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The Relationship Between Short-Term and Long-Term Effects of Air Pollution on Stroke Morbidity in Arak, Iran: Time Series Zero-Inflated Negative Binomial Regression

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Abstract

Background: Stroke, a leading cause of mortality and disability worldwide, is influenced by both non-modifiable and modifiable risk factors, including air pollution. Arak, Iran, is one of the country's most industrialized and polluted cities. This study investigates the association between short-term and long-term exposure to major air pollutants—$PM_{2.5}$, PM_{10}, O_3, SO_2, and NO_2—and stroke morbidity.

Methods: This prospective cohort study included all stroke patients registered in Arak between 2019 and 2022. Air pollutant concentrations were obtained from four monitoring stations, with short-term exposures defined as 1 week, 1 month, 3 months, and 6 months, and long-term exposures as 9, 12, 18, and 24 months. Data were analyzed using a time-series zero-inflated negative binomial regression model, adjusting for confounders including smoking and opium use.

Results: Short-term (3-month) exposure to NO_2, O_3, and SO_2 was significantly associated with increased stroke incidence, while short-term (1-week) exposure to these pollutants showed a negative association. PM_{10} and O_3 (6 months) and SO_2 (1–3 months) also demonstrated significant associations. Long-term (2-year) exposure to PM_{10}, NO_2, and SO_2 was strongly associated with stroke morbidity, whereas O_3 exposure showed an inverse relationship. $PM_{2.5}$ was not significantly associated in the short term but showed a positive, though nonsignificant, association in the long term.

Conclusion: Both short-term and long-term exposure to certain air pollutants are associated with stroke morbidity, with varying effects by pollutant and lag period. Reducing chronic exposure to PM_{10}, NO_2, and SO_2 may help lower the incidence of stroke in high-pollution settings.

Keywords: Air pollution, Stroke, Epidemiology, Morbidity, Arak

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Introduction

A stroke, caused by artery occlusion, stenosis, or rupture, is characterized by an acute disorder of cerebral blood circulation. Stroke is categorized into two subtypes, including ischemic and hemorrhagic, which differ in both etiology and risk factors (1,2). Stroke is a major cause of death and one of the leading causes of long-term severe disability in both developed and developing countries, accounting for nearly 6 million deaths (approximately 11% of all global deaths) and 132 million disability-adjusted life years lost in 2017 (2–4).

Even though various effective prevention strategies have been implemented in recent years, the incidence of stroke is still rising, especially in low- and middle-income countries, due to multiple factors such as lifestyle change, population aging, etc. (4). The risk factors of stroke are generally classified into two main parts: non-modifiable factors (e.g., age and race) and modifiable ones (e.g., air pollution, diabetes, and hypertension). Among those modifiable factors, air pollution, as one of the major

environmental problems, has been considered by a lot of researchers (1,5,6). Therefore, it is of public health significance to investigate air pollution to reach a better understanding of the relationship between air pollution and stroke, and hence to develop intervention measures and environmental policies (5).

Air pollution is a complex association of several components consisting of particulate matter (PM), ozone (O_3), sulfur dioxide (SO_2), nitrogen monoxide (NO), nitrogen dioxide (NO_2), and carbon monoxide (CO) produced by different sources. In recent years, these pollutants have attracted wide public attention due to their impact on public health and air quality (7,8). Air pollution has great effects on biological mechanisms such as systemic inflammation, apoptosis, and DNA damage through the production of reactive oxygen species and oxidative stress (7,9,10). Therefore, exposure to air pollution is one of the leading causes of mortality and morbidity, contributing to 6.5 million deaths and 167.3 million disability-adjusted life years (11). On the other hand, air pollution can lead to misbalancing in the autonomic nervous system, causing various complications in the human brain and thereby the incidence of stroke (3,12,13).

While numerous studies in Europe, North America, and Asia have demonstrated the immediate and long-term effects of air pollution on stroke morbidity and mortality,(14-16) few have thoroughly examined both in a high-pollution industrial setting in the Middle East. Our study fills this gap by analyzing detailed time-lag effects in Arak, Iran—an industrial city with consistently high pollutant levels.

