was found (Iqair ranking (2021) and ava, 2021). Other researchers in the same field found a significant association between mortality rate and PM₂.₅, but specifically due to diesel particulate matter (Conticini et al., 2020); likewise, an increase in the probability of dying from Covid-19 of 0.43% for each unit of increase in PM₂.₅, equivalent to a 3.3% increase in the mortality rate from each 1 µg/m³ of PM₂.₅ (Wu et al., 2020). Similarly, a significant association between fatality from Covid-19 and PM₂.₅ and PM₁₀ was found (Marqués et al., 2021).

Table 2: Mean concentration of air pollution and mortality rate by city, from Mar 1, 2019 to Aug 31, 2020

| City               | Population | PM₂.₅ (µg/m³) | PM₁₀ (µg/m³) | NO₂ (µg/m³) | Cases | Deaths | Mortality rate (per 100,000 inhabitants) | Mortality rate ratio |
|--------------------|------------|---------------|--------------|-------------|-------|--------|-----------------------------------------|---------------------|
| Tehran             | 9,135,000  | 38.4          | 36.7         | 45.3        | 73,080| 5580   | 56.7                                    | 2.7                 |
| Tabriz             | 1,558,603  | 19.7          | 18.8         | 23.2        | 37402.3| 2855.8| 29.9                                    | 1.4                 |
| Isfahan            | 2,132,000  | 26.9          | 25.7         | 31.7        | 51,156| 3906   | 39.7                                    | 1.9                 |
| Yazd               | 529,673    | 15.4          | 14.7         | 18.1        | 29,232| 2232   | 22.7                                    | 1.1                 |
| Shiraz             | 1,565,572  | 19.2          | 18.4         | 22.7        | 36,540| 2790   | 28.3                                    | 1.3                 |
| Mashhad            | 3,208,000  | 28.8          | 27.5         | 34          | 54,810| 4185   | 42.5                                    | 2.2                 |
| Ahvaz              | 1,244,000  | 15.7          | 25.7         | 18.6        | 29962.8| 2287.8| 23.2                                    | 1.1                 |
| Karaj              | 1,592,492  | 20            | 19.1         | 23.6        | 38001.6| 2901.6| 29.5                                    | 1.4                 |
| Kermanshah        | 1,026,000  | 17.3          | 16.5         | 20.4        | 32,886| 2511   | 25.5                                    | 1.2                 |
| Bandar Abbas       | 526,648    | 12.7          | 12.1         | 14.9        | 24116.4| 1841.4| 18.7                                    | 0.9                 |
| Zahedan            | 610,000    | 13.4          | 12.8         | 15.9        | 25,578| 1953   | 19.8                                    | 0.9                 |
| Rashtr             | 713,000    | 18.4          | 8.1          | 21.7        | 35078.4| 2678.4| 27.2                                    | 1.3                 |
Environmental Research 204 (2022) 112020
5

Table 3
Mean relative risk for mortality from Covid-19 per unit of increase in the concentration of PM$_{2.5}$ and NO$_2$ during the period from Mar 1, 2019, to Aug 31, 2020.*

| Variable | Incidence risk rate (IRR) (%) | P-value | 95% CI |
|----------|-------------------------------|---------|--------|
| PM$_{2.5}$ (μg/m$^3$) | 1.024 (1.5) | 0.092 | 0.992 | 1.045 |
| NO$_2$ (μg/m$^3$) | 1.051 (2.7) | 0.000 | 1.031 | 1.068 |
| Days (from first case) | 1.015 (1.4) | 0.002 | 1.009 | 1.024 |
| Hypertension (%) | 0.893 (0.5) | 0.669 | 0.872 | 1.011 |
| Diabetes (%) | 1.079 (4.2) | 0.012 | 1.046 | 1.089 |
| Obesity case (%) | 1.066 (5.4) | 0.017 | 1.019 | 1.098 |

*Poisson multivariate model, adjusted for two pollutants and comorbidities.

PM$_{10}$ particles concentrations was found in other studies (Setti et al., 2020; Fattorini and Regoli, 2020).

Regarding acute exposure studies, the author(s) concluded that NO2 is one of the key elements for developing Covid-19 and ozone and respiratory particles (Domingo and Rovira, 2020). Finally, another study, which considered the levels of contamination of CO, NO$_2$, SO$_2$, O$_3$, PM$_{10}$, and PM$_{2.5}$ in the air and the number of cases and deaths from Covid-19, found a statistically significant correlation between concentrations of CO, O$_3$ and PM$_{2.5}$ and the number of cases and deaths from Covid-19 (Khorsandi et al., 2021a). However, unlike the present work, it has the limitations of being a correlation study without adjusting covariates. A possible explanation for the variation in the results related to respirable particles between the studies is their composition, which can vary from city to city and modifies their toxic effects (Faridi et al., 2020). In the present analysis, NO$_2$ was found to contribute significantly to the risk of mortality. NO$_2$ is released into the environment due to incomplete combustion in vehicle engines, coal, oil, and natural gas combustion processes. As is known, exposure to this pollutant is related to an increased risk of mortality from respiratory and heart conditions (Monttazmanesh et al., 2020), mainly in highly populated cities with high industrial and vehicular activity (Deek, 2020; Ali and Islam, 2020).

