Environmental Air Pollution and Acute Cerebrovascular Complications: An Ecologic Study in Tehran, Iran

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ABSTRACT

Background: In this study, we aimed to assess the association between air pollution and cerebrovascular complications in Tehran, one of the most air-polluted cities in the world, among different subgroups of patients with stroke in 2004.

Methods: In this ecologic study, we calculated the daily average levels of different air pollutants including CO, NO\textsubscript{X}, SO\textsubscript{2}, O\textsubscript{3}, and PM\textsubscript{10} and also humidity and temperature on the day of stroke and 48 hours prior to stroke in 1491 patients admitted with the diagnosis of stroke in eight referral hospitals in different areas of Tehran. Then, we evaluated the association between the rate of stroke admissions and the level of the selected pollutants, humidity, and temperature on the day of stroke and 48 hours prior to stroke among different subgroups of patients.

Results: There was no significant association between the same-day level of the pollutants and the rate of stroke admissions, but an association was seen for their level 48 hours before stroke. These associations differed among different subgroups of age, sex, history of underlying diseases, and type of stroke. Same-day temperature had a reverse association in patients with hemorrhagic stroke and in patients without a history of heart disease or previous stroke. A direct significant association was seen for humidity level 48 hours before stroke in patients with a history of heart disease.

Conclusions: It is inferred that air pollution has a direct association with the incidence of stroke and these association differs among different subgroups of patients. The results of this study are not time-dependant and can be generalized to different times and regions. Moreover, these results may be useful for environmental health policy makers.

Key words: Air pollution, cerebrovascular complications, CO, humidity, NO\textsubscript{X}, O\textsubscript{3}, PM\textsubscript{10}, SO\textsubscript{2}, temperature, Tehran

INTRODUCTION

Air pollution is a health problem which results in several medical conditions in human beings. Many of these disorders,
especially respiratory diseases, are fully recognized.\[1,2\] Currently, the potential hazards of air pollution dramatically influence the human population. Old persons, children, patients with cardiovascular problems, pregnant women, and fetuses are more susceptible to these pollutants.\[3\] These side effects include respiratory diseases and exacerbations of cardiopulmonary diseases.\[4\]

Tehran is the capital of Iran, a metropolitan area with more than 12 million inhabitants, more than 3 million cars and many factories, which all lead the city to be one of the most air-polluted cities in the world.\[5\] In a study conducted in 2004 in Tehran, the air quality over 262 days was worse than the standard levels specified by the U.S. Environment Protection Agency (i.e., AQI = 100). Comparing with past years, the quality of Tehran's air in 2004 was still threatening to people, especially vulnerable populations.\[6\] Previous studies have indicated that there is a significant association between air pollution and a high rate of cardiovascular disease, including deep vein thrombosis and other atherosclerotic disorders such as myocardial infarction.\[7-9\] A study conducted in Seoul, South Korea, between 1995 and 1998 investigated the delayed effect of air pollution on mortality due to stroke, and the results showed that \( O_3 \) and \( \text{PM}_{10} \) had the highest relationship with mortality due to stroke on the same day. Meanwhile, CO, \( \text{SO}_2 \), and \( \text{NO}_2 \) densities at 48 hours before suggested a higher risk for mortality due to stroke.\[10\] A study conducted in Isfahan, the second most air-polluted city in Iran, showed that there is an association between air pollution and the development of atherosclerosis in its first stages in the early life and emphasized the importance of considering the harmful effects of air pollution on children.\[11\] Another study conducted in Isfahan suggested an independent association between air pollution and systemic inflammatory and coagulation responses by studying a genetic polymorphism in a tissue factor in atherosclerotic lesions.\[12\]

Although many studies have discussed the side effects of air pollution on human health, there is not yet a consensus on the vascular side effects of air pollution.\[13,14\] In order to provide more comprehensive data on the effects of air pollution on the health, we investigated the association between air pollution in Tehran and the number of stroke admissions in the main referral hospitals of Tehran. We hypothesized that the rate of stroke would be higher on more polluted days.

**METHODS**

This was a cross-sectional analytical study on the ecological level. The sample size was 1,491 patients primarily diagnosed as stroke in 2004. We assessed all patient files which satisfied inclusion criteria. The patients were admitted in eight referral hospitals, located in different areas of Tehran. These are the main referral hospitals in Tehran which figured out that more than 90% of patients with stroke would be admitted by them. Complementary data including age, sex, risk, and modifying factors on stroke including hyperlipidemia, hypertension, cardiovascular disease, diabetes, smoking status, and type of stroke were obtained from the patient’s file. In order to cover stroke in the younger group during analysis, the age cut-off point was defined as 40 years.

