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The relationship between particulate matter and kidney biomarkers in pregnant women: A case study in Yazd city

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Abstract
Background: Cities negatively affect the environment. Urban pollution levels have risen considerably, affecting sensitive groups such as pregnant women.
Methods: This study aimed to investigate the relationship between particulate matter and kidney biomarkers of pregnant women in Yazd from September to November 2023. Urea, uric acid, and creatinine levels were measured in 30 pregnant women (third trimester). The concentration of $PM_{2.5}$ was estimated using the land use regression (LUR) model and 5 independent variables of road networks, distance from the city center, building density, elevation, and slope. For each mother, the mean concentration of the modeled $PM_{2.5}$ was measured in multiple buffer rings drawn around her residential location. Generalized additive model (GAM) was employed to establish a relationship between $PM_{2.5}$ concentrations with physiological indicators.
Results: Average urea, uric acid, and creatinine were 18.06 ± 5.74, 3.65 ± 1.11, and 0.79 ± 0.12 mg/dL, respectively. The LUR model identified road networks and distance from the city center as critical factors contributing to increased particulate matter concentration. The GAM R^2 was 0.79, 0.31, and 0.28 for urea, uric acid, and creatinine, respectively. The mean $PM_{2.5}$ within a radius of 2000 m was identified as the most significant independent variable and showed an increasing impact on the renal parameters.
Conclusion: According to the results, reducing pollutant levels and preventing the creation of pollution hotspots via lowering road density are vital urban planning strategies to protect vulnerable groups, especially pregnant women.
Keywords: Particulate matter, Pregnant women, Environmental biomarkers, Urban pollution
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Introduction

Urbanization has been increasing worldwide for several decades and has undergone rapid and intense growth (1). This phenomenon has led to numerous challenges, including excessive population density, environmental degradation, inadequate infrastructure development, and issues such as traffic congestion, pollution, and insufficient access to essential services like water and sanitation (2). Air pollution is a highly complex phenomenon wherein various harmful substances, including gases, suspended particles, and biological molecules, contaminate the air (3). Pollutants can originate from natural sources such as wildfires, dust storms, and human activities, including transportation, energy production, and industrial processes (4). The harmful effects of air pollution can vary from respiratory irritation to chronic respiratory diseases, cardiovascular diseases, stroke, and lung cancer (5). The World Health Organization (WHO) estimates that air pollution causes 7 million premature deaths annually (6).

Some elements and substances that contribute to air pollution include nitrogen oxides, sulfur oxides, carbon monoxide, ozone, and particulate matter (PM) (7). PM is composed of solid or liquid particles suspended in the air, varying in size. The tiniest particles (less than 2.5 µm in diameter, known as $PM_{2.5}$) pose significant health risks as they can penetrate deep into the lungs and even enter the bloodstream (8). Research has shown that long-term exposure to high levels of $PM_{2.5}$ is associated with increased risks of respiratory diseases, including asthma and chronic obstructive pulmonary disease, premature death, cardiovascular diseases, and related strokes (9,10). Naturally, some population groups are more sensitive to the effects of air pollution than others, including children, the elderly, and pregnant women (11). Pregnant women exposed to air pollution during pregnancy may experience serious health effects for themselves and their developing

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fetuses. For example, air pollution in cities can increase the levels of PM in the air, harming pregnant women and leading to symptoms such as cough, headache, respiratory distress, and respiratory diseases (12). Research on the potential effects of PM on the health of pregnant women is increasing. Long-term exposure to high levels of PM is associated with various negative consequences for pregnant women, including increased risk of preterm birth, low birth weight, and preeclampsia. A study in China showed that high exposure to $PM_{2.5}$ during pregnancy increased blood glucose levels and the risk of gestational diabetes in Chinese women (13). Another study in California demonstrated that exposure to wildfire smoke, which contains high levels of particulate matter, is associated with an increased risk of preterm birth and fetal growth restriction (14).

The kidneys are vulnerable to environmental pollutants, as most ecological toxins are concentrated during filtration by the kidneys. This vulnerability affects up to 6% of women of reproductive age in high-income countries and is estimated to affect 3% of pregnant women (15). Serum urea, creatinine, and uric acid are three of the most commonly used biomarkers for assessing kidney function (16). Air pollution, mainly PM, ozone, and nitrogen dioxide, is identified as a potential risk factor for chronic kidney disease (2,4,17,18). Exposure to air pollution, particularly elevated levels of $PM_{2.5}$, is associated with impaired Kidney function in adults and children (19). Epidemiological studies have linked long-term exposure to traffic-related air pollution, including particles and ozone, to the risks of chronic kidney disease (20). In a cohort study involving African Americans, it was found that O_3 concentration was negatively correlated with estimated glomerular filtration rate (eGFR) and positively correlated with serum creatinine levels (21), suggesting that increased exposure to air pollutants such as PM may be associated with impaired kidney function.