The toxicological basis that explains these effects is because chronic exposure to NO$_2$ generates alterations in the respiratory and immune system since the airways and the inflammatory response are compromised, which facilitates the presence of complications in the event of infections by Covid-19 (Domingo and Rovira, 2020). Specifically, persistent exposure to NO$_2$ can cause lung changes, including alveolar hyperplasia, increased fibrin, and accumulation of inflammatory cells in the alveoli. Within the pathophysiology of Covid-19, these factors contribute to the “Cytokine storm” phenomenon that generates severe complications of the disease. Furthermore, it is recognized that NO$_2$ contributes to the decrease in oxygen saturation since, when combined with the hemoglobin, it produces Methemoglobin or Nitrosomyoglobin (Yao et al., 2020b).

In the multivariate model, the prevalence of obesity and diabetes was included as factors contributing to the risk of worsening Covid-19; both diseases were associated with increased mortality rates. Adjustment for comorbidities (hypertension, type 2 diabetes mellitus, and obesity) was explored in models with the prevalence of the general population and models with the prevalence of confirmed cases; the results of both versions of the analysis were similar in statistical significance and order of magnitude. Among the limitations in this study is the length of the time series that includes only the warm seasons in the country and the lack of adjustment for other confusing variables, such as the transmission rate and accessibility to medical services. Other factors that may influence this association include socio-economic variables, for example, in economic crises. On the time series, the averages of pollutants were obtained considering 18 months with daily measurements. This period is similar to other studies that used more than one year to estimate exposure; others used shorter periods (Domingo and Rovira, 2020). However, it is considered that the period contemplated is sufficient to have an estimate of the chronic exposure to the included pollutants, especially if it is taken into account that during the last five years, the concentrations have not changed significantly in the cities considered (Yao et al., 2020a).

Regarding other unmeasured variables, it can be said that the situation was the same for all cities, so it is considered that in any case, the effect is underestimated. It is recommended that later studies include sociodemographic variables more specifically and conduct studies with better geographic resolution.

Also, the results show a direct impact of NO$_2$ concentration in the atmosphere on the Covid-19 mortality rate. Results of age classification in Table 4 show that the age classes vulnerable to the lower air quality are at a higher risk of disease or even mortality with decreased air quality. Results showed that the Elderly (with 3.10%) and Children (with 2.90%) have the greatest vulnerability toward the air quality effect on the Covid-19 mortality rate, and Middle age and Adults showed the least vulnerability (Marquès and Domingo, 2021; Marquès et al., 2021).

4. Conclusion

An ecological study in 12 Iranian cities is done using the report of daily deaths from Covid-19 (March to August 2020) and validated daily data on air pollutants, considering average daily concentrations in each city in the last year to study the possible association of the Covid-19 mortality rate and Air quality. A Poisson regression model with generalized additive methods and adjustment variables is used to analyze the possibility and intensity of this assumed relationship. This paper showed that the NO2 atmospheric concentration is significantly associated with the increased mortality rate of Covid-19, even adjusting for comorbidities. These results were aligned and confirmed by most of the similar studies in the literature, and it is observed that improved air quality could reduce the risk of mortality of Covid-19. Also, it is recommended that the socio-economic parameters (i.e., level of education, economic status, social class, etc.) be considered a classification parameter since it might impact the covid-19 mortality rate.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A

Table 4
The direct and indirect impact of the air quality on the Covid-19 mortality rate in different age classes.

| Air Quality | Elderly | Middle Age | Adulthood | Children |
|-------------|---------|------------|-----------|----------|
|             | Direct  | Indirect   | Direct    | Indirect | Direct  | Indirect   | Direct    | Indirect |
| Covid-19 mortality rate | NO$_2$ | 3.10% | 2.04% | 2.80% | 1.85% | 2.10% | 1.42% | 2.90% | 1.97% |
| PM$_{2.5}$ | insignificant | 2.10% | insignificant | 1.91% | insignificant | 1.47% | insignificant | 2.04% |
| PM$_{10}$  | insignificant | 1.92% | insignificant | 1.75% | insignificant | 1.35% | insignificant | 1.88% |
| X1 | X2 | X3 | X4 | X5 | X6 | X7 | X8 | X9 | X10 | X11 | X12 | X13 | X14 | X15 | X16 | X17 | X18 | X19 | X20 | X21 | X22 | X23 | X24 | X25 | X26 | X27 | X28 | X29 | X30 | X31 | X32 |
|----|----|----|----|----|----|----|----|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| 1  |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| 0  | 1  |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| 0  | 0  | 0  | 1  |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| 0.11| 0.03| 0.58| 0.58| 1  |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| 0.13 | 0.19| 0.89| 0.89| 1  | 1  |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| 0.21 | 0.57| 0.69| 0.69| 0.55| 0.88| 1  |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| 0.19 | 0.54| 0.92| 0.92| 0.74| 0.76| 0.84| 1  |    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| 0.34 | 0.39| 0.67| 0.67| 0.94| 0.84| 0.58| 0.91| 1  |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| 0.92 | 0.78| 0.79| 0.79| 0.45| 0.67| 0.55| 0.82| 0.91| 1  |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| 0.66 | 0.65| 0.47| 0.47| 0.93| 0.76| 0.95| 0.52| 0.19 | 0.22| 1  |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |

