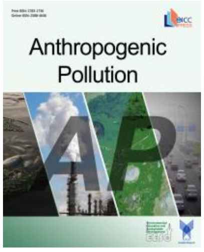

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Research Article

Comparing Trimester to Multi-Year Exposure Windows of Ambient Aerosol and Their Effects on Maternal Blood Biomarkers at Birth

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Abstract

Exposure to ambient aerosols during various lifetime windows may influence maternal blood biomarkers. This study investigates the impact of ambient aerosol exposure during distinct temporal windows (trimester-specific, gestational, and multi-year) on maternal liver biomarkers at delivery in highly polluted regions. Conducted in 2023–2024, the study enrolled 116 pregnant women from Khuzestan Province, Southwest Iran, a region with significant air pollution. Maternal blood samples were collected at birth and analyzed for liver enzymes (ALT: 5- 55 u/L, AST: 9- 51 u/L, ALP: 145- 702 u/L, GGT: 6.7- 99.5 u/L). The MODIS Aerosol Optical Depth (AOD) layers were averaged to create trimester-specific (AOD_{1st}, AOD_{2nd}, AOD_{3rd}), gestational (AOD_{gest}), and 2- and 5-year pre-delivery (AOD_{2y}, AOD_{5y}) aerosol exposure windows for each participant. Employing a multi-modeling approach using a Generalized Additive Model ($0.179 < R^2 < 0.693$), our analysis revealed that biomarkers are more sensitive to AOD levels during mid and late pregnancy compared to those reflecting longer-term exposure. Both urban and regional air quality significantly influenced oxidative stress markers in maternal blood. These findings highlight the liver as susceptible organs to particulate matter-induced oxidative stress and inflammation in highly polluted regions, emphasizing the need for stricter air quality regulations to protect maternal health.

Keywords: Air Pollution; Aerosol optical depth; Blood biomarker; Aerosol exposure

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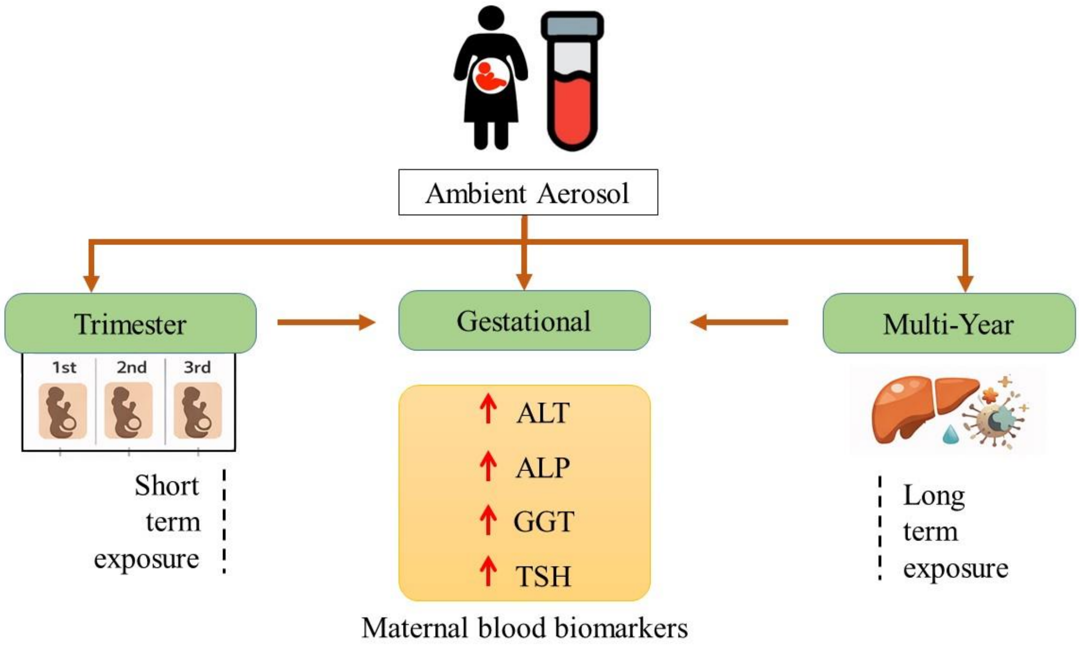
Graphical Abstract



1. Introduction

The Earth is currently experiencing unprecedented levels of pollution in the Anthropocene epoch. Municipal and industrial activities continuously pump out emissions, making air pollution a persistent challenge in densely populated urban areas (Yang et al., 2020). This problem can be occasionally exacerbated by regional factors that degrade air quality, such as dust storms triggered by climate change (Dey and Lewis, 2021), which highlights the multi-scale nature of air pollution, where both local and regional air quality significantly impact health outcomes. The OECD Environmental Outlook to 2050 warns that without policy intervention, ambient air pollution could become the leading cause of environmentally related deaths globally. For instance, global premature deaths, which were under 1.5 million in 2010, could exceed 3.5 million by 2050 solely due to the continued release of particulate matter (PM) into the atmosphere. The Asian continent is likely to be the most affected region, wherein excessive urban expansion, climatic vicissitudes, and demographic aging synergistically exacerbate environmental exigencies (OECD, 2012).

PM, specifically fine $PM_{2.5}$ and coarse PM_{10} (particles with an aerodynamic diameter less than 2.5 and 10 μm, respectively), poses significant health risks to urban populations due to their varying sizes and ability to penetrate deeper into the respiratory system (Mebrahtu et al., 2023). Furthermore, the impact of PM exposure on human health is not uniform, exhibiting significant variation based on demographics (race, gender, age) and physiological conditions like pregnancy (Nourouzi and Chamani, 2021). Studies have demonstrated that women, particularly during pregnancy, are highly susceptible to a broad spectrum of health complications due to ambient PM exposure (Bell et al., 2015, Park et al., 2023). Other studies, such as Hu et al. (2023), highlight the long-term effects of chronic exposure to air pollutants as a more important factor for pregnant women, suggesting a lack of consensus regarding the short-term versus long-term impacts of ambient PM on their health. Furthermore, the effects on the fetus seem to be trimester-specific, with the greatest susceptibility observed during late pregnancy, particularly the third trimester (Nourouzi and Chamani, 2021).