Daily information on Tehran’s air pollution in 2004 was supplied from the Centre for Control of Traffic, transportation and air pollution of Tehran. The data included daily levels of CO, \( \text{SO}_2 \), \( \text{NO}_2 \), \( \text{PM}_{10} \), ozone (\( O_3 \)), and meteorological variables (temperature and humidity). We used the information from seven air-check stations of the eleven stations in Tehran. Then, daily average levels of pollutants were separately calculated. We used the Air Quality Index (AQI) to describe air quality which consists of six levels, which are shown in Table 1.\[7\] Categories of pollutant density, necessary for calculating the air quality control index, are also shown in Table 1. In this table, the average 8-hour density was used for

| Category                        | PSI | \( O_3 \) (ppm)   | \( \text{SO}_2 \) (ppm) | \( \text{PM}_{10} \) (\( \mu \text{g/m}^3 \)) | CO (ppm) |
|---------------------------------|-----|------------------|-------------------------|---------------------------------|-----------|
| Good                            | 0-50| 0.069, 0.000     | -0.034, 0.000           | 0-54                            | 0.0- 4.4  |
| Medium                          | -100, 51 | -0.084, 0.070   | -0.144, 0.035           | 55-154                           | 4.5-9.4   |
| Unsafe for vulnerable persons   | -150, 101 | -0.104, 0.085   | -0.224, 0.145           | 155-254                          | 9.5-12.4  |
| Unsafe                          | -200, 151 | -0.124, 0.125   | -0.304, 0.225           | 255-354                          | 12.5-15.4 |
| Very unsafe                     | -300, 201 | -0.0374, 0.125  | -0.604, 0.305           | 355-424                          | 15.5-30.4 |
| Dangerous                       | -500, 301 | -0.604, 0.405   | -1.004, 0.605           | 425-604                          | 30.5-50.4 |

Table 1: Classes for density of pollutants in order to calculate Air Quality Control Index\[8\]
CO and O₃ and the average 24-hour density was used for SO₂ and PM₁₀. The density of PM₁₀ was assessed by using a non-dispersive infrared analyzer, the densities of O₃ and SO₂ were assessed by using light spectrometry, and temperature and humidity were assessed by the Vaisala model mp 113y and were analyzed continuously.¹⁵,¹⁶ Due to the lack of information on NO₂, NOₓ was used in some stations. According to the standard table of clean air, offered by the U.S. Environmental Protection Agency, the density of NO₂ and NOₓ was not mentioned in this classification. We analyzed the data by STATA software version 8. To evaluate the association between each pollutant and the rate of hospitalization separately, we used univariate analysis. We also used multi-variable Poisson regression in which the number of hospitalizations for each day was the dependent variable and the previously mentioned air pollutants with a P value lower than 0.2 in the univariate analysis were independent variables.¹⁷ Type one error in all analysis including regression was considered 0.05.

Table 2: Characteristics of studied subjects (n = 1491)

| Characteristic of participants | No. | Percent |
|-------------------------------|-----|---------|
| Age                           |     |         |
| Age < 40                      | 45  | 3       |
| Age > 40                      | 1404| 94      |
| Sex                           |     |         |
| Female                        | 727 | 48.8    |
| Male                          | 764 | 51.2    |
| Smoking status                |     |         |
| Non-smoking                   | 1165| 78.1    |
| Previous smokers              | 103 | 6.9     |
| Present smokers               | 181 | 12.1    |
| History of diseases           |     |         |
| Diabetes                      | 472 | 31.7    |
| Hypertension                  | 955 | 64.1    |
| Hyperlipidemia                | 324 | 21.7    |
| Cardiovascular disease        | 535 | 35.9    |
| Type of stroke                |     |         |
| Ischemic and embolic stroke   | 373 | 25      |
| Ischemic and thrombotic stroke| 567 | 38      |
| Ischemic stroke, lacunar      | 338 | 22.7    |
| Hemorrhagic, parenchymal      | 138 | 9.3     |
| Hemorrhagic, sub-arachnoid    | 44  | 3       |
| Stroke in the right hemisphere| 694 | 46.7    |

