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Potential Impact of Air Pollution on Multiple Sclerosis in Tehran, Iran

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Key Words
Air pollution · Iran · Multiple sclerosis · Particulate matter

Abstract
Background: Multiple sclerosis (MS) incidence has dramatically increased in Tehran, Iran. The health impact of air pollution in Tehran underscores the attention to a possible association to this environmental risk factor. In this study, the authors aimed to analyze the spatial distribution of prevalent MS cases and their association with the spatial patterns of air pollution. ***Methods:*** Patient records meeting McDonald's criteria for definite MS diagnosis with disease onset during 2003–2013 were obtained. Next, the location of 2,188 patients was successfully geo-referenced within Tehran metropolis by geographic information system (GIS) bureau of Iran's post office based on their phone numbers. A cluster analysis was performed using the average nearest neighbor index (ANNI) and quadrat analysis. The long-term exposures of MS patients to particulate matter (PM_{10}), sulfur dioxide (SO_2), nitrogen oxide (NO), nitrogen dioxide (NO_2), and nitrogen oxides (NOx) were estimated using the previously developed land use regression models. ***Results:*** Prevalent MS cases had a clustered pattern in Tehran. A significant difference in exposure to PM_{10}, SO_2, NO_2, and NOx ($p < 0.001$) was observed in MS cases compared with controls. ***Conclusion:*** This study revealed the potential role of long-term exposure to air pollutants as an environmental risk factor in MS.

Introduction

Multiple sclerosis (MS) is an inflammatory demyelinating disease affecting more than two million people worldwide [1]. Meta-regression analyses of studies on MS epidemiology has revealed an almost universal increase in prevalence and incidence of MS over time, and a general increase in incidence of MS in females has been observed [2]. Several studies suggest that MS incidence and prevalence have dramatically increased in Tehran over the last two decades [3–5]. Findings from the Global Burden of Disease (GBD) 2010 study suggested that disability-adjusted life years (DALYs) lost due to MS increased from 1990 to 2010 for both genders and all age groups in Iran. Ranks of death and DALYs attributable to MS in Iranian women increased from rank 90 to 74 and 122 to 105, respectively in this period [6–8].

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Sunlight exposure has been hypothesized to be a likely environmental candidate to explain the geographic variations in MS prevalence and the change in risk among migrants [9]. To date, the role of vitamin D in MS pathogenesis is the most biologically plausible explanation for a disproportional increase of MS among women [2, 10]. Studies in Iran and India comparing areas with different grades of air pollution observed higher prevalence of vitamin D deficiency in women and toddlers in the more polluted sites [11, 12]. However, knowledge of the association between the spatial distribution of air pollution and the prevalence of MS in Iran is currently lacking.

Today, Tehran is well-known for high levels of air pollution. Previous studies reported that this megacity is heavily polluted and the entire population is exposed to air pollutants well above the air quality guideline values of the World Health Organization [13, 14]. Spatial distribution of prevalent MS cases in Georgia, United States, suggested that urban attributes, especially particulate matter with aerodynamic diameter ≤10 μm (PM_{10}) may have a potential role in the etiology of MS in females [15]. In addition, there are studies suggesting that air pollutants (PM_{10}) could enhance the susceptibility of MS patients to infections and increase the relapse rate among them [16, 17]. In this study, the authors aimed to analyze the spatial distribution of MS incident cases to investigate its association with long-term exposure to air pollution. The study is based on integrating health system and environmental data from various sources.

Methods

Study Area

This population-based study was conducted in Tehran, Iran (Latitude: 35° North, Longitude: 51° East). The weather is typically sunny, with average annual bright sunshine of 2,800 h and an annual mean cloud cover of 30%. The average elevation is approximately 1,200 m above sea level, and the city covers a large area of 613 km^2. Tehran has an urban resident population of over 8.2 million people, though the daytime population has been estimated at more than 10 million people due to diurnal migration from the outlying areas [13, 18].

Prevalent MS Cases

Iranian MS Society (IMSS) records were studied to obtain annual incidence data. Briefly, the IMSS is the only center in the surveyed area that registers MS patients and provides wide facilities (medical, rehabilitation, and vast social welfare) for the members. Only patients approved by neurologists with MS fulfilling McDonald or the Poser criteria (up to 2001) are registered in the IMSS. A trained interviewer explains the purpose of the registry for patients in the IMSS, and after obtaining informed consent, patients are asked to complete structured interview questions [4]. Records of 2,188 patients meeting McDonald's criteria for definite MS diagnosis were obtained from IMSS (with disease onset during 2003–2013). Thereafter, they were successfully geo-referenced within Tehran by GIS bureau of Iran's post office based on their provided residence phone number.