Serum biomarkers include a diverse range of indicators essential for assessing various aspects of body functioning, particularly during pregnancy (Ji et al., 2024). These include markers for liver function and bone health, all critical for maternal well-being. Elevated liver enzymes, for example, can signal liver inflammation or damage, potentially affecting maternal health (García-Romero et al., 2019). While some increase in enzyme levels is expected during pregnancy, abnormally high levels can indicate serious disorders requiring immediate medical intervention. Existing literature indicates that elevated levels of serum biomarkers can reflect the maternal response to environmental stressors such as ambient aerosol content. For instance, Nourouzi and Chamani (2021) demonstrated that increasing mean monthly concentrations of $PM_{2.5}$ might stimulate further production of liver enzymes while adversely affecting maternal health. Similarly, Yousefzadeh et al. (2024) found statistically significant associations between atmospheric aerosol content and maternal oxidative stress, showing that the effects of PM could be more severe during the third trimester of pregnancy. Ji et al. (2024) discovered a link between exposure to PM_{10} during pregnancy and alterations in biomarkers linked to inflammation, heart health, metabolism, cancer risk, and brain function in mothers. Despite the growing body of literature, few studies have jointly considered both the temporal scale (trimester vs. multi-year) and spatial context (urban vs. regional) of aerosol exposure.

The southwest region of Iran presents a notable case study area for assessing the effects of air pollution on pregnant mothers due to its significantly high levels of air pollution and PM content at a global scale (Zallaghi et al., 2021). Strong evidence from the region suggests that the concentration of ambient air pollutants, particularly PM, can increase sharply, causing short-term health damage (including respiratory mortalities) across various groups (Dastoorpoor et al., 2019). Moreover, the combined adverse effects of environmental issues such as climatic and air pollution problems in the region have been found to significantly affect pregnancy outcomes (Khodadadi et al., 2022). To deepen our understanding of how pregnant women in this region respond to air pollution, this study aimed to achieve three key objectives. First, we established a baseline by measuring serum enzyme levels in delivering mothers in this highly polluted region. This data will serve as a valuable comparison point for future studies on the health of pregnant women living in polluted areas. Second, we employed a multi-modeling approach to assess the impact of both short- and long-term air pollution on pregnant women in the region, thus identifying which exposure time windows (from multi-year to specific trimesters) most significantly influence maternal health. Finally, by recruiting participants from a broad geographical area, the modeling approach allowed us to differentiate between the effects of regional air quality and specifically urban air quality on pregnant women. To our knowledge, this is the first study to simultaneously evaluate the temporal (short vs. long term) and spatial (urban vs. regional) dimensions of aerosol exposure on enzymatic blood markers among pregnant women in Khuzestan Province. This dual-scale approach provides novel insights into differential pollutant effects in a vulnerable population.

2. Material and Methods

2.1. Study region

Khuzestan Province, located in southwest Iran (Figure 1), spans an area of 64,000 km^2 (47°40' to 50°33' E longitude and 29°57' to 33°00' N latitude) and is home to over 4,710,000 people. Known for its extreme temperatures, agricultural productivity, and industrial activities, Khuzestan starkly contrasts with other regions of Iran. It is entirely bordered by the northern Zagros mountains and a southern water body, forming a fertile plain. This province is a critical center for oil extraction (Velayatzadeh, 2020). It also ranks among the most polluted areas in the country, largely due to frequent dust storms and intensive industrial (particularly petrochemical) activities (Rahimi et al., 2024). The climate in Khuzestan varies significantly: the southern regions near the sea are hot and humid, while the northern areas, with altitudes exceeding 3,700 meters above sea level, experience cooler and more humid conditions (Vafa et al., 2021). Ahvaz City, covering 8,150 km^2 (48°40' E longitude and 31°20' N latitude), serves as the administrative center and the most densely populated area within the province, with approximately 1,056,000 inhabitants (the zoom in Figure 1). Long-term observations indicate that the mean annual temperature in Ahvaz is 25.3°C, fluctuating between 23.4°C and 26.9°C since the 1950s (Rahimi et al., 2024). Air pollution and the consequent deterioration of air quality have become primary concerns for both Khuzestan Province and its capital city, Ahvaz. Over the past decade, the mean concentration of $PM_{2,5}$ Ahvaz has been recorded at 63.27 $\mu g/m^3$ by the Khuzestan Department of Environment.

2.2. Selection of the Maternal Cohort and Biomarker Measurement

We created a list of all women in early pregnancy in Khuzestan province in 2023. We found that the majority of pregnancies meeting our criteria were expected to result in births between January and February 2024, and we selected this cohort as our case participants. Initially, we excluded all mothers with a history of respiratory, cardiovascular, or other chronic diseases that could potentially impact bodily functions, leading to biased results. We also excluded mothers whose Body Mass Index (BMI) (Khanna et al., 2022) was outside the normal range. We then interviewed the remaining pregnant women to identify and exclude smokers, those exposed to secondhand smoke (passive smokers), those with high mobility outside their neighboring areas (except for routine shopping and errands), and those who had changed their residence in the past five years. Exposure was assigned based on each participant's residential address at the time of delivery. This information was verified through in-person field visits and spatially matched using high-resolution urban maps.