Air pollution mapping refers to the visual representation of air quality data in a specific area (22), aiming to identify regions with high pollution levels and provide decision-makers with tools to formulate air quality-improving policies (23). A well-established method for generating pollution maps is land use regression (LUR) (24). It has a set of statistical methods to predict air pollutant concentrations in different areas such as urban (25) and industrial (26) environments relying on independent auxiliary variables such as distance to high-traffic roads, building density, number of vehicles, etc. Using LUR, several attempts has been made to examine the relationship between air pollution and parents' physiological conditions during different pregnancy stages. For example, a study in Isfahan city were investigated the effects of carbon monoxide and ambient particulate matter on fetal growth and liver enzymes. The findings indicated that an increase in monthly average concentrations of CO and $PM_{2.5}$ may lead to increased production of liver enzymes and decreased birth weight and height (27). Another study was conducted the association between exposure to ambient particulate matter and traffic-related indicators with glucose tolerance in healthy pregnant women in Sabzevar city, using the land-use regression approach. This research showed that PM1, $PM_{2.5}$, and PM10 exposure were significantly associated with higher fasting blood glucose (FBG) concentrations (28). Conducting studies that link exposure to air pollution with increased risk of respiratory diseases, cardiovascular diseases, and other health issues in sensitive groups such as pregnant women is necessary. In this study, pregnant women living in Yazd city, who shared similar lifestyles and pregnancy periods, were selected as the target group to assess the effects of air pollutants on the performance and overall kidney health of pregnant women. Accordingly, this research aimed investigate the relationship between average pollutant concentrations at the mothers' residential area and urea, creatinine, and uric acid levels in pregnant women.

Materials and Methods

Study area

Yazd city is located in the center of Iran and is recognized as the capital of Yazd Province. The approximate area of this city is about 76.5 km^2, located between 50° 78' to 51° 93' E Longitude and 32° 11' to 32° 69' N Latitude. The city's average elevation from the global mean sea level is 1200 m. Topographically, the city is situated on a low-gradient alluvial plain (29). With a population of over 600 000 residents, Yazd city ranks as the fifteenth most populous city in Iran. Surrounded by the central desert of Iran and the Loot Desert, the city has a hot and dry climate. The average temperature in summer generally exceeds 40 °C, and the annual average temperature is 19.9 °C. Precipitation in this city is much less than evaporation and transpiration, typically averaging only 7.67 mm during winter. The compact formation of impervious surfaces in the city, the intensive development of numerous air-polluting industries nearby (such as the ceramic tile, steel, chemical, and non-metallic mineral industries, and the frequent occurrence of dust storms has increase the pollution level of the city in recent years (30).

Selection of mothers

A cohort of 30 expectant mothers within the conventional and low-risk pregnancy ages for women (18-40 years) wholeheartedly volunteered to take part in this study from September to November 2022. Following a thorough explanation and signing an informed consent form approved by the Clinical Research Ethics Committee. They were healthy and had no history of chronic diseases, including heart diseases such as high blood pressure, kidney diseases, or liver diseases. Moreover, these individuals were unexposed to cigarette smoke, either personally or by close contacts, and maintained a consistent place of residence during pregnancy. They had a normal pregnancy without known conditions such as high blood pressure, diabetes, liver or kidney diseases, or preeclampsia. They were in their third trimester of pregnancy, beyond 36 weeks of gestation. geographical coordinates of each participant's residential address was documented using GPS (Figure 1).

Calculation of kidney biomarkers

Pregnant women who were in their third trimester during September to November 2022 were sampled, with a focus on those at or beyond week 36 of pregnancy, and $PM_{2.5}$ was calculated from 9 months earlier than sampling to the end of 2022. Blood samples (5 mL) were collected from pregnant individuals. The blood samples for biochemical analysis of kidney factors, including urea, creatinine, and uric acid, were collected in plain tubes with clot activators and transferred to the laboratory. The samples were centrifuged, and the serum was separated and stored at -80 °C for further analysis. Urea, creatinine, and uric acid are well-known metabolites in biological bodies that are produced throughout the body and increase in the blood due to decreased kidney function (31). Urea, creatinine, and uric acid were measured using an automated analyzer device (Biotecnica, BT3000, Rome, Italy) and commercial kits provided by Delta Darman Part (32).

