Journal of Air Pollution and Health (Summer 2026); 11(3): 377-394

Original Article

Available online at https://japh.tums.ac.ir

Association of ambient air pollution with preterm birth risk: A 20 year cohort study in Tehran

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ARTICLE INFORMATION

Article Chronology:
Received 14 December 2025
Revised 30 July 2026
Accepted 02 August 2026
Published 29 September 2026

Keywords:
Preterm birth; Air pollution; Carbon monoxide (CO); Cohort study; Maternal exposure

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ABSTRACT

Introduction: Exposure to ambient air pollution is a critical environmental health risk, with growing evidence linking it to adverse pregnancy outcomes. However, long-term data from Iran remain limited. This study aimed to investigate the association between maternal exposure to major air pollutants and the risk of preterm birth in Tehran.

Materials and methods: This cohort study utilized 20 years of data (2000–2020) from the Tehran Lipid and Glucose Study (TLGS). We analyzed 697 pregnancies, assessing maternal exposure to Particulate Matter ($PM_{2.5}$, PM_{10}), Ozone (O_3), Carbon monoxide (CO), Nitrogen dioxide (NO_2), and Sulfur dioxide (SO_2) from 10 validated monitoring stations. Historical $PM_{2.5}$ concentrations (pre-2010) were reconstructed using archival data. The association between pollutant exposure and preterm birth was analyzed using Generalized Estimating Equation (GEE) models, adjusting for maternal age and Body Mass Index (BMI).

Results: The incidence of preterm birth was 3.7% (26 cases). The adjusted GEE analysis showed a positive and statistically significant association between maternal CO exposure and preterm birth (coefficient = 0.537; 95% CI: 0.158 to 0.917; P = 0.005).

Conclusion: No statistically significant associations were observed for $PM_{2.5}$, PM_{10}, NO_2, SO_2, and O_3 in the adjusted models. Our findings provide evidence suggesting a potential association between maternal exposure to ambient carbon monoxide and preterm birth in this urban population. These findings highlight the potential public health relevance of traffic-related CO exposure for pregnant women in highly polluted urban settings.

Please cite this article as: Khoddam Sh, Ramezani Tehrani F, Borgheipour H, Mousavi M, Mohammadi H. Association of ambient air pollution with preterm birth risk: A 20 year cohort study in Tehran. Journal of Air Pollution and Health. 2026;11(3):377-394. Doi: https://doi.org/10.18502/japh.v11i3.22626

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Introduction

Preterm birth, defined as delivery before 37 completed weeks of gestation, remains one of the leading causes of neonatal morbidity and mortality worldwide [1]. In 2020, approximately 13.4 million babies were born preterm worldwide, with a prevalence rate of 9.9% [2]. In Iran, preterm birth rates are estimated around 9–10%, with higher prevalence in densely populated urban areas such as Tehran [3].

Pregnancy is a uniquely sensitive period during which both the mother and fetus are especially vulnerable to environmental exposures [4]. Physiological changes—including increased tidal volume, altered vascular regulation, and enhanced oxidative stress sensitivity—render the maternal–fetal unit more susceptible to airborne pollutants [5, 6]. Among these, six criteria pollutants have received Particular attention: fine ($PM_{2.5}$) and coarse (PM_{10}) particulate matter, Carbon monoxide (CO), Nitrogen dioxide (NO_2), Sulfur dioxide (SO_2), and Ozone (O_3). Their biological plausibility stems from converging mechanistic evidence and epidemiological associations.

Particulate matter ($PM_{2.5}$ and PM_{10}), once inhaled, enters the bloodstream and induces systemic inflammation through activation of oxidative stress pathways [7] This process leads to placental vascular dysfunction, reduced nutrient and oxygen transport, and may ultimately trigger premature labor via cytokine-mediated inflammatory cascades [8]. Several studies have shown that these particles can cross the placental barrier and accumulate in placental and fetal tissues, exacerbating oxidative damage and contributing to developmental disturbances [9, 10].

Carbon monoxide poses additional risk by competing with oxygen for binding sites on maternal and fetal hemoglobin, resulting in hypoxic stress that may activate neuroendocrine pathways initiating early uterine contractions [11, 12]. Nitrogen dioxide similarly compromises placental perfusion through endothelial dysfunction and pro-inflammatory signaling, and is frequently elevated in traffic-dense urban areas [13].