Previous meta-analyses and multi-country studies have reported significant associations between short-term exposure to NO_2, SO_2, and PM and increased risk of stroke admissions (5,17–19), as well as between long-term exposure to $PM_{2.5}$ and NO_2 and elevated stroke incidence (20–21). However, the magnitude and direction of these associations vary by region, pollutant, and exposure duration, underscoring the need for context-specific research.

Arak, located in Markazi Province, has a population of more than 520,000 people according to the latest census in 2016. Air pollution has become an important environmental issue in Arak, mainly due to the rapid industrialization and urbanization of the city over the recent decades(22–24). Accordingly, huge amounts of air pollutants are continuously discharged into the air due to the activities of various industries and traffic present within and around the city. Therefore, it is important to characterize the exposure-response relationships between air pollution and stroke in this polluted city. This study aimed to examine the association between short and long-term exposures to air pollutants, including PM_{10}, $PM_{2.5}$, O_3, SO_2, and NO_2, with the incidence of stroke in Arak, Iran, during 2019– 2022.

Materials and Methods

Study Design

This study is a prospective cohort study in which all patients diagnosed with stroke were enrolled. The information on these patients was extracted from the registration program for stroke patients established in the city of Arak, Iran, from 2019 to 2022. After registration in the program, a total of 1010 patients were included in the analysis and followed up accordingly.

The inclusion criteria were as follows: living in Arak, and confirmed stroke cases who were hospitalized by a neurologist according to World Health Organization criteria (25). The patients whose exact date of hospitalization was not known were naturally excluded from the study.

The stroke registration program records demographic and clinical information about patients, such as the daily number of new stroke cases, the exact date of the event, and the hospitalization.

Assessment of Environmental Futures

In this study, the relationship between the occurrence of stroke and 6 pollutants, including $PM_{2.5}$, PM_{10}, O_3, NO_2, and SO_2, has been investigated. Both the short-term (1week, 1month, three months, and 6 months) and long-term effects (9, 12, 18, and 24 months) of the concentration of the pollutants on the incidence of stroke were evaluated. Pollutant concentrations were evaluated using arithmetic mean concentrations over specified short-term and long periods.

The pollutant data were obtained from 4 air quality monitoring stations during the study period. (2017-2022). The hourly concentration data were processed such that the zero and negative data of the stations were removed. Only stations with hourly data of more than 75% during one year (according to WHO criteria) were considered (26–28). Across stations, the proportion of missing data was 8.4% for $PM_{2.5}$, 7.9% for PM_{10}, 5.6% for O_3, 9.2% for SO_2, and 6.8% for NO_2. Then, the daily mean concentrations of $PM_{2.5}$, PM_{10}, NO_2, and SO_2, and the maximum daily 8-hour mean concentrations of O_3 were calculated.

Exposure Assessment

We evaluated both short-term (1 week, 1 month, 3 months, 6 months) and long-term (9 months, 12 months, 18 months, 24 months) exposure windows. These intervals were selected based on prior studies on lag effects in air pollution epidemiology (19, 29–31) and the WHO exposure assessment guidelines.

Statistical Analysis

To analyze the data, we have used a time series zero-inflated negative binomial regression approach. This statistical methodology is particularly pertinent when

dealing with count data exhibiting excess zeros and overdispersion. The fitting process involves employing maximum likelihood estimation in which the model can capture the intricate relationships between variables and the occurrence of zeros in the count data. Overdispersion, which occurs when the variability in the data exceeds what is expected based on the assumed statistical distribution, was checked using the likelihood ratio test (LRT). The model for time "*i*" includes two parts for the count process and the zero inflation as follows, in which π_i is the logistic link function for the probability of zero counts process and *f* is the negative binomial distribution.

$$\Pr(y_i = j) = \begin{cases} \pi_i + (1-\pi_i) f(y_i = 0) \\ (1-\pi_i) f(y_i) \end{cases}$$

The results are formed in the count and zero-inflated sections and can be interpreted as the exponential of the estimated coefficients. The first part shows the impact of variables on the number of events, while the second part shows the impact on whether an event is not observed.

Estimates are presented as relative risks (RR) or odds ratios (OR) per 10-unit increase in pollutant concentration.