Table 3: Statistical significance level of association of average air pollutants with number of hospital admission for stroke

| Pollutants                  | P value * relationship of pollutants on the same day with number of stroke admission | P value * relationship of pollutants on 48 hours before with number of stroke admission |
|-----------------------------|---------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|
| Dust particles smaller than 10 μm | 0.550                                                                                 | 0.610                                                                                 |
| Sulfur dioxide              | 0.021                                                                                 | 0.050                                                                                 |
| Mono oxide carbon           | 0.100                                                                                 | 0.036                                                                                 |
| NOₓ                         | 0.350                                                                                 | 0.145                                                                                 |
| Ozone                       | 0.015                                                                                 | 0.006                                                                                 |
| Temperature                 | 0.020                                                                                 | 0.017                                                                                 |
| Humidity                    | 0.140                                                                                 | 0.032                                                                                 |

*ANOVA test (for Categorical Variables) or univariate regression (for Interval Variables)
day level of the pollutants had no significant effect on the number of admitted stroke patients. As shown in Table 5, the level of NO\textsubscript{X} at 48 hours before had a significant effect on the number of hospitalizations ($P = 0.02$).

As shown in Tables 4 and 5, multivariate Poisson regression was used to assess the association of same-day and 48 hours before stroke pollutant levels in different variables strata. Same-day temperature had a significant reverse association with hemorrhagic stroke admission ($P = 0.034$), and in patients without a history of heart disease ($P = 0.046$) or previous stroke ($P = 0.043$). Also, temperature at 48 hours before had a significant reverse association with hemorrhagic stroke admission ($P = 0.017$). The humidity level 48 hours before had a direct significant association with the stroke admission of patients with the history of heart disease ($P = 0.007$). Same-day nitrogen oxide level had a significant direct association with the stroke admission of patients with the history of hypertension ($P = 0.031$). The nitrogen oxide level 48 hours before stroke had a significant direct association with stroke admission of patients aged over 40 years ($P = 0.025$), patients with the history of hypertension ($P = 0.005$), and in patients without history of hyperlipidemia ($P = 0.032$). The carbon monoxide (CO) level 48 hours before stroke had a significant direct association with stroke admission in female cases ($P = 0.019$), with ischemic stroke admission ($P = 0.013$), stroke admission in patients with the history of hypertension ($P = 0.005$), diabetics ($P = 0.009$), and non-smoking cases ($P = 0.008$). The sulfur dioxide level 48 hours before had a significant direct association with admission of patients with a history of heart disease ($P = 0.004$) and past smokers ($P = 0.003$).

**DISCUSSION**

Stroke is a multi-factorial disease that is influenced by several genetic and environmental factors including life style and environmental conditions.\[18\] The level of NO\textsubscript{X} on the same day had a significant association with the occurrence of stroke, and factors including CO, SO\textsubscript{2}, and NO\textsubscript{X}, temperature and humidity 48 hours before stroke had a significant association with stroke admission.\[19\] These associations were different among different subgroups of age, sex, history of underlying diseases, and type of stroke. It could be concluded that the effect of pollutants on stroke 48 hours before stroke was higher than its effect on the same day as stroke which might be due to a requirement for an incubation time of these pollutants at least 48 hours before influencing the brain. In this study, in comparison with other similar studies, more pollutants were used for studying this relationship. In a study conducted by Lokken in the U.S.A. published in 2009, upon examining 1 101 patients with proven stroke, it was shown that observing hospitalized patients and not having a control group may have resulted in an underestimation of the relationship between air pollution and stroke.\[20\] Therefore, it might be inferred that the true associations are stronger than the associations which were shown in this study. In a study conducted by Hu in the U.S.A. in 2008, it was determined that for people who live in polluted areas and areas without any green space, the risk of mortality is higher in cases of stroke. In our study, we found a similar result in that there was a relationship between mortality as a result of stroke with pollutants including carbon monoxide and ozone on the day of stroke and carbon dioxide 48 hours before stroke.\[21\] In a study that was conducted by Oudin in Sweden in 2009, upon studying 556 912 persons (contrasting our study and most previous studies), it was shown that there was no association between air pollution, especially between the NO\textsubscript{X} index and hospitalizations due to stroke.\[22\] In a study conducted by Wang in Australia, it was found that there was a significant association between temperature and hospitalization due to stroke and even there was association between the type of stroke with temperature,\[23\] similar to the results of our study. In a study conducted by Henrotin in Dordjon, France from 1994-2004, it was found that there was a significant association between increasing amounts of O\textsubscript{3} and PM\textsubscript{10} and ischemic stroke, but there was no important relationship with hemorrhagic stroke.\[24\] However, in our study, there was a significant relationship between ischemic stroke and carbon monoxide 48 hours before stroke and a significant relationship between hemorrhagic stroke and temperature on the same day and 48 hours before stroke in which temperature was a protective factor. The hazards of air pollution should be considered in all age groups even in young adults,\[25\] and the impacts on elderly should be underscored. In terms of limitations, one weak point of our study was some missing information in the files. Also, it
Table 4: Association between the same-day level of the pollutants and stroke admission in the different variables strata through multivariate poisson regression