Sulfur dioxide (SO_2), a byproduct of fossil fuel combustion, is associated with increased expression of pro-inflammatory cytokines and oxidative DNA damage in placental cells [14]. Exposure to ozone during pregnancy, particularly during the second and third trimesters, is associated with an increased risk of preterm birth. Higher ozone concentrations are linked to a greater likelihood of delivering prematurely [15].

This mechanistic foundation aligns with emerging evidence from Iran. For instance, Dastoorpoor et al. found that short-term increases in PM_{10} and CO were significantly associated with preterm deliveries in Ahvaz [16]. Ranjbaran et al. reported similar findings in Tehran, linking $PM_{2.5}$ and NO_2 to increased daily preterm birth rates [17]. Aghaei et al. demonstrated that first-trimester exposure to $PM_{2.5}$ and CO was significantly associated with both preterm birth and low birth weight in Tehran [18]. Norooziyan et al., using quantile regression in Mashhad, found that PM_{10} and CO, particularly during the third trimester, had the strongest associations with early delivery [19]. Lastly, Janghorbani and Piraei reported a significant correlation between higher air quality Index , Pollutant Standards Index (PSI), values during pregnancy and preterm birth in Isfahan, although trimester-specific analyses showed weaker links [20].

Despite these insights, most existing studies are constrained by short observation periods, regional scope, or focus on single pollutants.

Therefore, a comprehensive analysis incorporating all six major pollutants over a long-term horizon remains lacking.

This study addresses that gap by leveraging 20 years of data from the Tehran Lipid and Glucose Study (TLGS), a large-scale, prospective cohort based in East Tehran [21]. By integrating individual-level maternal data with high-resolution exposure estimates for $PM_{2.5}$, PM_{10}, NO_2, SO_2, CO, and O_3, this study aims to provide the most comprehensive assessment to date of the relationship between ambient air pollution and preterm birth in Iran.

Therefore, the primary objective of this study was to examine the association between long-term maternal exposure to ambient air pollutants, including $PM_{2.5}$, PM_{10}, CO, NO_2, SO_2, and O_3, and the risk of preterm birth among participants of the Tehran Lipid and Glucose Study. We hypothesized that higher gestational exposure to ambient air pollutants, particularly traffic-related pollutants such as CO and NO_2, would be associated with increased odds of preterm birth.

Materials and methods

Study design and participant selection

This prospective cohort study leveraged data from the Tehran Lipid and Glucose Study (TLGS), a large-scale, population-based longitudinal cohort initiated in 1999 in District 13 of eastern Tehran, Iran. The TLGS cohort was designed to investigate the epidemiology and risk factors of non-communicable diseases, with a focus on cardiometabolic disorders. At baseline, the cohort included 15,005 participants aged ≥3 years, recruited through stratified multistage cluster sampling to ensure representativeness of Tehran's urban population [22]. Follow-up examinations were conducted triennially, encompassing detailed biochemical, anthropometric, and clinical assessments.

For the present study, all pregnancies reported within the TLGS cohort between 1999 and 2019 were evaluated. Pregnancy data were extracted from obstetric records, including self-reported pregnancy histories, hospital delivery logs, and TLGS follow-up questionnaires. A total of 1,032 pregnancies were initially identified. After applying exclusion criteria, 697 pregnancies met eligibility requirements and were included in the final analysis. The participant selection process is illustrated in Fig. 1. Key exclusion criteria were:

- Pregestational diabetes: Women with preexisting type 2 diabetes (n=41) or fasting glucose ≥126 mg/dL at conception (n=19)[23].
- Multifetal pregnancies: All twin/triplet pregnancies (n=12) to eliminate confounding by unique obstetric risks.
- Incomplete exposure data: Pregnancies lacking geocoded residency data or pollution measurements (n=263).

Exclusion criteria were applied sequentially and reported as mutually exclusive categories for the purpose of the participant flowchart. to address intra-individual correlation (e.g., 18% of women contributed multiple pregnancies), statistical adjustments for familial clustering were implemented (see Statistical Analysis). Ethical approval was granted by Shahid Beheshti University of Medical Sciences, and all participants provided written informed consent for data usage.