Preparation of particle density and distribution map

In this study, particulate matter $PM_{2.5}$ was used as a dependent parameter which was influenced by land use, mainly urban traffic. This reference field data (Table 1) was obtained from 13 ground stations measured by (33).

This study used six independent parameters, including

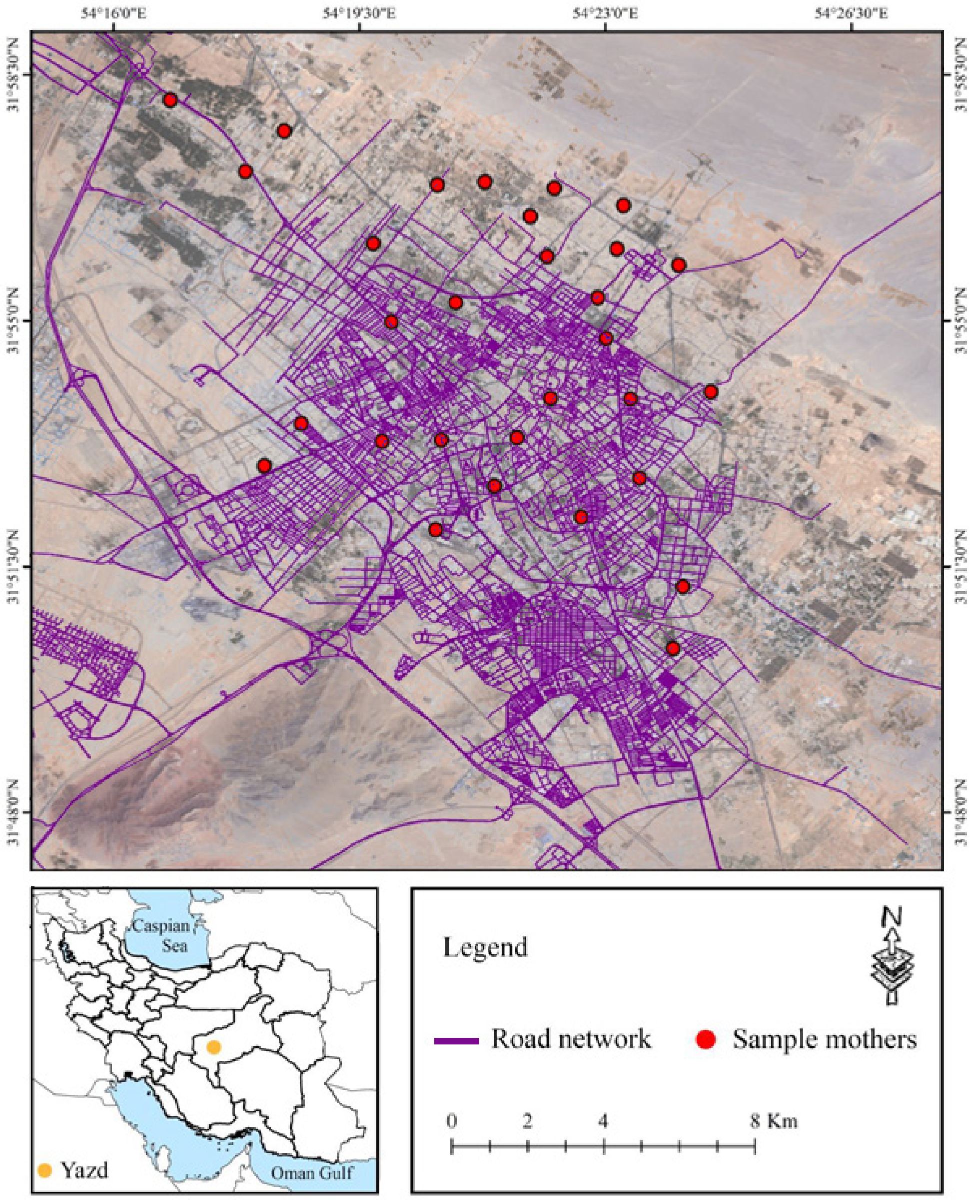

Figure 1. Map of Yazd city with its road network, along with the locations of pregnant women