Cluster Analysis

We applied two methods, namely average nearest neighbor index (ANNI) and quadrat analyses within a GIS to measure the clustering pattern of MS patients from 2003 to 2013 [19–21]. In the ANNI analysis, we calculated the distance between each MS case and the nearest MS case. Thereafter, we calculated the average distance between MS cases and compared with the distance of random cases within the study area. If the observed average distance of the MS cases was smaller than expected average distance of random distribution (nearest neighbor ratio), we considered the MS patients to have a clustered pattern [22, 23].

In quadrat analysis, we have overlayed the areas of equal size on the study area – known as quadrats or quads – and counted the number of MS cases in each square quadrat. One of the main points in this analysis is the size of the applied quads. Traditionally, the size of quads is identified as twice the size of the mean area per feature [24]. Thus, we have applied the following equation to calculate the length of a side of each quadrat:

$$L = \sqrt{\left\{2 \times \left(\frac{A}{N}\right)\right\}}.$$

where L is the length of a side of each quadrat, A is the area of extend for MS cases, and N denoted the total observed number of MS cases. Thereafter, we have calculated the expected counts of MS cases for a random distribution in the study area based on Poisson distribution. We first calculated the probability of x number of MS cases occurring in any given quadrat or $P(x)$ as the following equation:

$$P(x) = \frac{e^{-\lambda}\lambda^{X}}{X!}.$$

where e is the Euler's constant, X is the observed number of MS cases, and λ is the average number of MS cases per quad. In addition, λ was calculated based on the following equation:

$$\lambda = \frac{n}{k}.$$

where n is the total number of MS cases and k is the total number of quads. We then multiplied the $P(x)$ results by the total number of MS cases to get the number of quads expected to contain that number of MS cases. Therefore, we created two frequency tables: one for observed distribution, observed proportion, and observed cumulative proportion and the other one for expected distribution, expected proportion, and expected cumulative proportion based on Poisson distribution. We compared the largest absolute difference of the observed and expected cumulative proportions with the critical value of Kolmogorov-Smirnov test [21]. If the largest absolute difference was greater than the critical value, we considered the difference statistically significant and rejected the null hypothesis that MS cases have random distribution over the study area.

Long-Term Air Pollution Exposure Assessment

We have estimated long-term exposure of all MS cases using previously developed land use regression (LUR) models for 2010 calendar year to estimate long-term exposure to air pollutants in Tehran [13, 18, 25]. In brief, hourly data for particulate matter (PM_{10}), sulfur dioxide (SO_2), nitrogen oxide (NO), nitrogen dioxide (NO_2), and nitrogen oxides (NOx) were obtained from 23 air quality monitoring stations in 2010. We then generated 210 potentially predictive variables in six classes and seventy-three sub-classes within GIS and used as spatial predictors. The six classes were traffic surrogates, land use, distance variables, population density, product variables, and geographic location. Multiple linear regression was used to correlate the measured air pollutant concentrations with the most predictive variables. A standard approach was developed for the LUR model building and finally the resulting equation was used to estimate the outdoor pollutant concentrations at the residential address for each individual MS patient within the city. These estimates were assumed to reliably reflect the spatial distribution of pollution during the entire seven-year period as seen elsewhere [26]. We have also created 8,752 random controls (fourfold of MS cases) as the control group using Geospatial Modeling Environment software, version 0.7.2.1 RC2 (GUI) (Spatial Ecology, LLC), and estimated individual exposure of each control. The independent samples t test was used to compare the difference in exposure to various air pollutants in MS patients and random points.

Results

Cluster Analysis

The ANNI analysis revealed that there was a clustered pattern for the MS cases in 2003–2013 in Tehran. There was less than 1% likelihood that this clustered pattern could be the result of random chance (nearest neighbor ratio = 0.56; Z score = –39.4 standard deviations; $p < 0.001$). The length of the quads was calculated as 768 meters. The largest absolute difference between observed and expected cumulative proportions in the frequency table was 0.35, while the critical value of Kolmogorov-Smirnov test was 0.03, and this again demonstrates that MS cases have a clustered pattern in Tehran.

MS and Air Pollution

As depicted in figure 1, various air pollutant levels were estimated based on LUR models and MS patients were located on the map and their exposure to air pollutants was determined. Our analysis demonstrated that the annual mean exposure of PM_{10}, SO_2, NO, NO_2, and NOx in MS cases were 99.1 $\mu g/m^3$, 58 parts per billion (ppb), 125.2, 48.1, and 113 ppb, respectively. However, in our random controls, the mean exposures for the mentioned pollutants were 93 $\mu g/m^3$, 52.5 ppb, 108.9, 41.1, and 102 ppb, respectively.