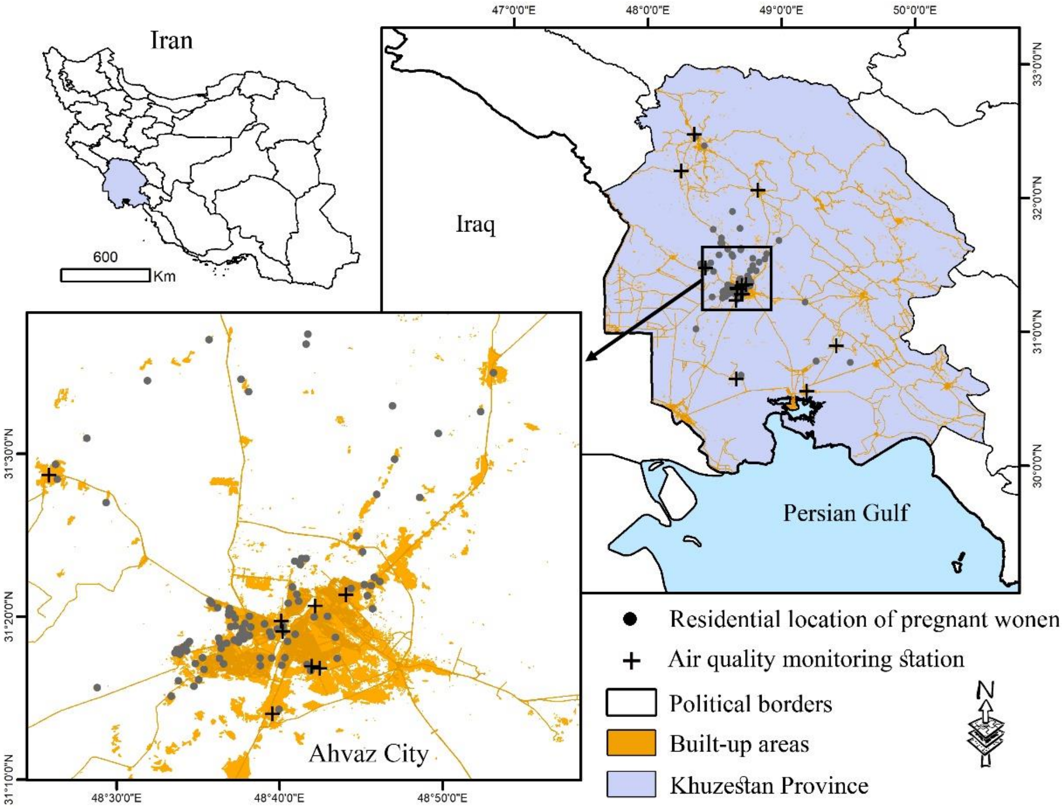


Figure 1. Residential locations of pregnant women across Khuzestan Province, Southwest Iran, with a focus on Ahvaz City

We excluded any mother who had changed residence during pregnancy or within the previous five years. Participants did not engage in outdoor activities such as walking in parks, exercising, or participating in city events, which are more common in larger metropolitan populations.

Their movement was limited to brief local errands within walking distance. This low-mobility, home-centered lifestyle was culturally and socioeconomically characteristic of the study population and was confirmed through structured interviews and local health records. These criteria, consistent with validated approaches in similar studies, ensured that the spatially assigned AOD values accurately represented their true exposure throughout pregnancy.

Additionally, we ensured that all participants shared similar lifestyles and dietary habits, characterized by high carbohydrate consumption and moderate to low meat intake. The sample size was calculated using the formula: $n = Z^2\sigma^2/d^2$, where $Z = 1.96$ for 95% confidence, $\sigma = 12$, and $d = 2.5$ (desired precision), yielding a minimum required sample size of 88. Home addresses of the participants were verified through direct field surveys and referenced against high-resolution urban maps to ensure accurate spatial assignment of participants within the MODIS AOD layers.

To assess maternal health following spontaneous delivery with normal physiological parameters, blood samples (4 mL) were collected from mothers. We measured the concentrations of several biomarkers: liver enzymes [alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT)]. These biomarkers are essential for monitoring maternal health during pregnancy (Nourouzi and Chamani, 2021). Notably, abnormal levels can indicate pregnancy-related complications such as gestational diabetes or preeclampsia, potentially affecting nutrient processing, waste elimination, oxidative stress, and inflammation (Ji et al., 2024). Biochemical analyses of AST, GGT, ALP, and ALT were performed using a Biotecnica BT 1500 analyzer (Italy), following manufacturer protocols. All tests were conducted in duplicate, and intra-assay coefficients of variation were below 5%, confirming high analytical precision. Duplicate analyses were conducted to ensure data accuracy, and results from both runs were highly concordant. Measurements were conducted in accordance with the ethical standards and guidelines as approved by the Isfahan Islamic Azad University under the ethical code: IR.IAU.KHUISF.REC.1402.285.

2.3. Predictor Variables and Air Pollution Exposure

The variables representing the distribution and intensity of air pollution across the province were generated as proxies using satellite imagery and stationary local factors (elevation and road density), known to contribute to air pollution in the region. Satellite images provide timely acquisition of aerosol content in the atmosphere during various time intervals. Hence, daily (1 km) Aerosol Optical Depth (AOD) data at an optical depth of 470 nm, retrieved from the Moderate Resolution Imaging Spectroradiometer (MODIS) instrument aboard NASA's Aqua and Terra satellites, were employed as a proxy for atmospheric aerosol content in the region (Yousefzadeh et al., 2024). Higher AOD values serve as a quantitative proxy for increased atmospheric aerosol load, indicating potentially higher concentrations of fine and coarse PM, which are associated with more severe air pollution.

Given the free access to the Google Earth Engine platform (Pérez-Cutillas et al., 2023), we applied a temporal filter to average AOD layers for various time profiles. Based on the birth date of each newborn, AOD values were averaged to obtain mean AOD layers for each trimester: first ($\mathrm{AOD_{1st}}$), second ($\mathrm{AOD_{2nd}}$), and third ($\mathrm{AOD_{3rd}}$) trimesters. The mean of these three layers was calculated to determine the AOD for the entire gestation period ($\mathrm{AOD_{gest}}$). These four layers represent the acute exposure of the participants to air pollution in the region. Additionally, the temporal profile was extended to include AOD variables representing chronic exposures to atmospheric aerosol content for 2 years ($\mathrm{AOD_{2y}}$) and 5 years ($\mathrm{AOD_{5y}}$) prior to delivery.

We recognized that AOD layers might not significantly change over short periods, especially during trimesters. Therefore, collinearity analysis was performed using the Variance Inflation Factor (VIF) and ANOVA Tukey post hoc analysis. We hypothesized that AOD values are distinct and have independent predictive value if the VIF is less than 5.0 and show significant differences with a p-value of less than 0.05. Each AOD layer was individually and collectively validated using $\mathrm{PM_{10}}$ data collected during the same time periods. We selected 14 ground monitoring stations that spatially covered the regions where the participants resided. We plotted AOD vs. PM data and used the correlation coefficient (r) to evaluate the significance of the relationship, assuming that AOD data can only be used with a significant association with PM data (p-value < 0.05).