Table 1. Particulate matter concentration (μg/m^3) in Yazd city

Particulate matter	Descriptive Statistics			
	SD	Min	Max	Average
Spring	74.46	83	223	87.26
Summer	65.59	74	213	82.93
Autumn	61.36	67	208	76.28
Winter	69.42	71	240	155.62

distance from the road, land slope, elevation above sea level, distance from the city center, construction density, and distance from intersections, to predict the dispersion of $PM_{2.5}$. The road map within the Yazd city area was obtained from the National Cartographic Center, and the distance was calculated using the Euclidean distance function (34) in the ArcGIS software. Critical intersections within the city were also identified in the ArcGIS environment, and the distance map from these intersections was calculated using the Euclidean distance tool. Azadi square was selected as the central point for the distance from the city center, and the distance from other areas to this square was calculated using the Euclidean distance. The Normalized Difference Built-up Index (NDBI) was used to calculate the building density. The NDBI was computed using a Landsat 8 satellite image acquired in autumn 2022 based on near-infrared (NIR) and short-wave infrared (SWIR) band information according to Equation (1), and its values range from + 1 to -1 (35). The closer the value of this index to one, the higher the density of the construction in that pixel. To calculate the land elevation and slope, the data obtained from the STR satellite were used; since Landsat satellite images and STR satellite digital elevation maps are computed at a cell scale of 30 m. All data were transformed to UTM geographic coordinates (36) with equal rows and columns and a cell spacing of 30 m for $PM_{2.5}$ calculation in LUR.

$$NDBI = (NIR\text{-}SWIR)/(NIR\text{-}SWIR) \quad (1)$$

Implementation of LUR model

After obtaining the dependent and independent data, the LUR model was executed in the R environment to predict the concentration of $PM_{2.5}$ in Yazd city. The support vector machine (SVM) method was used for training the LUR model. To train the LUR model, the data were introduced to the algorithm in the form of ASCII maps, and the training process was performed using 70% of the data. Additionally, the cross-validation method (37) was used to evaluate the accuracy of the model's output and obtain the best results. Finally, the coefficient of determination (37) was used for all data to measure the model's accuracy (38).

Modeling the relationship between suspended particles and kidney indices

With the estimated parameters of the performance of pregnant women' kidneys, their precise residential locations, and by generating a map of the density and spatial distribution of suspended particles in the city, the modeling of the relationship between these two parameter sets was investigated. Since numerous studies have shown that the effect of pollutant parameters often occurs in the form of neighboring impacts for an individual or a point (39), the effect of pollutant distribution was calculated for each pregnant mother at various radial distances. For this purpose, five buffer circles with radii of 1000, 2000, 3000, 4000, and 5000 m were drawn around each pregnant mother's residence, and the average level of $PM_{2.5}$ was calculated within each buffer. In the end, for all mothers, urea, uric acid, and creatinine levels were considered separately as dependent parameters, and the average level of $PM_{2.5}$ within each buffer was regarded as the influencing parameter. To model the relationship between the dependent and independent parameters, an advanced method called the generalized additive model (GAM) was used (40).

Results

All pregnant women aged 18-40 years with an average of 29 ± 6.16. They were in the third trimester of pregnancy, between weeks 36 to 40. The calculated mean levels of urea, creatinine, and uric acid in pregnant women were 18.06 ± 5.74, 0.79 ± 0.12, and 3.65 ± 1.11 mg/dL, respectively. The results of comparing the mean levels of renal parameters between different age groups of pregnant women are presented in Table 2. Based on the p-values, the urea level in mothers aged 30 to 35 years was approximately 19.12 mg/dL; in mothers aged 18 to 25 years, it was on average 16.87 mg/dL. However, no significant difference was found between maternal age and urea level ($P = 0.32$).

Furthermore, mothers aged above 35 had significantly higher uric acid levels, with an average of 3.87 mg/dL, compared to younger mothers, who had an average of 3.48 mg/dL ($P = 0.52$). Unlike urea and uric acid, the difference in creatinine levels varied significantly among different age groups ($P = 0.01$). In young mothers (aged 18 to 25 years), the creatinine level differed considerably from other groups, with an average of 0.74 mg/dL, and the age group of 25 to 30 years also differed from other groups. Mothers aged above 30 had a mean blood creatinine level of 0.815 mg/dL, significantly higher than the earlier age groups.