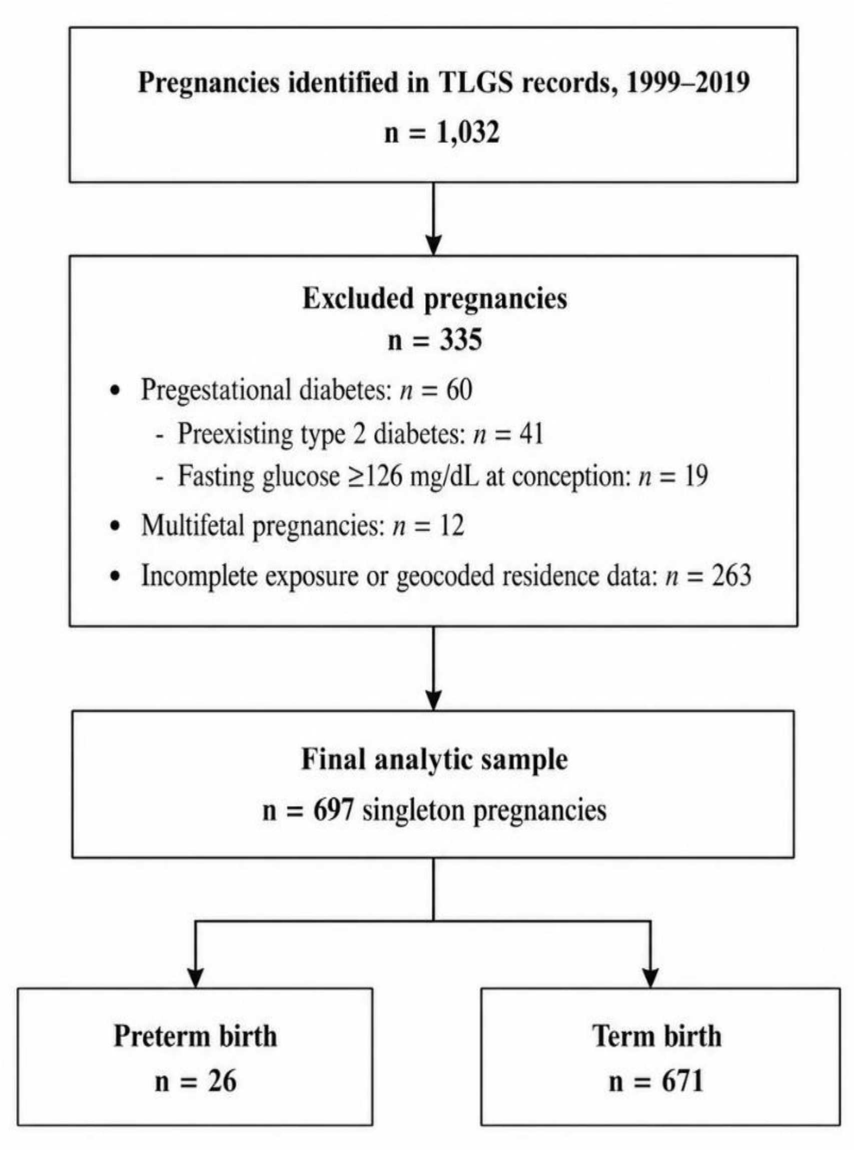

Fig. 1. Flowchart of participant selection and exclusions

Air pollution exposure assessment

Hourly ambient air pollution data were obtained from 10 governmental monitoring stations in eastern Tehran (Figure 2), strategically selected to cover the residential areas of TLGS participants. Five stations were operated by the Tehran Air Quality Control Company (AQCC), and five by the Department of Environment (DOE).

Pollutants measured included $PM_{2.5}$, PM_{10} (μg/m^3), NO_2, SO_2, O_3 (ppb), and CO (ppm). The stations used beta-attenuation monitors (BAM-1020, Met One Instruments) for particulate matter and ultraviolet fluorescence analyzers (Thermo Scientific Model 43i) for gaseous pollutants, with quarterly calibration following EPA protocols [24]. Table 1 provides the coordinates of the monitoring stations along with their respective operational time frames.