In addition to AOD layers, the Digital Elevation Model (DEM) of the region, acquired from ASTER DEM at 30 m resolution (Abrams et al., 2020), and the density of the road network were utilized as other stationary variables. DEM values increase gradually towards the northern area of the province with an altitudinal range of 3700 m, transitioning from coastal sandy regions to moderately-vegetated cooler areas in the north, thus serving as a variable indicating regional air quality. The road layer of the province was obtained from the Iranian Cartographic Center and applied for Kernel Density analysis to identify areas with relatively higher road density. Ahvaz City and smaller cities exhibited higher values, indicating larger traffic volumes and the presence of gasoline-based vehicles as the main sources of air pollution in these areas.

2.4. Model Building and Statistical Analysis

The modeling procedure involved biomarkers as dependent variables and air pollution data and proxies as independent variables. Maternal age was examined for its potential influence on biomarker levels using preliminary non-parametric tests. However, instead of excluding age-sensitive biomarkers, we interpreted the modeling results in light of this influence. Age was not treated as a confounder in the final models due to the narrow and relatively uniform age distribution of the cohort (mean: 25.4 ± 6.18 years), which limited the risk of age-related bias. Due to the non-normal distribution of biomarker concentrations, the Kruskal-Wallis test was employed to detect significant differences in biomarker concentrations across maternal age groups divided into five equally-divided classes, ranging from 18 to 38 years, which is the age range of the maternal participants.

Prior to modeling, a Levene's test for homogeneity of variances was conducted across biomarker groups categorized by region. Results showed no significant variance heterogeneity ($p > 0.05$), indicating acceptable data consistency for regression modeling. To assess the potential confounding effect of maternal characteristics, all GAM models were re-run including maternal age, pre-pregnancy weight, and height as covariates. The conditional modeling framework, which minimized variability through selection (e.g., excluding smokers, those with chronic diseases, or variable lifestyles), ensured minimal confounding from these factors. Nonetheless, their inclusion did not meaningfully alter the strength, direction, or significance of observed associations, confirming the stability of model outputs (Appendix A). To minimize potential bias arising from redundant information or confounding factors, colinear predictor variables and age-dependent biomarkers were excluded from subsequent analyses.

Given the identification of non-linear relationships between certain variables, a Generalized Additive Model (GAM) was employed using the mgcv package in R software (version 1.8–42, (Wood, 2011)). Unlike a linear model, GAM allows for flexible, non-linear relationships between the response variable (biomarkers) and the explanatory variables (including air pollution data and proxies). The model's performance was evaluated by plotting observed versus predicted values of the biomarkers and calculating the coefficient of determination (R^2). Additionally, the Restricted Maximum Likelihood (REML) method was used within the mgcv package to estimate the model parameters and smooth curves, a core feature of GAMs. F-test was also used to compare the fit of nested models (models with and without specific terms), helping to select the most parsimonious model that adequately explains the data. Figure 3 depicts a flowchart summarizing the key steps carried out in this study.

3. Results

The study encompassed 116 cases, consisting of infants born between January 11th and February 24th, 2024. The average daily birth rate among mothers who met the screening criteria was 3.38 across Khuzestan Province. Maternal ages ranged from 18 to 38 years, with a mean of 25.4 ± 6.18. This narrow age range reflects a relatively homogeneous cohort. Based on screening records, none of the mothers were classified as overweight or obese prior to pregnancy. The mean BMI of the cohort was less than 25 kg/m². Participants represented a well-distributed spatial sample across the province, including the capital city of Ahvaz, as well as the northern highland and southern coastal areas (Figure 1). Table 1 summarizes the results of serum biomarker measurements from delivering mothers. Comparative analysis indicates that the mean ALT concentration was 18.7 ± 9.7 U/L, while the mean GGT concentration was 17.2 ± 13.0 U/L. The Kruskal-Wallis test revealed that most serum biomarkers were independent of maternal age (Table 1), except for AST, which was excluded from further modeling due to its significant dependence on maternal age.

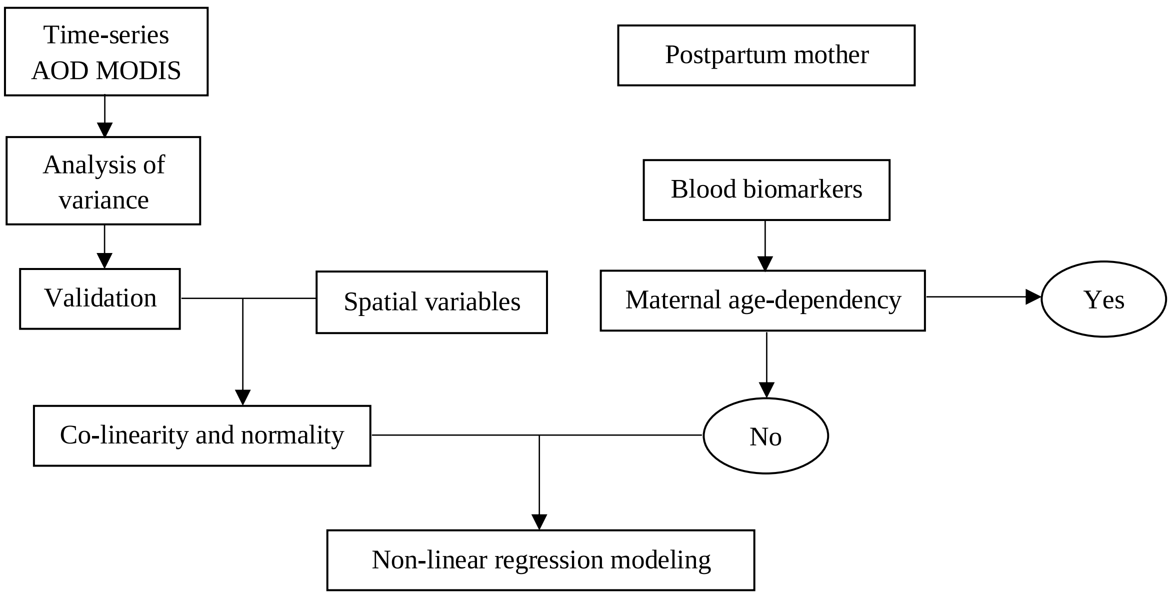


Figure 2. Research flowchart

Table 1. Summary Statistics and Statistical Tests of Blood Markers- ALT, AST, ALP, and GGT- Measured from Delivering Mothers