The spatial distribution map of $PM_{2.5}$ in Yazd and its outskirts was influenced by six factors in Figure 2. According to the presented model, the concentration of $PM_{2.5}$ was very high in the city center, with an annual average of 240 μg/m^3, which decreased as we moved towards the outskirts of the city and away from the construction density, reaching 70 μg/m^3 in some areas such as the southern regions. The coefficient of determination for the LUR model, by comparing the calculated actual

Table 2. Comparison of mean renal parameters among age groups of pregnant women

Parameter	Comparison	Sum of squares (SS)	Degrees of freedom (df)	Average of squares	F	Sig.
Urea	Between the group	115.3	3	38.4	1.16	0.32
	Inside the group	4806.4	146	32.9		
	Total	4921.8	149			
Uric acid	Between the group	2.7	3	0.9	0.74	0.52
	Inside the group	181.8	146	1.2		
	Total	184.5	149			
Creatinine	Between the group	0.17	3	0.05	4.00	0.01
	Inside the group	2.14	146	0.01		
	Total	2.32	149			

Table 3. Values of the inflation factor, variance, and relative importance of the parameters used for LUR modeling

Variable	Relative importance	VIF	Variable	Relative importance	VIF
Road	0.27	1.61	Height	0.05	3.67
Slope	0.07	2.36	Intersection	0.14	4.55
Distance from the city center	0.24	2.38	Construction density	0.23	4.41

values of suspended particles against the predicted values in Figure 3, was found to be 0.77, indicating the model's capability for predicting $PM_{2.5}$ in the study area. As shown in Table 3, values of the inflation factor, variance, and relative importance of the parameters used for LUR modeling, none of the parameters used for implementing the LUR model exhibited high linearity (greater than 6.00). Among the sensitive parameters, distance from roads, distance from the city center, and distance from intersections were identified as the most essential parameters, with 0.27, 0.24, and 0.23, respectively. Based on this, it can be concluded that the spatial distribution of suspended particles in Yazd can be successfully predicted using transportation-related parameters, especially roads, and intersections, which have a higher density in the city center.

In the GAM, the minimum value of the standard error distance was obtained for predicting urea. In contrast, this distance increased for the parameters of uric acid and reached its maximum value for creatinine, particularly in the radial ranges of 2000 and 3000 m. The level of urea in pregnant women depends not only on the level of suspended particles in the vicinity of their residence but also on the levels of suspended particles up to a distance of 5000 meters in Figure 4. However, as shown in Table 4, the highest effect can be observed in the 2000-meter radial range. Regarding uric acid, the concentration of $PM_{2.5}$ only led to a significant impact at radial distances of 2000 ($P=0.04$) and 5000 ($P=0.03$) m, while in other radii, suspended particles had a minimal effect in buffers of 1000, 3000, and 4000 m. For the parameter of creatinine, a significant effect was observed only in the 2000-m buffer ($P=0.03$), and other radial distances did not show a significant impact. In Figure 5, the accuracy of the models used is demonstrated. For the urea model, the coefficient of determination (R2) was found to be 0.83, indicating a high confidence level in predicting the impact of particulate matter on changes in urea levels in pregnant women. However, the R^2 values were obtained for uric acid and creatinine as 0.42 and 0.38, respectively. One of the main factors contributing to the lower R^2 values in these two models was the lack of a significant effect of particulate matter at certain radial distances. Additionally, the impact of age and other parameters on creatinine, as mentioned in this study, could contribute to the lower R^2 value in the creatinine model for pregnant women.

Table 4. Significance of input parameters in GAM

Parameter	Creatinine		Uric acid		Urea	
	F	*P* value	F	*P* value	F	*P* value
c-1000	0.22	4.92	0.11	3.29	0.03*	0.14
c-2000	0.03*	3.73	0.04*	2.79	0.02*	1.28
c-3000	0.41	3.94	0.15	6.74	0.01*	2.83
c-4000	0.38	1.77	0.16	4.19	0.00*	1.14
c-5000	0.07	1.07	0.03*	3.44	0.02*	1.49

* Significant parameters in GAM.

Discussion

The city of Yazd has been grappling with notably high levels of air pollution attributed to factors such as industrial expansion, increased vehicular activity, and inadequate traffic management (28). Our research findings underscore that the highest concentration of $PM_{2.5}$ is concentrated within the city center, averaging an annual measure of 240 μg/m^3. n contrast, concentrations are comparatively lower in the suburban regions, notably in the southern areas, where levels reach 70 μg/m^3. While WHO recommends a maximum airborne $PM_{2.5}$ level of 10 μg/m^3, the observed concentrations in Yazd vastly exceed