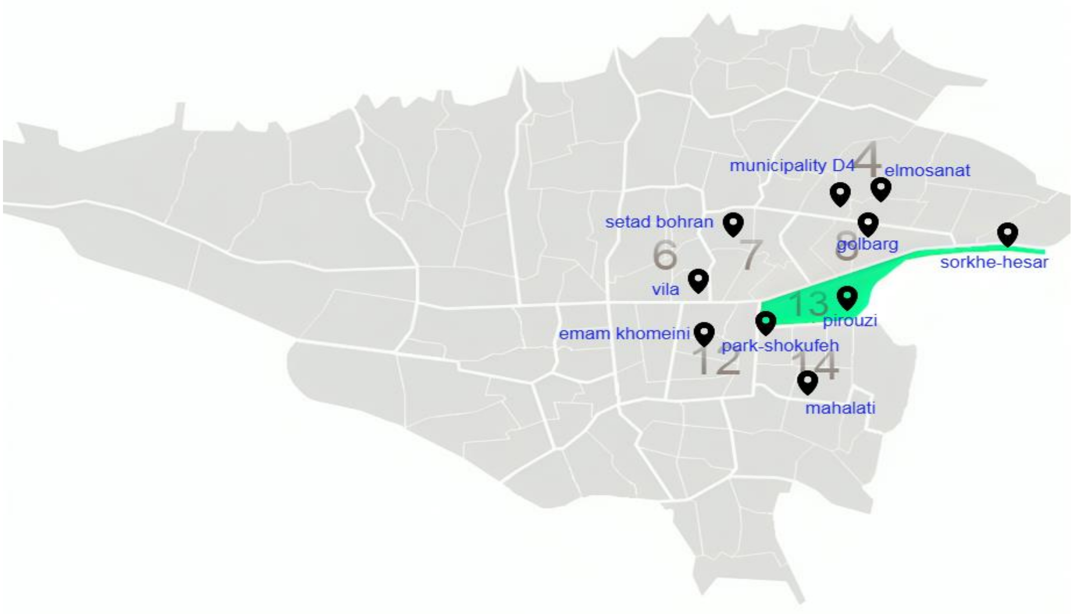

Fig. 2. Location of air pollution monitoring stations considered for the TLGS

Table 1. Coordinates and Operational Timeframe of the Stations

Station Name	Coordinates	Organization	Timeframe
Pirouzi	35.6959, 51.4936	AQCC	2011-2020
Mahalati	35.6606, 51.4666	AQCC	2010-2020
Golbarg	35.7302, 51.5045	AQCC	2007-2020
Municipality Region 4	35.7422, 51.4907	AQCC	2008-2020
Setad Bohran	35.7268, 51.4313	AQCC	2010-2020
Sorkheh Hasar	35.7167, 51.5819	DOE	2000-2017
Park Shokufeh	35.6857, 51.4507	DOE	2011-2020
Emam Khomeini	35.6846, 51.4227	DOE	2008-2020
Vila	35.7077, 51.4145	DOE	2001-2006
ElmoSanat	35.7398, 51.5114	DOE	2011-2020

AQCC: Air Quality Control Company

DOE: Department of Environment

Historical $PM_{2.5}$ estimation

As $PM_{2.5}$ monitoring only began in Tehran in 2010, data prior to this year were reconstructed using archival Total Suspended Particulate (TSP) measurements from three long-established stations (Sorkheh Hesar, Imam Khomeini, Villa). In the absence of Tehran-specific parallel monitoring data, this indirect reconstruction approach was based on conversion relationships previously reported in international studies of particulate matter size fractions [25, 26]. We applied the following conventional conversion ratios:

$PM_{10} = 0.56 \times TSP$ ($R^2 = 0.89$)

$PM_{2.5} = 0.58 \times PM_{10}$ ($R^2 = 0.78$)

This reconstruction approach may have introduced several sources of uncertainty. First, the TSP-to-PM_{10} and PM_{10}-to-$PM_{2.5}$ conversion ratios were not derived from a Tehran-specific parallel monitoring campaign and may not fully capture local changes in fuel composition, traffic patterns, dust events, and industrial sources over time. Second, the chemical composition and size distribution of particulate matter may have changed during the 20-year study period. Third, reconstructed $PM_{2.5}$ estimates are likely to be less precise than directly monitored concentrations, particularly for earlier years. Therefore, findings related to $PM_{2.5}$ should be interpreted cautiously, and potential exposure misclassification is acknowledged as a methodological limitation.