Covariates included: Age, sex, smoking status (current, former, never), passive smoking, opium use, hypertension, diabetes, seasonality and long-term trends, daily mean temperature, and humidity. Lag periods were incorporated by averaging pollutant concentrations over the specified exposure windows before each stroke event. Analyses were performed in R 4.1.3, with $p < 0.05$ considered significant.

Results

Table 1 shows the demographic and clinical characteristics of the patients participating in the study. The mean age of the participants was 70.67 years (S.D.: 12.8). Out of all the participants, 52.77% were male, 22.38% were smokers, 10% were passive smokers, 15.54% had a history of opium use, 80.69% had high blood pressure, and 30.4% had diabetes.

Table 1. Demographics and clinical characteristics of participants

Variable	Category	Mean (±SD) or N (%)
Age (Years)		70.67 (±12.8)
Gender	Female	477 (47.23)
	Male	533 (52.77)
Smoking	Yes	226 (22.38)
	No	784 (77.62)
Passive smoker	Yes	101 (10.0)
	No	909 (90.0)
Opium	Yes	157 (15.54)
	No	853 (84.46)
Hypertension	Hypertensive	815 (80.69)
	Normotensive	195 (19.31)
Diabetes	Yes	307 (30.40)
	No	703 (69.6)

Table 2 presents the data summarized of air pollutants from air quality monitoring stations in the city of Arak between 2017 and 2021. The daily means of air pollution levels ranged between 2.9- 194 μg/m³ for $PM_{2.5}$, 11.3- 206.7 μg/m³ for PM_{10}, 3.8- 56.8 ppb for O_3, 1.5- 179.5 ppb for SO_2, and 7.4-56 ppb for NO_2. Stroke effect sizes associated with every 10-unit increase in the levels of air pollutants in the short and long term are shown in Tables 3 and 4, respectively.

The model results of the count process indicated that the cumulative effect of a 10 μg/m³ increase in PM_{10} concentrations within one week, one month, three months and six months corresponded to a 1% (95% CI 0.96% to 1.04%), 1.02% (95% CI 0.98% to 1.06%), 1.02% (95% CI 0.99% to 1.06%) and, 1.01% (95% CI 0.97% to 1.05%) increase in daily stroke incidences respectively (Table 3). For NO_2, the related significant association was found to be 1.14% (95% CI 1.01% to 1.29%) during three months.

The model results of the Zero-inflated model showed that increases of 10 units in PM_{10} and O_3 at six months were significantly associated with 1.18% (95% CI 1.06% to 1.33%) and 2.37% (95% CI 1.34% to 4.21%) increases in daily stroke incidences. Also, there are positive significant associations between the increases of 10 ppb in SO_2 with 1.57% (95% CI 1.02% to 2.4%) and 2.54% (95% CI 1.05% to 6.11%) increases in daily stroke hospitalizations, respectively, during 1- and 3-month periods (Table 3).

For long-term exposure, the increase of NO_2 levels (10 units) significantly increased the stroke hospitalization, with RR values and 95% CIs of 1.22(1.07-1.4) and 1.17(1.07-1.3) over 9 and 12 months, respectively. Also, the odds ratios of stroke were 3.81 (95% CI 1.76-8.26) at 18 months and 1.21 (95% CI 1.06-1.39) at 24 months for each 10 μg/m³ increase in NO_2 (Table 4). The Zero-inflated model showed a statistically significant increase of 4.67 (95% CI 1.31-16.7) and 4.36 (95% CI 1.06-17.9) in stroke admissions per 10 units increase in PM_{10} and SO_2 at 24 months.