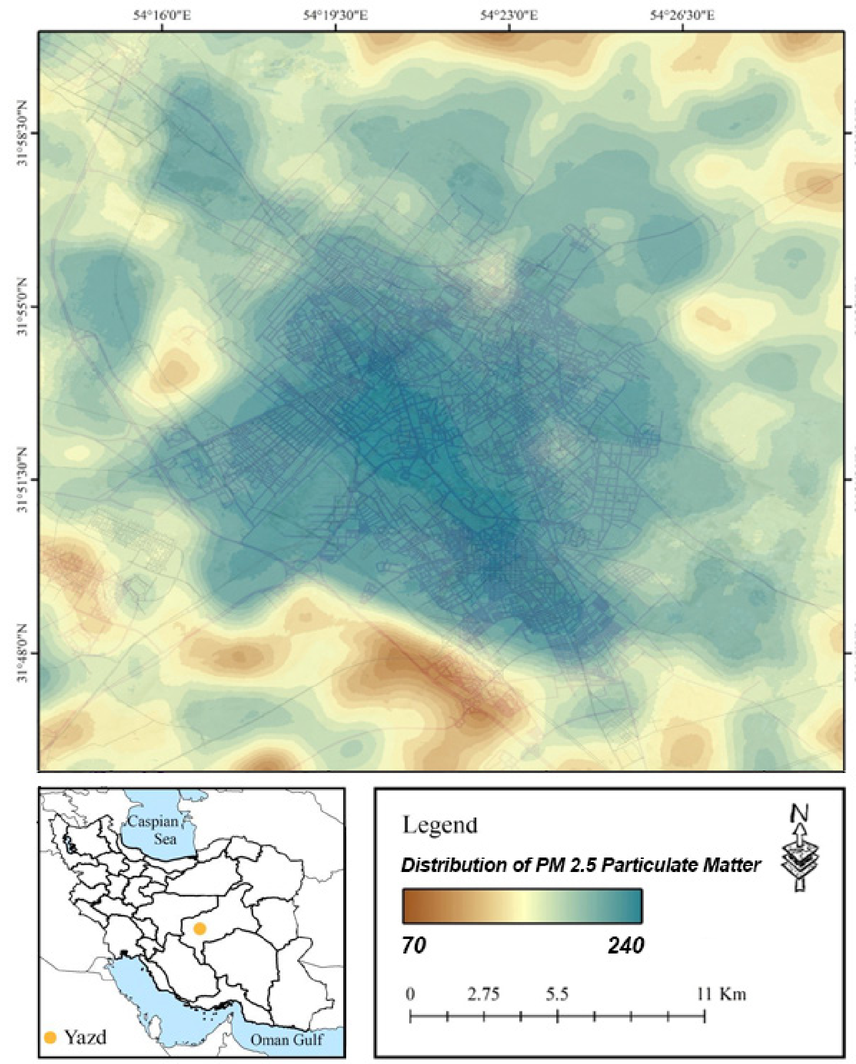

Figure 2. Spatial distribution of particulate matter resulting from the implementation of the land regression model in Yazd city and its outskirts

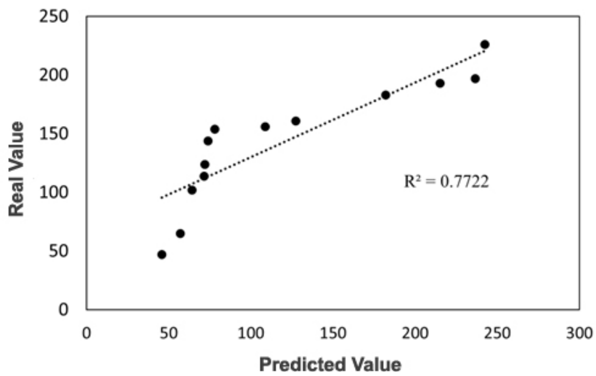

Figure 3. Coefficient of determination of the land regression model for predicting the distribution of particulate matter ($PM_{2.5}$)

this threshold. This concerning pollution poses significant risks to vulnerable groups, especially pregnant women. A compelling study demonstrated that an increase in the concentration of PM to levels above 50 and 100 μg/m^3 may disrupt the physiological functions of pregnant women, mainly kidney function. The results of this study indicated no significant difference between the age of mothers and the levels of urea and uric acid. However, it's important to approach the notable variations in creatinine levels in relation to age with caution, considering the potential influence of age and environmental conditions (41).

The SVM-LUR model achieved an acceptable coefficient of determination (42). The model considered building density and traffic as the most important independent variables. Additionally, the road network was identified as a more influential factor in the distribution of $PM_{2.5}$ as compared to simialr studies (43,44). Furthermore, major city intersections were considered effective parameters, and the results indicated that, in addition to road density, they also played a significant role in determining particulate matter concentrations. Studies that emphasized the importance of intersections in traffic density and particulate matter distribution corroborated the present research findings (45,46).