Spatiotemporal exposure assignment

For each pregnancy, exposure was assigned as follows:

- **Residential geocoding:** Participant addresses were mapped to neighborhood centroids using ArcGIS 10.8.
- **Station selection:** The nearest active monitoring station within a 5 km radius was linked to each residence.
- **Temporal alignment:** Daily pollutant averages were aggregated over the entire gestational window, defined as 280 days prior to delivery (estimated via last menstrual period or ultrasound dating).

Missing data (9% of days) were imputed using standard spatial interpolation (Inverse Distance Weighting) and temporal imputation (7-day moving averages).

Statistical analysis

Model specification

Generalized Estimating Equations (GEE) with an exchangeable correlation structure were used to account for repeated pregnancies from the same mother (n=121 women). This was selected because repeated pregnancies from the same mother were expected to be correlated, but the correlation was not assumed to depend systematically on the time interval between pregnancies. This structure is appropriate when each cluster contains a small number of repeated observations and when within-mother correlations are assumed to be relatively constant across pregnancies.

The logit link function modeled the probability of preterm birth as:

$$\text{logit}(P(Y_{ij} = 1)) = \beta_0 + \beta_1 X_{ij} + \gamma Z_i$$

Where Y_{ij} denotes the preterm birth status of pregnancy j in woman i; X_{ij} denotes exposure to a single pollutant for pregnancy j in woman i; and Z_i denotes the time-invariant covariates, namely maternal age and body mass index [27]. A separate model of this form was fitted for each of the six pollutants; no model contained more than one pollutant term.

Analysis workflow

Separate GEE models were fitted for each air pollutant. Initially, unadjusted models were estimated to examine the crude association between each pollutant and preterm birth. Subsequently, adjusted models were fitted for each pollutant separately, controlling for maternal age and Body Mass Index (BMI).

Model coefficients with 95% confidence intervals and P-values were reported for the GEE models. Pollutant concentration distributions were summarized using means, medians, interquartile ranges, and minimum–maximum values to contextualize exposure levels.

Software

Analyses were performed in Stata 16 (StataCorp), using xtgee for GEE models and mice for imputation[28]. Spatial mapping utilized ArcGIS 10.8.

Results and discussion

Characteristics of the study population

The women in this study had a mean age of 31.0 years (SD: 8.3) at the time of pregnancy, reflecting a relatively mature reproductive age typical for urban populations. Their average pre-pregnancy BMI was 27.3 (SD: 5.3), placing the cohort, on average, in the overweight category.

Among the 697 singleton pregnancies analyzed in this study, 26 cases (3.7%) resulted in preterm birth, defined as delivery before 37 completed weeks of gestation.

According to the data, spontaneous abortion was the most common adverse outcome, occurring in 88 cases (12.6% of all pregnancies), followed by gestational hypertension (4.6%), preterm birth (3.7%), and gestational diabetes (3.3%). Stillbirth had the lowest prevalence, occurring in only 10 pregnancies (1.4% of cases).

Pollution exposure levels

Ambient air pollutant concentrations indicated persistently poor air quality in eastern Tehran throughout the study period. Based on the available daily monitoring data, mean PM_{10}

concentration was 87.74 μg/m³, exceeding the WHO annual guideline value of 15 μg/m³ by nearly six-fold. $PM_{2.5}$ concentrations also remained elevated, with average levels of approximately 30–35 μg/m³, substantially higher than the WHO annual guideline value of 5 μg/m³. These results suggest that pregnancies in this cohort occurred against a background of chronically elevated ambient air pollution.

To provide additional context for the exposure environment, Table 2 summarizes the distribution of daily ambient concentrations for all six pollutants during the study period.