Discussion

This study is one of the few studies conducted in Iran that systematically examines the relationship between the short-term and long-term exposure to air pollutants and the incidence of stroke hospitalization. Based on the evaluation of the two models applied in the present study, a significant positive association was found between the increased risk of stroke incidence and short-term three-month exposure to NO_2, O_3, and SO_2. These results were consistent with a meta-analysis comprising 23

Table 2. Summary statistics for air pollutant concentrations in Arak, Iran, 2017-2022

Air pollutants	Mean ± SD	Minimum	Percentile			IQR	Maximum
			25th	50th	75th		
$PM_{2.5}$ (μg/m³)	27.92 ± 15.1	2.85	17.9	25.36	34.26	16.36	193.98
PM_{10} (μg/m³)	65.68 ± 43.2	11.3	38.85	60.3	81.4	42.55	206.7
O_3 (ppb)	25.72 ± 7.8	3.81	20.18	25.35	30.9	10.72	56.78
SO_2(ppb)	17.18 ± 12.5	1.45	10.95	14.2	18.9	7.95	179.5
NO_2 (ppb)	19.02 ± 7.3	7.4	13.5	18.01	22.12	8.62	56.02

IQR = interquartile.

Table 3. Stroke effect sizes associated with every 10 units increase in the levels of air pollutants, including $PM_{2.5}$, PM_{10}, O_3, SO_2, and NO_2 in the short term

Model	Pollutants	1 week		1 month		3 months		6 months	
		RR/ OR	95% CI	RR/OR	95% CI	RR/ OR	95% CI	RR/ OR	95% CI
Standard Poisson regression model (RR)	$PM_{2.5}$	0.92	0.84-1.15	0.97	0.88-1.08	0.98	0.89-1.08	0.89	0.79-0.99
	PM_{10}	1.00	0.96-1.04	1.02	0.98-1.06	1.02	0.99-1.06	1.01	0.97-1.05
	O_3	0.8*	0.65-0.98	0.94	0.77-1.15	1.09	0.92-1.30	1.04	0.88-1.23
	NO_2	0.89	0.79-1	1.03	0.91-1.16	1.14*	1.01-1.29	0.91	0.75-1.09
	SO_2	0.76*	0.59-0.96	1.12	0.94-1.35	0.72*	0.6- 0.88	0.81*	0.69-0.96
Zero-inflated model (OR)	$PM_{2.5}$	1.04	0.85-1.28	1.25	0.98-1.06	0.66	0.38-1.16	0.71	0.47-1.06
	PM_{10}	1.00	0.92-1.10	0.95	0.88-1.04	0.97	0.8-1.17	1.18*	1.06-1.33
	O_3	0.72	0.44-1.16	1.39	0.91-2.13	2.91*	1.21-7.02	2.37*	1.34-4.21
	NO_2	0.31*	0.16-0.62	0.19*	0.07-0.49	0.008*	0.01-0.44	0.87	0.51-1.48
	SO_2	1.34	0.81-2.21	1.57*	1.02-2.40	2.54*	1.05-6.11	1.36	0.85-2.17

*P < 0.05, RR = relative risk, OR = odds ratio, CI = confidence interval.

Table 4. Stroke effect sizes associated with every 10 units increase in the levels of air pollutants, including $PM_{2.5}$, PM_{10}, O_3, SO_2, and NO_2 in the long term

Model	Pollutants	9 months		12 months		18 months		24 months	
		RR/ OR	95% CI	RR/ OR	95% CI	RR/ OR	95% CI	RR/ OR	95% CI
Standard Poisson regression model (RR)	$PM_{2.5}$	0.94	0.85-1.04	1.13	1.03-1.24	0.82	0.72-0.93	1.02	0.88-1.19
	PM_{10}	1.00	0.96-1.04	0.98	0.95-1.02	1.03	0.98-1.07	1.03	0.97-1.08
	O_3	1.00	0.88-1.15	1.42	1.25-1.61	1.11	0.94-1.31	0.78*	0.65-0.94
	NO_2	1.22*	1.07-1.39	1.17*	1.07-1.29	1.76	1.38-2.25	0.45	0.32-0.64
	SO_2	0.94	0.85-1.04	0.96	0.85-1.08	0.92	0.82-1.03	1.03	0.93-1.13
zero-inflated model (OR)	$PM_{2.5}$	0.58	0.36-0.94	1.05	1.02-1.07	1.28	0.9-1.84	0.34	0.03-4.21
	PM_{10}	1.45	1.22-1.72	1.03	1.01-1.04	1.07	0.95-1.2	4.67*	1.31-16.7
	O_3	5.02	2.23-11.3	0.93	0.85-1.01	2.8	1.67-4.71	0.92*	0.87-0.98
	NO_2	1.08	0.75-1.55	0.81	0.78-0.84	3.81*	1.76-8.26	1.21*	1.06-1.39
	SO_2	0.57	0.32-1.01	0.97	0.95-0.99	0.58	0.38-0.87	4.36*	1.06-17.9