Blood marker	Statistical parameters				Normality (K-S)		Kruskal Wallis *	
	Min	Max	Mean	Std De.	Statistic	Sig.	Chi^2	Sig.
ALT (u/l)	5.0	55.0	18.7	9.7	0.130	0.000	3.456	0.485
AST (u/l)	9.0	51.0	20.3	8.3	0.119	0.000	15.403	0.004
ALP (u/l)	145.0	702.0	338.7	93.3	0.116	0.001	1.603	0.808
GGT (u/l)	6.7	99.5	17.2	13.0	0.237	0.000	1.102	0.894

** The degrees of freedom for this test were set to 4, corresponding to the predefined maternal age groups*

The MODIS AOD layers underwent averaging contingent upon the birth dates of individual infants using the functionality facilitated within the cloud-based processing infrastructure of GEE (Table 2). The highest AOD values were recorded during the second trimester of pregnancy, averaging 0.383 ± 0.041. AOD observations are graphically represented in Figure 4, depicting notable variability in AOD values across the region, particularly concentrated around Ahvaz City. This phenomenon accentuates the suboptimal air quality prevalent in Ahvaz City, where the majority of the maternal cohort was situated. The lowest AOD values were observed in the third trimester, a critical period for maternal health impacts. On average, the mean AOD throughout the gestation period was high (0.334 ± 0.033) and slightly exceeded the 5-year mean AOD values recorded in the region.

The ANOVA Tukey post hoc test indicated significant variations in AOD values between trimesters, highlighting notable seasonal differences in air quality. AOD values from the second trimester (AOD_{2nd}) were statistically similar to those for the entire gestation period (AOD_{gest}). Furthermore, similar statistical consistency was observed between the 2-year and 5-year AOD values, suggesting that despite significant seasonal variability, the atmospheric aerosol content has remained relatively stable annually over the study period from 2019 to 2023. Among the AOD variables, AOD_{2y} exhibited a significantly high VIF value, leading to its exclusion from the modeling procedure.

In addition to AOD values, Kernel and DEM layers were prepared and used as predictor variables in this study (Figure 3). The DEM layer illustrates a gradual increase in altitude towards the north. Additionally, the high density of roads within the Ahvaz territory resulted in significantly higher Kernel values around the city compared to the surrounding areas. The assessment of AOD validity is presented in Figure 4, which shows that AOD values are valid in representing the atmospheric content of the region with r = 0.621 (p-value < 0.05). Among the AOD layers, the lowest association between AOD and PM_{10} data was observed during the third trimester, as its exclusion increased the overall AOD validity. Conversely, the highest validity was associated with the first trimester, as its exclusion decreased the correlation coefficient between the remaining AOD-PM_{10} pairs.

Table 2. Descriptive statistics, normality test results, and ANOVA Tukey post hoc test results for AOD layers over various (pregnancy) periods

AOD statistics		AOD layer					
		AOD_{1st}	AOD_{2nd}	AOD_{3rd}	AOD_{gest}	AOD_{2y}	AOD_{5y}
AOD value	Min	0.243	0.270	0.190	0.281	0.297	0.277
	Max	0.435	0.457	0.352	0.397	0.436	0.373
	Mean	0.307	0.383	0.289	0.334	0.365	0.329
	Stdev	0.030	0.041	0.038	0.033	0.030	0.023
Normality	KS stat.	0.078	0.080	0.117	0.083	0.082	0.060
	Sig.	0.089	0.073	0.011	0.055	0.058	0.200
Tukey post-hoc	1	-	-	$0,289^{a}$	-	-	-
	2	$0,306^{b}$	-	-	-	-	-
	3	-	$0,383^{c}$	-	$0,383^{c}$	-	-
	4	-	-	-	-	$0,334^{d}$	$0,334^{d}$
Collinearity (VIF)		4.639	3.426	1.840	2.372	9.797	2.125

Similar superscript letters indicate no statistically significant difference (p > 0.05)

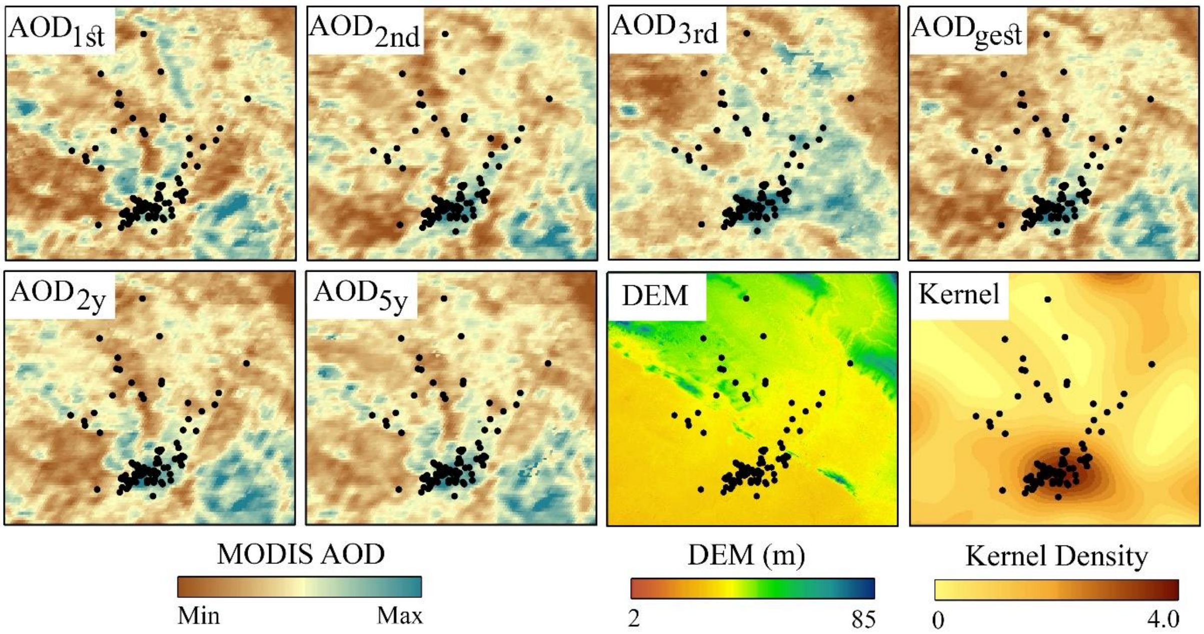


Figure 3. AOD layers, DEM and Kernel layers in a zoom to the area around the Ahvaz City provided in Figure 1 for representation of the dense Ahvaz area