| Regression | Holiday RR (CI) | The day after holiday RR (CI) | SO_2 RR (CI) | CO RR (CI) | NO_x RR (CI) | Humidity RR (CI) | Temperature RR (CI) |
|------------|----------------|-------------------------------|-------------|-----------|-------------|-----------------|-------------------|
| Total      | 0.87 (0.76,1.04) | 1.07 (0.93,1.23) | 1.04 (0.85,1.26) | 1.02 (0.90,1.13) | 1.01 (0.91,1.13) | 1.00 (0.99,1.01) | 0.99 (0.98,1.00) |
| Age under 40 | 0.79 (0.34,1.79) | 0.98 (0.42,2.23) | 1.12 (0.35,3.32) | 0.93 (0.48,1.77) | 1.01 (0.95,1.07) | 1.01 (0.98,1.03) | 1.00 (0.94,1.05) |
| Age above 40 | 0.87 (0.75,1.00) | 1.05 (0.91,1.21) | 1.05 (0.85,1.28) | 1.03 (0.91,1.15) | 1.01 (0.99,1.01) | 1.00 (0.98,1.01) | 0.98 (0.96,1.01) |
| Male sex    | 0.95 (0.78,1.14) | 1.04 (0.95,1.14) | 1.03 (0.82,1.26) | 0.96 (0.82,1.12) | 1.01 (0.99,1.02) | 1.00 (0.97,1.00) | 0.97 (0.94,1.01) |
| Female sex  | 0.81 (0.65,0.98) | 1.12 (0.91,1.35) | 1.06 (0.79,1.39) | 1.09 (0.92,1.28) | 1.01 (0.99,1.02) | 1.00 (0.99,1.00) | 1.00 (0.98,1.00) |
| Holiday      | 1.04 (0.76,1.51) | 1.14 (0.76,1.69) | 0.86 (0.48,1.52) | 0.84 (0.60,1.15) | 1.02 (0.99,1.05) | 1.00 (0.98,1.01) | 0.99 (0.97,1.00) |
| The day after holiday | 0.94 (0.71,1.22) | 0.94 (0.69,1.25) | 1.23 (0.83,1.50) | 1.13 (0.89,1.41) | 1.01 (0.98,1.02) | 1.00 (0.98,1.01) | 0.99 (0.97,0.99) |

Bold indicates P < 0.05. Hx = History

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was not a study on the individual level, i.e., it was performed on the ecologic level and the results were analyzed on the group level, so there may be bias in this study. On the other hand, since Tehran is a big city and there are few stations for assessing air pollutants, it was not possible to determine accurate amounts of dangerous pollutants in persons with stroke. Also, the time of stroke was not accessible as an exact hour. In this study, potential confounding factors may have been due to risk factors which were dependent on time (time-varying), day, month, or climate conditions in which these confounding factors were considered in the multivariate analysis. Since diagnosis of stroke was performed in this study without having any information of the air pollution status by the physicians, patients, and even the research team, a considerable bias is not expected.

### Table 5: Association between the 48 h before stroke level of the pollutants and stroke admission in the different variables strata through multivariate poisson regression