*P < 0.05, RR = relative risk, OR = odds ratio, CI = confidence interval.

million participants from 68 studies, which revealed the associations between NO_2, SO_2, and an increased risk of total stroke hospitalizations (1). A nationwide time-series analysis surveyed over two million ischemic stroke cases in 172 cities in China also supported these results (14). However, a statistically significant negative association was found between the short-term one-week exposure to these pollutants and the increased incidence of stroke. The relationship between air pollution and stroke risk is complex and may not follow a simple linear pattern. It is possible that at low levels of air pollutants within a week, there is a negative association with stroke risk, but this trend could reverse at higher levels of exposure. Additionally, confounding factors like temperature, humidity, and socioeconomic status could also play a role in the relationship between air pollution and stroke risk (3). In a time series analysis conducted in Dublin and Cork, Ireland, as cities with low concentrations of air pollutants, it was found that there was no significant association between the admission of all strokes and concentrations of the air pollutants (32). Previous studies have shown that daily changes in Europe are ten times

lower than those in Asia. These smaller changes in air pollution levels lead to a lower ischemic stroke risk, making it more difficult to distinguish the link between air pollution levels and ischemic stroke (12). The meta-analysis conducted by Shah et al found that there is a significant association between air pollution and stroke. They estimated that for every 10 μg/m^3 increment of $PM_{2.5}$, there is a 1.1% increase in daily hospital admissions for stroke. Similarly, for every 10-ppb increment of SO_2, NO_2, and O_3, the increase in hospital admissions for stroke was estimated to be 1.6%, 1.2%, and 0.1% respectively (33). However, it is important to note that the results varied across studies due to differences in air pollution levels, outcome definitions, weather conditions, population susceptibility, and sociodemographic characteristics. Our findings of no statistically significant positive associations between $PM_{2.5}$ and stroke on short-term exposure were unexpected. While some previous studies have reported negative associations between PM and stroke, these findings have been limited to specific lag periods, locations, seasons, or other categories of stroke events (34–36). In the study conducted in 248 cities of China, a weak inverse relationship with $PM_{2.5}$ was noted for hemorrhagic stroke in the primary analyses (lag 0 day), but this connection attained statistical significance when alternative single-day exposures (lag 1 or 2 days) or moving average exposures (lag 0–1, 0–2, or 0–3 days) were used as the exposure metric (4). New research has revealed that there is no significant connection between air pollution and overall hemorrhagic stroke. This suggests that air pollutants may specifically elevate the risk of intracerebral hemorrhages and not subarachnoid hemorrhage (12). The Swedish study demonstrates the impact of air pollutant concentration on ischemic stroke admissions. The study found a 13% increase in ischemic stroke admissions on days with high (>30 μg/m^3) compared to low (<15 μg/m^3) concentrations of PM_{10} (12). This highlights the potential health risks associated with elevated air pollutant levels, even when the mean concentration is relatively low at 16 μg/m^3. However, in the present study, the zero-inflated model indicated a significant positive correlation between the number of stroke cases and a six-month exposure to PM_{10}, with an increase of 10 μg/m^3. Several recent studies have reported a significant positive association between stroke cases and short-term exposure to $PM_{2.5}$ and PM_{10} (1, 29, 37–39). The retrospective study involving 504 stroke patients revealed that exposure to air polluted with SO_2 during the acute period of stroke had negative effects on the course of the condition. It was found that regardless of the patient's clinical profile, such exposure worsened the prognosis in terms of functional status and death within 10 days. However, there was no significant effect on functional status and prognosis for the subsequent three months, and no relationship between PM pollution and post-stroke functional status (40). Based on previous studies, it has been established that exposure to environmental NO_2 is linked to a higher risk of stroke in heavily polluted areas. Additionally, O_3 is a secondary pollutant known for its strong oxidizing properties. While concentrations of other pollutants like $PM_{2.5}$ have decreased in recent years, ambient O_3 levels have remained stable or even increased globally.