Various air pollutants had an exponential distribution and were significantly inter-correlated ($p < 0.001$) except for NO and SO_2. Principal component analysis revealed that the main effect of air pollutants could be attributed to PM_{10} and SO_2.

A significant difference ($p < 0.001$, independent samples t test) in exposure to PM_{10}, SO_2, NO_2, and NOx but not for NO was observed in MS cases compared with random controls generated on the Tehran map as the proxy control group.

Discussion

In this study, we first tried to analyze the pattern of MS incident cases to find out whether there is a clustered pattern in Tehran. We then tried to investigate the relationship of exposure to long-term air pollution in MS cases with the exposure of a control group as a proxy for exposure of general population in Tehran. In the absence of control of any potential confounding variables, the analyses are restricted to a comparison of those spatial patterns. Our results indicated that (a) the MS cases in Tehran had a clustered pattern, and (b) there was a statistically significant spatial correlation between the clustering of MS cases and the concentration patterns of PM_{10}, SO_2, NO_2, and NOx.

A recent study in Tehran demonstrated that a higher risk of MS in the northern zones of this mega city had a direct relation to the socioeconomic status of their inhabitants [27]. A clustered pattern of MS prevalence was also observed in Georgia, United States, best predicted by models including both per capita income and PM_{10} for females, but only per capita income for males suggesting a potential role of PM_{10} in the etiology of MS in females [15].

While etiologic inferences cannot be drawn from our analyses, the observed pattern may promote the hypothesis of a direct or indirect link between air pollution and MS. In Tehran, air pollution levels are high enough to have a visible impact on air, reducing also the sun light intensity. Thus, one may hypothesize a link between reduced sun light exposure due to air pollution and MS. Vitamin D synthesis under the influence of UVB (Ultraviolet-B) in the skin is the major source for the body requirements, while dietary sources of vitamin D are responsible for a small portion of the requisites. Interestingly, a previous correlation study reported lower mean serum 25(OH) vitamin D concentrations in a population living in more polluted areas as compared to those living in the less polluted area [11]. Hosseinpanah et al. [12]