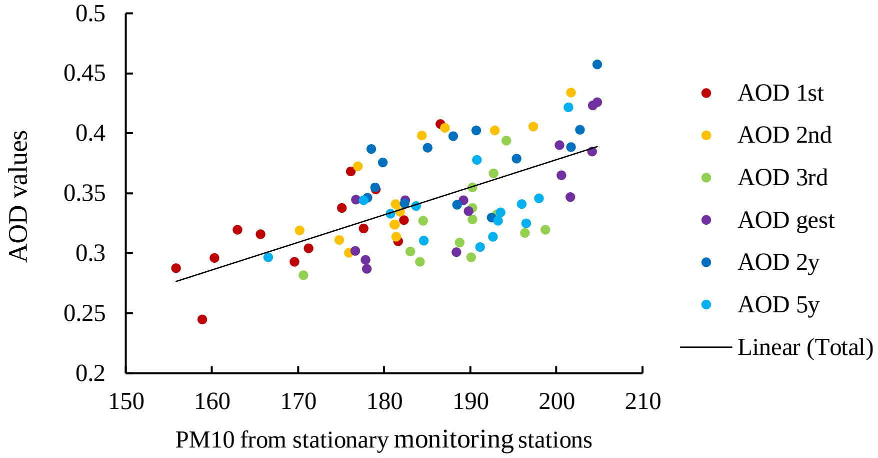


Figure 4. Validity results of AOD layers based on all observations during the selected AOD time profiles

The modeling phase of the research utilized normally distributed and non-collinear AOD values, in conjunction with DEM and Kernel data (Table 3 and Figure 5). To account for potential maternal confounding, the robustness of our findings was tested by adjusting GAM models for maternal age, weight, and height. These covariates were selected based on their known relevance to maternal biomarker levels and pregnancy-related physiological variation. The results remained stable, indicating that the associations between aerosol exposure and maternal biomarkers were not driven by these maternal covariates. All smooth curves representing AOD values displayed an upward trend, suggesting that higher AOD values may correspond to increased levels of maternal serum biomarkers. This supports a potential dose-response relationship between ambient aerosol exposure and oxidative stress during pregnancy. Similarly, Kernel data indicated that areas with higher levels of road and built-up density exhibited the highest concentrations of biomarkers. Conversely, higher DEM values exhibited a negative correlation with biomarker concentrations.

These spatial indicators (DEM and Kernel) highlight environmental disparities that may underlie urban–rural differences in maternal exposure. Regarding AOD_{1st} and AOD_{5y}, most relationships were predominantly linear. However, DEM, as well as AOD layers in certain biomarkers (particularly ALT and ALP), displayed notably nonlinear associations, which were statistically significant in explaining the variability in biomarker concentrations. Such nonlinear patterns suggest that even moderate increases in exposure may have disproportionate physiological effects during critical periods.

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Table 3. Parametric coefficients and Approximate significance of smooth terms generated by GAM model: p-values: **ns** = not significant (p > 0.010); p = 0.010, 0.001, or <0.001 as indicated. (+) and (–) indicate the direction of the association

Model parameters		Biomarker ALP	ALT	GGT
Intercept		324.02 ($p < 0.001$)	18.62 ($p < 0.001$)	15.88 ($p < 0.001$)
F-test values	$s(\mathrm{AOD}_{1st})$	F = 1.726, ns (–)	F = 0.209, ns (–)	F = 0.001, ns (–)
	$s(\mathrm{AOD}_{2nd})$	F = 1.369, p = 0.010 (+)	F = 4.854, p = 0.001 (+)	F = 0.273, ns (+)
	$s(\mathrm{AOD}_{3rd})$	F = 2.288, ns (+)	F = 9.335, p = 0.001 (+)	F = 2.527, ns (+)
	$s(\mathrm{AOD}_{gest})$	F = 2.648, p = 0.010 (+)	F = 4.606, p = 0.010 (+)	F = 1.556, ns (+)
	$s(\mathrm{AOD}_{5y})$	F = 2.928, ns (+)	F = 2.184, ns (+)	F = 4.571, p = 0.010 (+)
	$s(\mathrm{Kernel})$	F = 7.168, p < 0.001 (+)	F = 2.333, p = 0.010 (+)	F = 0.536, ns (+)
	$s(\mathrm{DEM})$	F = 1.726, p < 0.001 (–)	F = 7.615, p < 0.001 (–)	F = 1.626, ns (–)
REML		603.70	672.63	362.78
Deviance (%)		60.6	64.5	16.4
R2		0.567	0.693	0.179