In this study, the long-term effects of exposure to pollutants on stroke incidence from 9 to 24 months have been considered. A positive, strong relationship between two-year exposure to PM_{10}, NO_2, and SO_2 with the incidence of stroke was observed. Whereas, exposure to O_3 has been found to potentially decrease the risk, as indicated by an odds ratio of 0.92 (95% CI: 0.87–0.97) and a relative risk of 0.78 (0.65-0.94). The finding of the inverse association between O_3 exposure and stroke hospitalization is in line with a previous study that also observed a similar relationship among Medicare beneficiaries(41).

In both models, there was a positive but non-significant relationship between the long-term one-year exposure to $PM_{2.5}$ and stroke incidence. These findings are consistent with existing evidence. A combined analysis of six European cohorts investigated the relationship between long-term exposure to air pollution and the incidence of stroke. The study revealed a higher risk associated with increased levels of $PM_{2.5}$ (hazard ratio of 1.10 [95% CI 1.01–1.21] per 5 μg/m^3 increase) and NO_2 (hazard ratio of 1.08 [95% CI 1.04–1.12] per 10 μg/m^3 increase) (10). The analysis of 23,423 Denmark residents, with 1,078 cases of stroke, revealed a hazard ratio (HR) of 1.13 (95% CI 1.01–1.25) for ischemic stroke per 3.9 μg/m^3 (IQR) rise in annual mean of $PM_{2.5}$. The results also indicated similar hazard ratios (HRs) for both 3-year and 23-year averages of PM2.5 levels (2). The 2019 meta-analysis found a significant relationship between long-term exposure to higher $PM_{2.5}$ levels and all-cause stroke within a 1 to 4-year exposure period (5). Also, the findings from the China cohort study conducted by Huang et al and the Korean retrospective study by Noh et al both indicated a significant correlation between long-term exposure to elevated levels of $PM_{2.5}$ and an increased risk of hemorrhagic stroke (16,42).

The evaluation of 30-day all-cause hospital readmission in US fee-for-service Medicare beneficiaries aged 65 years and older, hospitalized for ischemic stroke in 2014 to 2015, revealed that higher average annual exposure to CO, NO_2, $PM_{2.5}$, and SO_2 was associated with increased risks of readmission, while O_3 exposure showed a decrease in risk. Therefore, they concluded that long-term exposure to main air pollutants, even at levels lower than national thresholds, correlated with increased 30-day readmission for all causes after stroke incidence (10). The Beijing health management cohort study from 2013 to 2018

found that even a small increase in the concentrations of $PM_{2.5}$, SO_2, and NO_2 is associated with a higher risk of cerebrovascular disease. Specifically, for every 1 μg/m^3 increase in $PM_{2.5}$, the risk increased by 1.02; for SO_2, the risk increased by 1.06; and for NO_2, the risk increased by 1.02 (43). The study suggests that reducing long-term exposure to these pollutants could significantly benefit the health of individuals, especially those who are more susceptible to cerebrovascular disease. In this study, the correlation between stroke and air pollution was studied. It is recommended that further studies investigate the relationship between the type of stroke, the territory of stroke, and the severity of cerebrovascular accident and air pollution.

Conclusion

This study investigated the association between short-term and long-term exposure to air pollutants and the incidence of stroke hospitalization in Arak, Iran. Further research is recommended to investigate the relationship between the type of stroke, the territory of stroke, and the severity of cerebrovascular accident and air pollution. Reducing exposure to air pollution could be an important strategy for preventing stroke. Both short-term and long-term exposure to certain air pollutants are associated with stroke morbidity in Arak, Iran. Strategies to reduce chronic PM_{10}, NO_2, and SO_2 exposure may significantly lower stroke risk in similar urban-industrial environments.

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Competing interests

All authors declared no conflict of interest.

Ethical issues

All stages of research were conducted following the Declaration of Helsinki and the Ethical Statements of the Ethics Committee of Arak University of Medical Sciences. This study was approved by the Ethics Committee of Arak University of Medical Sciences (Ethical code: IR.ARAKMU.REC.1401.126).

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