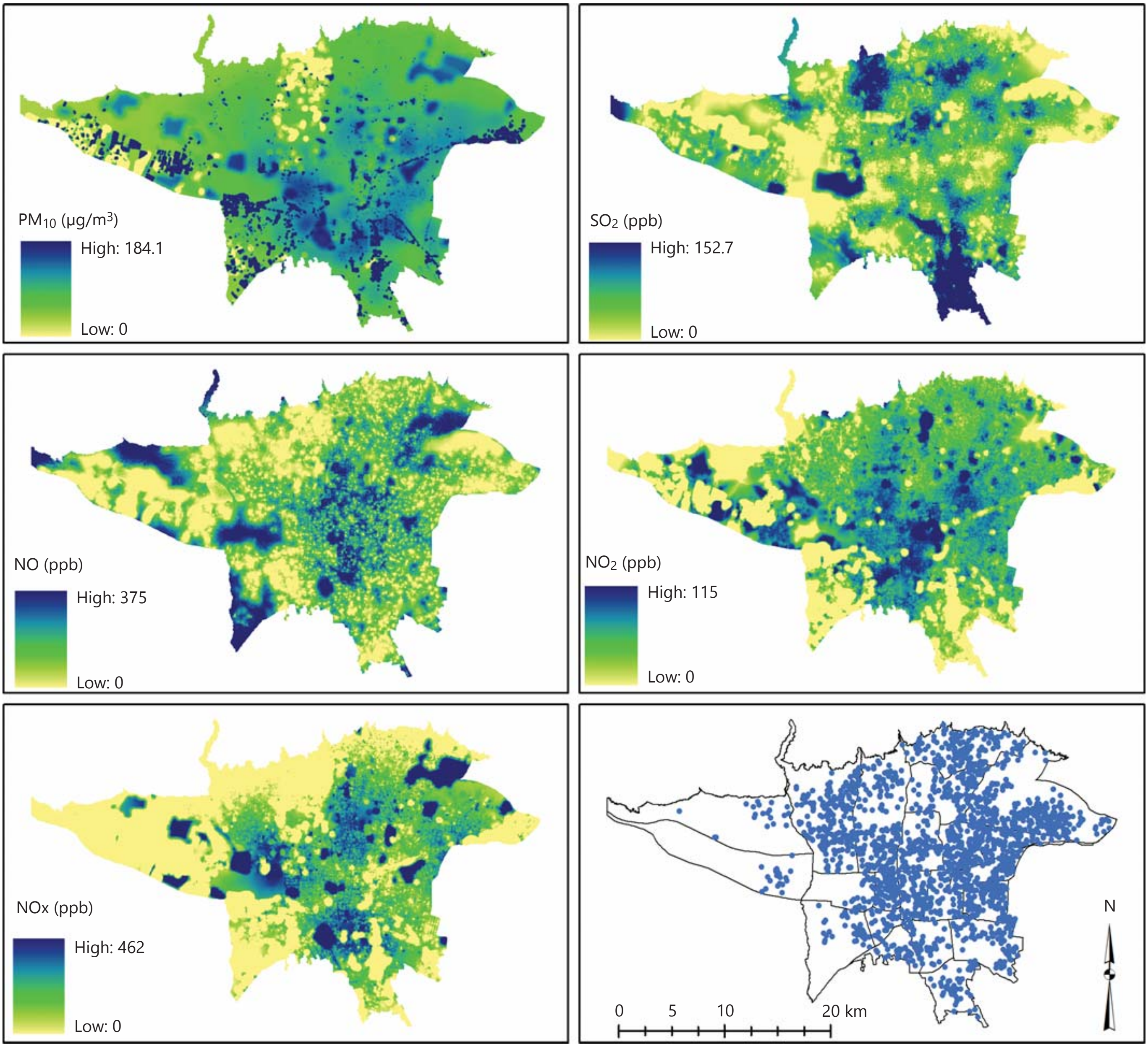

Fig. 1. Particulate matter ≤10 µm (PM_{10}), sulfur dioxide (SO_2), nitrogen oxide (NO), nitrogen dioxide (NO_2), and nitrogen oxides (NOx) levels estimated by land use regression models. The last figure shows on the Tehran map locations where there is a high prevalence of MS.

found that the ground level of UVB was significantly higher in the low polluted area (Ghazvin) as compared with Tehran. They also reported that the average blood vitamin D levels were significantly higher in women from the low polluted area and was related to the degree of haze or pollution over these cities [12]. As both studies were merely comparisons between low and high pollution levels, the observed correlations may be explained by other factors that differ between areas with low and high pollution levels. However, a study in Isfahan, a highly prevalent region for MS in Iran [28], revealed significant negative associations between ultraviolet radiation (UVB) and air quality index (AQI). In essence, UVB was positively associated with 25(OH) vitamin D levels in mothers and their neonates in Isfahan, and the AQI had an inverse and independent association [29].

Our data did not facilitate the direct investigation of the association between MS relapses and short-term exposure to air pollution, which is another possible hypothesis of relevance in the course of this chronic disease. Oikonen et al. found MS relapses to be in the highest quartile following peak levels of PM_{10}, CO, NOx and SO_2 in south-western Finland, after excluding the acidic gases (NOx and SO_2) and due to their strong interaction with other environmental variables, MS relapses were only associated with peak amounts in PM_{10} level [16]. In a further study, Oikonen et al. [17] showed relapses to be more frequent following high levels of PM_{10} in MS patients not using β-interferon. MS relapses occurred over twice as often following high numbers of adenovirus infections in this group, while in patients receiving β-interferon, therapy protected against an enhanced susceptibility to infections caused by PM_{10} [17]. Hence, inhalable particles could contribute to seasonal variation in MS relapse occurrence possibly by predisposing to airway infections. Prolonged exposure to moderate levels of diesel engine exhaust, a major contributor to particulate air pollution [30], induced a neuroinflammatory response in different regions of the rat brain, TNF-α and IL-1α protein levels and were specifically increased in the striatum of rat brains [31].

The design of this study limits the ability to draw any etiologic conclusions. Although we have individual-level data available for MS patients, the cases are not derived from a prospective cohort nor is the general population – thus the denominator – defined. Therefore, at this stage, we cannot derive spatially resolved incidence or prevalence rates. The observed correlation between the spatial clustering of MS cases and the spatial patterns of major air pollutants may be confounded by a range of other spatially correlated variables, which were unavailable in this study, such as other environmental factors or factors related to population age structure, occupational exposures, or lifestyle co-determined by socio-economic conditions. As recently shown, the socio-economic geography of Tehran explains the substantial discrepancies in life expectancy [32]. It will only be through a prospective population-based cohort with extended follow up that the potential role of air pollutants and its interrelation with the vitamin D pathway in MS pathogenesis may be elucidated. The study is also limited by the fact that both used cluster analysis methods assume that the population density is homogenous in the area.

Conclusions

This study shows the need to invest in research about the role of ambient air pollutants in the new onset as well as the development of MS. The potential role of long-term exposure to hazardous environmental factors in the MS pathogenesis is not well established but may be relevant in particular in countries with continued environmental degradation and high incidence of MS.

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