For model training, only the normalized annual average residential differentiation index was utilized in this study. Topographic parameters were of relatively low importance, similar to some previous studies (47,48). The

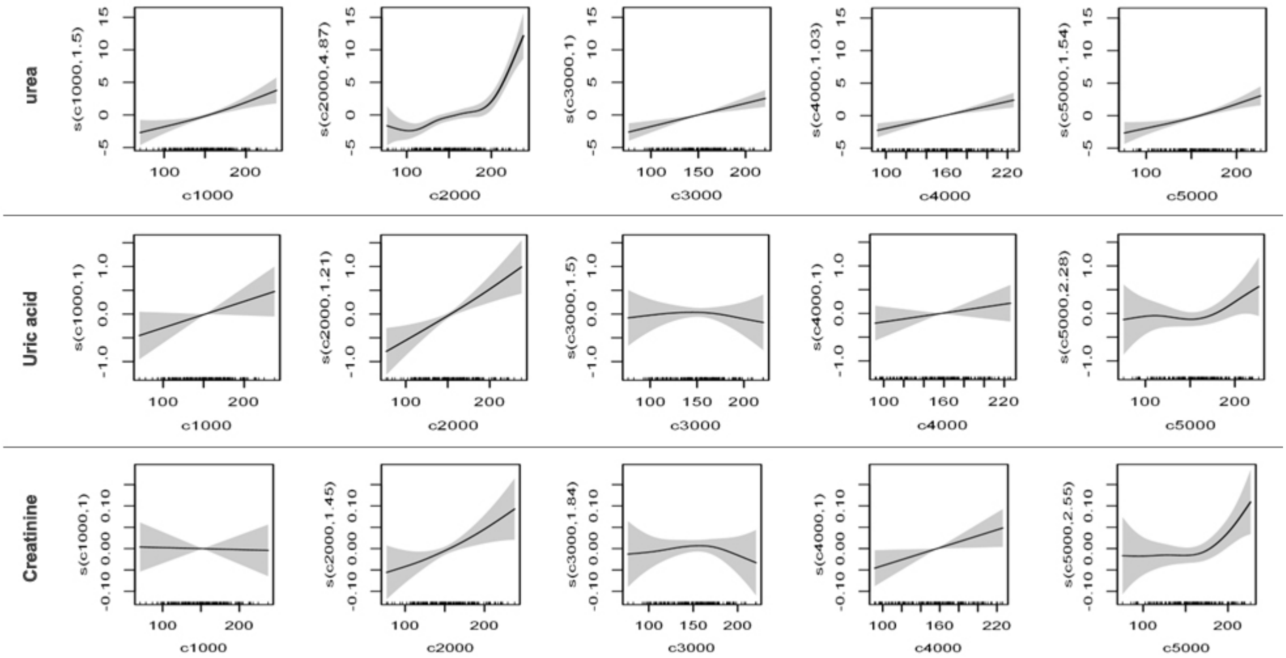

Figure 4. The partial effect of air pollution on urea, uric acid, and creatinine within buffer zones ranging from 1 (1000 m) to 5 (5000 m) kilometers

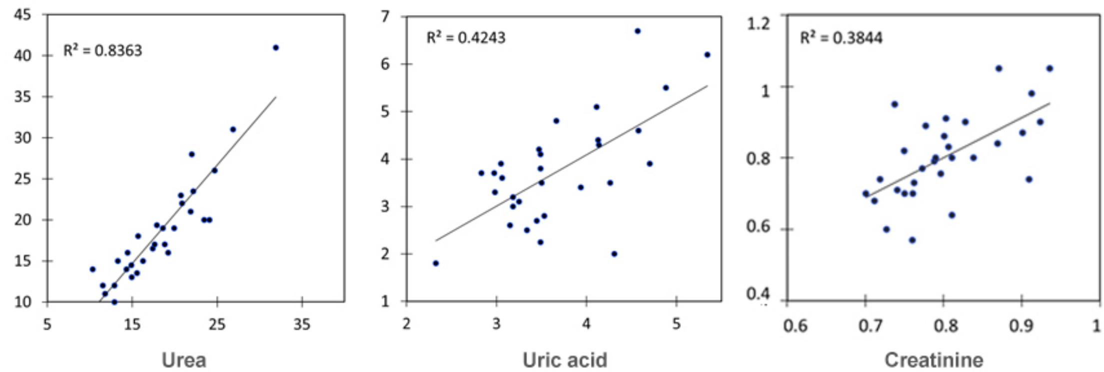

Figure 5. Accuracy of generalized additive models for predicting urea, uric acid, and creatinine in pregnant women