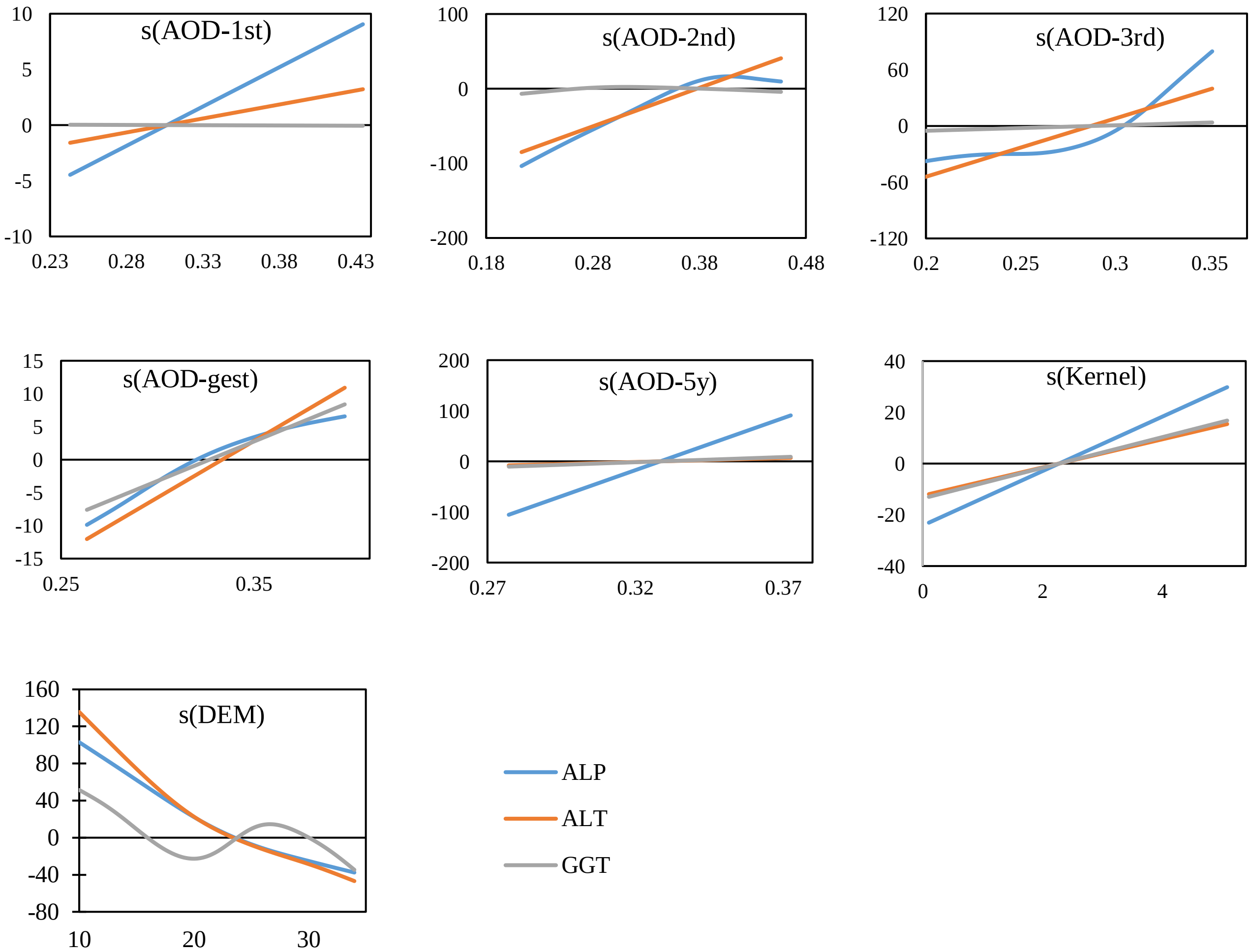

Figure 5. Smooth curves of the predicting variables generated using the GAM model

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AOD_{1st} demonstrated insignificance in explaining the variability of maternal serum biomarkers. Moreover, AOD_{gest}, AOD_{5y} and Kernel were found to be marginally significant in predicting the levels of ALT and GGT at the 0.010 significance level (Table 3). The most influential predictors were DEM (except for GGT), AOD_{3rd} (except for ALP and GGT) and AOD_{2nd} (except for GGT).

The models with the highest accuracy were developed for ALT (R^2= 0.693, explained deviance= 64.5%), followed by ALP (R^2= 0.567, explained deviance= 54.2%). Conversely, the least significant model was GGT, which was constructed using AOD_{5y} as the sole significant variable at the 0.010 level. These findings indicate that short- and medium-term exposures during mid-to-late pregnancy are more strongly linked to maternal liver enzyme responses than longer-term exposure histories, underscoring the importance of temporal specificity in environmental health assessments.

4. Discussion

Pregnant women exhibit heterogeneous responses to increasing air pollution levels. Unlike readily apparent health effects, such as respiratory issues, enzymatic responses are more subtle and manifest only at critically high pollutant concentrations (Johnson et al., 2020). In the study region, the concentration of aerosol content was found to be significantly high with AOD values exceeding 0.3 during most time profiles. However, the oxidative responses did not result in major health outcomes while postpartum mothers exhibited favorable health conditions following a natural delivery. Moreover, pregnancy itself can induce elevations in certain enzyme levels beyond limited ranges. For example, placental isoenzyme production during pregnancy led to a doubling of ALP levels compared to the normal limits (Johnson et al., 2020). Therefore, while the observed increases cannot be solely attributed to air pollution exposure, variations in enzyme levels were found to correlate with air quality.

The present study revealed a differential influence of exposure timing on enzymatic variations. AOD concentrations during mid-to-late pregnancy (AOD_{2nd} and AOD_{3rd}) were more strongly associated with fluctuations in maternal liver enzymes than those reflecting longer-term exposures such as AOD_{5y}. This implies that the maternal enzymatic response may be more acutely triggered by short-term exposure variations, especially in the later stages of pregnancy. During this period, the developing fetus is especially susceptible to the detrimental effects of air pollution (Ji et al., 2024), when we observed the highest AOD values—about 15% higher than the annual mean of the past five years. This finding aligns with existing literature that highlights the short-term effects of air pollution on blood biomarkers in pregnant women (Yousefzadeh et al., 2024). However, this appears to diverge from studies like Hu et al. (2023), which posit that chronic exposure to PM and other pollutants is a more significant factor influencing changes in various maternal blood markers. These contrasting findings point to a nuanced interplay between acute and chronic exposures, suggesting that each may act through different biological mechanisms or at distinct stages of pregnancy. While these studies highlight the differential influence of short-term versus chronic exposures on serum enzyme variations, both converge on the adverse effect of ambient aerosol on pregnant women, underscoring the critical importance of improved air quality measures to safeguard vulnerable urban populations.