| Regression | Co RR (CI) | SO₂ RR (CI) | NOₓ RR (CI) | Humidity RR (CI) | Temperature RR (CI) |
|------------|------------|-------------|-------------|------------------|---------------------|
| Total      | 1.11 (0.98, 1.23) | 1.14 (0.93, 1.37) | 1.01 (1.001, 1.02) | 1.00 (0.99, 1.00) | 1.00 (0.98, 1.00) |
| Age under 40 | 1.04 (0.54, 1.99) | 1.09 (0.34, 3.41) | 1.00 (0.94, 1.06) | 1.09 (0.97, 1.03) | 1.00 (0.95, 1.05) |
| Age above 40 | 1.11 (0.98, 1.24) | 1.12 (0.91, 1.36) | 1.01 (1.001, 1.02) | 1.00 (0.99, 1.00) | 1.00 (0.98, 1.00) |
| Male       | 1.01 (0.86, 1.18) | 1.19 (0.90, 1.55) | 1.01 (0.99, 1.02) | 1.01 (0.99, 1.01) | 1.00 (0.98, 1.01) |
| Female     | 1.22 (1.03, 1.43) | 1.10 (0.83, 1.44) | 1.01 (0.99, 1.02) | 1.00 (0.99, 1.00) | 1.00 (0.98, 1.01) |
| Ischemic stroke | 1.17 (1.03, 1.31) | 1.17 (0.95, 1.43) | 1.01 (0.99, 1.02) | 1.01 (0.99, 1.01) | 1.00 (0.99, 1.01) |
| Hemorrhagic stroke | 0.84 (0.60, 1.15) | 0.95 (0.54, 1.65) | 1.02 (0.98, 1.045) | 0.99 (0.98, 1.00) | 0.97 (0.94, .99) |
| With diabetes | 1.34 (1.09, 1.64) | 1.16 (0.83, 1.62) | 1.02 (0.99, 1.03) | 1.00 (0.99, 1.01) | 1.00 (0.98, 1.01) |
| Without diabetes | 1.02 (0.88, 1.169) | 1.16 (0.91, 1.46) | 1.01 (0.99, 1.02) | 1.00 (0.99, 1.00) | 1.00 (0.98, 1.00) |
| With HTN | 1.21 (1.04, 1.39) | 1.15 (0.90, 1.45) | 1.02 (1.004, 1.02) | 1.00 (0.99, 1.00) | 1.00 (0.98, 1.00) |
| Without HTN | 0.94 (0.78, 1.13) | 1.14 (0.81, 1.58) | 1.00 (0.98, 1.01) | 1.01 (0.99, 1.01) | 1.00 (0.98, 1.01) |
| Hx stroke | 1.18 (0.93, 1.47) | 1.35 (0.92, 1.96) | 1.01 (0.99, 1.03) | 1.01 (0.99, 1.01) | 1.00 (0.98, 1.02) |
| Without Hx stroke | 1.09 (0.95, 1.23) | 1.08 (0.86, 1.35) | 1.01 (0.99, 1.02) | 1.00 (0.99, 1.00) | 1.00 (0.98, 1.00) |
| Hyperlipidemia | 1.24 (0.96, 1.59) | 1.43 (0.99, 2.07) | 1.01 (0.98, 1.03) | 1.00 (0.99, 1.01) | 0.99 (0.97, 1.01) |
| Without Hyperlipidemia | 1.08 (0.95, 1.22) | 1.07 (0.85, 1.34) | 1.01 (1.001, 1.02) | 1.01 (0.99, 1.01) | 1.00 (0.99, 1.01) |
| Not smoker | 1.19 (1.04, 1.35) | 1.01 (0.80, 1.26) | 1.01 (1.002, 1.02) | 1.00 (0.99, 1.00) | 1.00 (0.99, 1.01) |
| Smoker quit | 0.92 (0.58, 1.44) | 2.53 (1.35, 4.70) | 1.03 (0.99, 1.06) | 1.02 (0.99, 1.03) | 1.00 (0.96, 1.03) |
| Smoker | 0.85 (0.61, 1.17) | 1.56 (0.93, 2.60) | 1.00 (0.96, 1.03) | 1.00 (0.98, 1.01) | 0.99 (0.96, 1.02) |
| Ischemic heart | 1.04 (0.86, 1.25) | 1.57 (1.15, 2.12) | 1.01 (0.99, 1.02) | 1.01 (1.002, 1.01) | 1.01 (0.99, 1.02) |
| Without Ischemic heart | 1.14 (0.98, 1.31) | 0.97 (0.75, 1.23) | 1.01 (0.99, 1.02) | 1.00 (0.99, 1.00) | 0.99 (0.98, 1.00) |
| Expired | 1.29 (0.91, 1.81) | 1.50 (0.90, 2.48) | 1.01 (0.97, 1.03) | 1.01 (0.99, 1.01) | 1.00 (0.97, 1.02) |
| Not expired | 1.12 (0.99, 1.26) | 1.11 (0.90, 1.36) | 1.01 (1.002, 1.02) | 1.00 (0.99, 1.00) | 1.00 (0.98, 1.00) |

Bold indicates P < 0.05. Hx = History

### CONCLUSION

Based on our findings and compared to previous studies, we can infer that air pollution and temperature are effective factors in the occurrence of cerebral stroke. However, they do not have any effect on mortality from stroke. Although this study was conducted in 2004, but considering the large sample size and as the findings of this study are not time-dependant, they can be generalized to different population in different times. According to the significant relationship indicated in this study, it can be concluded that policies should be considered for decreasing air pollution and consequently decreasing stroke, complications, and the mortality rate due to stroke. This could be regarded as an effective step on behalf of the organizations responsible for a healthy environment. We suggest conducting more
studies at individual level to describe the role of each pollutant in causing stroke in the future.

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