study showed that particulate matter concentrations had the highest impact on urea, uric acid, and creatine at a radial distance of 2000 meters. Thus, it can be concluded that in the city of Yazd, PM concentrations at a radial distance of 2000 m are influential as a measure of local and regional effects on pregnant women. In the case of uric acid, highly significant results were obtained. It was observed that the average concentration of PM had a significant effect at a radial distance of 5000 meters, while at a distance of 1000 meters (indicating the local impact of particulate matter on pregnant women), this effect was not significant. Therefore, higher importance can be attributed to more considerable radial distances regarding the mobility range of pregnant women, and similar results have been presented in previous studies (49).

Air currents play an essential role in this phenomenon. Due to air currents, pollutant concentrations vary at a fixed location, typically moving horizontally depending on wind flow and surface temperature, both above and below the ground surface. Assuming that these horizontal flows usually occur within small to 5-km radii, it can be concluded that the influence of larger radii on uric acid concentration, which affects pregnant women, is more significant. This issue is discussed and examined in previous studies (27). Therefore, it is essential for pregnant women to pay attention to the average concentration of particulate matter, which forms hotspots, to maintain their health (50).

The kidneys are highly susceptible to all environmental pollutants by concentrating most environmental toxins during filtration. Given the high mortality and morbidity associated with renal disease, becomes imperative to identify environmental risk factors and comprehend their impact on kidney health (51). Increasing evidence suggests that environmental pollutants play a role in the progression of kidney disease and require greater attention (52). Environmental air pollution, mainly suspended particles, ozone, and nitrogen dioxide, has emerged as a potential risk factor for chronic kidney disease (17,53–55). Previous studies have demonstrated a connection between higher levels of air pollutants and the prevalence of chronic kidney disease (4,56). Exposure to air pollution, especially particles with a diameter of ≤ 2.5 micrometers, is associated with impaired kidney function in adults and children (57). Epidemiological studies have linked long-term exposure to traffic-related air pollution, including particles and ozone, to the risks of chronic kidney disease (20).

Conclusion

This study evaluated the activity and performance of pregnant women in terms of creatinine, urea, and uric acid concentrations as indicators of maternal health, which are influenced by various levels of pollutants, particularly particulate matter, in the city of Yazd. The LUR method was used to generate a map of particulate matter concentrations in the city of Yazd, which showed higher concentrations in central areas and gradually decreased as moving towards surrounding areas. No significant difference was observed in urea and uric acid concentrations among different age groups of mothers. The LUR model demonstrated that the road network and distance from the city center were among the most influential factors in increasing particulate matter concentrations. The average particulate matter concentration within a 2000-m radius was identified as the most significant independent variable. These findings underscore the significance of reducing pollutant levels across the city and curbing the formation of pollution hotspots. Achieving this involves strategies such as lowering road traffic density. Incorporating these insights into urban planning becomes essential to safeguard the health of sensitive groups, especially pregnant women.

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Authors' contributions

Conceptualization: Atefeh Chamani.
Data curation: Reman Mohammed Mahgoob Al-Azzawi.
Formal analysis: Atefeh Chamani.
Funding acquisition: Atefeh Chamani.
Investigation: Reman Mohammed Mahgoob Al-Azzawi.
Methodology: Reman Mohammed Mahgoob Al-Azzawi.
Project administration: Atefeh Chamani.
Resources: Atefeh Chamani.
Software: Reman Mohammed Mahgoob Al-Azzawi
Supervision: Atefeh Chamani.
Validation: Atefeh Chamani.
Visualization: Reman Mohammed Mahgoob Al-Azzawi.
Writing–original draft: Reman Mohammed Mahgoob Al-Azzawi.
Writing–review & editing: Atefeh Chamani

Competing interests

The authors declare no conflicts of interest or competing financial or personal relationships that could have influenced the results or interpretation of this study.

Ethical issues

This study was approved by the Research Ethics Committees of the Islamic Azad University - Isfahan (Khorasgan) Branch in accordance with the ethical principles and the national norms and standards for conducting Medical Research in Iran. (Ethical code: IR.IAU.KHUISF.REC.1401. 245). All the ethical guidelines and safety procedures were considered during the experimental period.

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