Our findings suggest a multifactorial influence of air quality on enzymatic activity in maternal blood samples, operating at two distinct levels. Firstly, urban air pollution demonstrated a significant impact, with AOD values positively correlated with enzymatic activity. Higher levels of enzymatic activity were observed in the densely populated areas of Ahvaz City, indicating the presence of multiple air pollutant sources within urban environments. These sources potentially contribute to elevated PM-AOD levels and associated increases in enzymatic activity. Corroborating our conclusions, Khodadadi et al. (2022) reported that rise in air pollutant emissions in Ahvaz City is a primary factor in acute health effects on pregnant women. Studies conducted in urban environments across China, the United States, and Western Europe also link increasing maternal health problems and oxidative stress to urban air pollution. Potential causal mechanisms underlying the observed associations may involve pollutant-induced oxidative stress and systemic inflammation. Inhaled particulate matter can translocate into the bloodstream, triggering hepatic stress responses that elevate liver enzyme production. Additionally, immune-modulatory effects during pregnancy may amplify susceptibility, particularly in later trimesters when placental function intensifies metabolic demands.

Secondly, the overall air quality of the province appeared influential, as evidenced by the significance of altitude range in the majority of the models. Mothers residing in the northern region, characterized by high elevation, a temperate climate, and a significant distance from southern dust sources along the Persian Gulf coast (as noted by Masoumi and Moradhaseli (2023)), exhibited a healthier profile with normal enzyme levels. This suggests that cleaner air quality in these regions may contribute to a more balanced enzymatic response. Supporting this

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conclusion, Yousefzadeh et al. (2024) demonstrated that pregnant women living near non-vegetated, arid dune dust sources are more prone to maternal oxidative stress compared to those impacted by urbanized industrial activities. This evidence reinforces the interpretation that regional environmental conditions, not just urban air pollution, play a substantial role in shaping maternal health outcomes. The interplay between altitude, pollution exposure, and maternal response highlights the need for spatially targeted air quality policies in regions with diverse topography.

This study employed a multi-modeling approach, revealing that most biomarkers were sensitive to specific environmental factors. This sensitivity produced consistent response patterns, reducing the likelihood of chance findings. ALT emerged as the most responsive biomarker, suggesting that exposure to the region's high aerosol content triggered oxidative stress and inflammation in participants. It underscores the liver's central role in detoxification and metabolism, responding to these inflammatory signals, as evidenced by changes in other liver enzymes as well. These findings contribute to existing knowledge by aligning with Johnson et al. (2020), Nourouzi and Chamani (2021) and Ji et al. (2024) who reported air pollution-induced oxidative stress and inflammation in pregnant residents. Moreover, the liver appears to be responsive to these stressors through oxidative stress and inflammation pathways. These findings emphasize the importance of monitoring air quality to mitigate the biochemical impacts of aerosol exposure during pregnancy.

Strengths of this study include its geographically diverse maternal cohort, use of a multi-modeling framework capturing nonlinear relationships, and the integration of high-resolution MODIS AOD satellite data with local ground-based validation. These methodological features enhance the robustness and applicability of our findings, particularly in highly polluted and data-limited regions. However, some limitations must be acknowledged. The sample size, though sufficient for the modeling framework, was restricted to a single province, limiting generalizability. Despite extensive pre-selection controls, residual confounding due to unmeasured maternal or microenvironmental characteristics cannot be ruled out. Moreover, AOD data serve as a proxy for ambient PM exposure and may introduce exposure misclassification at the household level.

Finally, the single timepoint of blood collection (at delivery) constrained the temporal resolution of biomarker fluctuation assessments. Future research should incorporate longitudinal biomarker sampling and a larger, multi-site sample to verify and expand these findings.

5. Conclusion

This study investigated the multifaceted influence of air quality and its associated variables on enzymatic activity in pregnant women. Employing a multi-modeling approach, we observed a differential response across various biomarkers to specific environmental factors. Our results highlight the critical role of aerosol exposure timing during pregnancy. The second and third trimesters exhibited a stronger association with enzymatic variations compared to prolonged exposure patterns, suggesting that short-term air quality fluctuations during these critical periods may drive enzymatic changes. Furthermore, we observed a significant impact of both regional and urban air pollution. Higher enzymatic activity levels were found in densely populated areas and low-elevation southern regions. This geographical variation indicates that both local pollution sources and broader environmental conditions contribute to maternal oxidative stress and enzymatic alterations.

Ethics approval
This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Islamic Azad University, Isfahan (Khorasgan) Branch, under the ethical code: IR.IAU.KHUISF.REC.1402.285.

Consent to participate
Informed consent was obtained from all individual participants included in the study.

Consent to publish
Not Applicable

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Authors Contribution

Azizeh Shajravi: Conceptualization, Data curation, Formal analysis, Methodology, Software, Writing – original draft, Atefeh Chamani: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Writing – review & editing. Soheil Sobhanardakani: Conceptualization, Methodology, Supervision, Writing – original draft, Zainab Zamanpour: Conceptualization, Formal analysis, Methodology

Availability of data and materials

Data will be made available on request.

Conflict of interests

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

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Appendix A: Parametric coefficients and approximate significance of maternal covariates and environmental predictors in the GAM model

Model Parameters	ALP	ALT	GGT
Intercept	324.11 ($p < 0.001$)	18.35 ($p < 0.001$)	15.91 ($p < 0.001$)
AOD (Second Trimester)	$F = 1.358$, $p = 0.010$ (+)	$F = 4.912$, $p = 0.001$ (+)	$F = 0.289$, ns (+)
DEM	$F = 1.605$, $p < 0.001$ (–)	$F = 6.732$, $p < 0.001$ (–)	$F = 1.588$, ns (–)
Kernel Density	$F = 7.110$, $p < 0.001$ (+)	$F = 2.459$, $p = 0.010$ (+)	$F = 0.519$, ns (+)
Maternal Age	$F = 0.109$, $p = 0.841$ ns	$F = 0.105$, $p = 0.845$ ns	$F = 0.162$, $p = 0.688$ ns
Maternal Weight	$F = 0.190$, $p = 0.750$ ns	$F = 0.202$, $p = 0.742$ ns	$F = 0.245$, $p = 0.679$ ns
Maternal Height	$F = 0.123$, $p = 0.826$ ns	$F = 0.167$, $p = 0.803$ ns	$F = 0.212$, $p = 0.711$ ns
Smoking Status	NA (excluded)	NA (excluded)	NA (excluded)
REML	601.31	674.12	363.9
Deviance Explained (%)	0.603	0.643	0.166
R^2	0.564	0.691	0.183