Table 1A
Correlative analysis of study variables
Gilbert, M., Pullano, G., Pinotti, F., Valdano, E., Poletto, C., Hendryx, M., Luo, J., 2020. COVID-19 prevalence and fatality rates in association with severe air pollution levels in the Covid-19 epidemic in China. Science 368 (6490), 493–497.

Lu, H., Stratton, C.W., Tang, Y.W., 2020. Outbreak of pneumonia of unknown etiology in Wuhan, China: the mystery and the miracle. J. Med. Virol. 92 (4), 401.

Marques, M., Domingo, J.L., 2021. Positive association between outdoor air pollution and the incidence and severity of COVID-19. A review of the recent scientific evidences. Environ. Res. 111930.

Marques, M., Rovira, J., Nadal, M., Domingo, J.L., 2021. Effects of air pollution on the potential transmission and mortality of COVID-19: a preliminary case-study in Tarragona Province (Catalonia, Spain). Environ. Res. 192, 110015.

Mostamansesh, S., Shoebi, P., Hanaei, S., Mahmoud-Elsayed, H., Dalvi, B., Malakan Rad, E., 2020. Cardiovascular disease in COVID-19: a systematic review and meta-analysis of 10,898 patients and proposal of a triage risk stratification tool. Egypt. Heart J. 72 (1), 1–17. https://doi.org/10.1016/j.ehyj.2020.00705-x.

Nouri, Z., Norouzi, N., Norouzi, N., Ataei, E., Azizi, S., 2021. Virologic microparticle fluid mechanics simulation: COVID-19 transmission inside an elevator space. Int. J. Comput. Mater. Sci. Eng. 2150007.

Safari-Faramani, R., Rajati, F., Tavakol, K., Hamzeh, B., Pasdar, Y., Moradinazar, M., Najafi, F., 2019. Prevalence, awareness, treatment, control, and the associated factors of diabetes in an Iranian Kurdish population. J. Diabetes Res. 2019.

Setti, L., Passarini, F., De Genaro, G., Barbieri, P., Licen, S., Perrone, M.G., Miani, A., 2020. Potential role of particulate matter in the spreading of COVID-19 in Northern Italy: first observational study based on initial epidemic diffusion. BMJ open 10 (9), e029143.

Sohrabi, C., Alaei, Z., O’Neill, N., Khan, M., Kerwan, A., Al-Jabir, A., Agba, R., 2020. World Health Organization declares global emergency: a review of the 2019 novel coronavirus COVID-19. Int. J. Surg. 76, 71–76.

Stiel, D.M., Evans, G.J., To, T.M., Brook, J.R., Burnett, R.T., 2020. An ecological analysis of long-term exposure to PM2.5 and incidence of COVID-19 in Canadian health regions. Environ. Res. 191, 110052. https://doi.org/10.1016/j.envres.2020.110052.

Wu, X., Nethery, R.C., Sabath, M.B., Braun, D., Dominici, F., 2020. Air pollution and COVID-19 mortality in the United States: strengths and limitations of an ecological regression analysis. Sci. Adv. 6 (45), eabd4049. https://doi.org/10.1126/sciadv.abd4049.

Xie, J., Zhu, Y., 2020. Association between ambient temperature and COVID-19 infection in 122 cities from China. Sci. Total Environ. 744, 138201.

Yao, Y., Pan, J., Liu, Z., Meng, X., Wang, K., Han, H., Wang, W., 2020a. Temporal association between particulate matter pollution and case fatality rate of COVID-19 in Wuhan. Environ. Res. 189, 109941. https://doi.org/10.1016/j.envres.2020.109941.

Yao, Y., Pan, J., Wang, W., Liu, Z., Han, H., Qiu, Y., Meng, X., Wang, W., 2020b. Association of particulate matter pollution and case fatality rate of COVID-19 in 49 Chinese cities. Sci. Total Environ. 741, 140396. https://doi.org/10.1016/j.scitotenv.2020.140396.

Zoran, M.A., Savastru, R.S., Savastru, D.M., Tastan, M.N., 2020a. Assessing the relationship between ground levels of ozone (O3) and nitrogen dioxide (NO2) with coronavirus (COVID-19) in Milan, Italy. Sci. Total Environ. 740, 140005.

Zoran, M.A., Savastru, R.S., Savastru, D.M., Tastan, M.N., 2020b. Assessing the relationship between surface levels of PM2.5 and PM10 particulate matter impact on COVID-19 in Milan, Italy. Sci. Total Environ. 738, 119825. https://doi.org/10.1016/j.scitotenv.2020.119825.