Table 2. Distribution of daily ambient air pollutant concentrations in East Tehran during the study period

Pollutant	Unit	Mean	SD	Median	Q1	Q3	IQR	Min	Max
CO	ppm	3.29	2.04	2.67	1.90	4.18	2.29	0.03	25.39
NO_2	ppb	30.59	18.90	28.72	17.35	40.80	23.45	0.00	215.09
O_3	ppb	18.03	14.82	15.77	7.92	25.02	17.10	0.00	214.21
PM_{10}	μg/m³	87.74	55.25	81.21	56.94	109.46	52.52	1.97	1976.37
$PM_{2.5}$	μg/m³	29.28	19.37	26.13	20.21	34.83	14.63	7.32	1021.35
SO_2	ppb	16.25	18.45	11.63	5.64	19.01	13.37	0.00	358.48

Across the daily ambient monitoring data, median CO concentration was 2.67 ppm (IQR: 1.90–4.18), while median PM_{10} and $PM_{2.5}$ concentrations were 81.21 µg/m³ (IQR: 56.94–109.46) and 26.13 µg/m³ (IQR: 20.21–34.83), respectively. Because extreme daily values were observed for some pollutants, medians and interquartile ranges were used to provide a robust summary of exposure distributions.

Before performing the regression analysis, the Kolmogorov-Smirnov test confirmed the non-normal distribution of the exposure variables. Therefore, no specific transformations were required in the GEE models, and the coefficients were interpreted directly.

Analytical findings of the GEE models

Analytical findings of the GEE models are presented in Table 3. In the adjusted GEE model, CO exposure showed a positive and statistically significant association with preterm birth (coefficient = 0.537; 95% CI: 0.158 to 0.917; P = 0.005). This finding suggests that higher CO exposure was associated with a greater likelihood of preterm birth in this cohort. In contrast, $PM_{2.5}$, PM_{10}, NO_2, SO_2, and O_3 did not show statistically significant associations with preterm birth in the adjusted models.

Table 3. Results of the GEE models examining the association between ambient air pollutants and preterm birth

Pollutant	Outcomes	Model1 Coefficient (95% CI)	P-value	Model 2 Coefficient (95% CI)	P-value
CO	Group	0.473 (0.113, 0.832)	0.010	0.537 (0.158, 0.917)	0.005
	Time	-0.330 (-0.375, -0.284)	<0.001	-0.335 (-0.383, -0.288)	<0.001
	Group×Time	-0.010 (-0.051, 0.031)	0.621	-0.011 (-0.053, 0.031)	0.612
NO_2	Group	0.681 (-7.68, 9.04)	0.873	0.212 (-8.40, 8.82)	0.962
	Time	-1.81 (-2.87, -0.75)	0.001	-2.24 (-3.31, -1.16)	<0.001
	Group×Time	-0.36 (-1.31, 0.59)	0.457	-0.51 (-1.45, 0.44)	0.294
O_3	Group	0.655 (-1.89, 3.20)	0.614	-0.032 (-2.72, 2.65)	0.981
	Time	0.84 (0.52, 1.17)	<0.001	0.84 (0.50, 1.17)	<0.001
	Group×Time	-0.15 (-0.44, 0.14)	0.317	-0.16 (-0.46, 0.13)	0.280
$PM_{2.5}$	Group	1.51 (-3.29, 6.31)	0.537	1.87 (-3.03, 6.77)	0.454
	Time	-1.40 (-2.01, -0.79)	<0.001	-1.75 (-2.36, -1.14)	<0.001
	Group×Time	-0.10 (-0.65, 0.44)	0.706	-0.18 (-0.72, 0.36)	0.512
PM_{10}	Group	1.39 (-7.07, 9.86)	0.747	1.85 (-6.81, 10.53)	0.674
	Time	4.08 (2.77, 5.39)	<0.001	3.55 (2.22, 4.88)	<0.001
	Group×Time	-0.17 (-1.13, 0.79)	0.725	-0.31 (-1.26, 0.65)	0.529
SO_2	Group	1.91 (-1.41, 5.24)	0.259	1.56 (-1.95, 5.06)	0.384
	Time	-4.27 (-4.69, -3.85)	<0.001	-4.29 (-4.73, -3.85)	<0.001
	Group×Time	-0.08 (-0.46, 0.30)	0.683	-0.08 (-0.47, 0.30)	0.681

Model 1: Unadjusted model

Model 2: Adjusted for maternal age and BMI

These findings are further illustrated in Fig. 3, which depicts the mean CO exposure levels across six phases of pregnancy for both groups: mothers who experienced preterm birth and those who did not. As seen in the graph, the mean CO levels were consistently higher in the preterm birth group (solid line) compared to the full-term group (dashed line) throughout all phases of pregnancy. Notably, in the early phases, the difference between the two groups was more pronounced, highlighting a potential critical window of vulnerability to CO exposure.

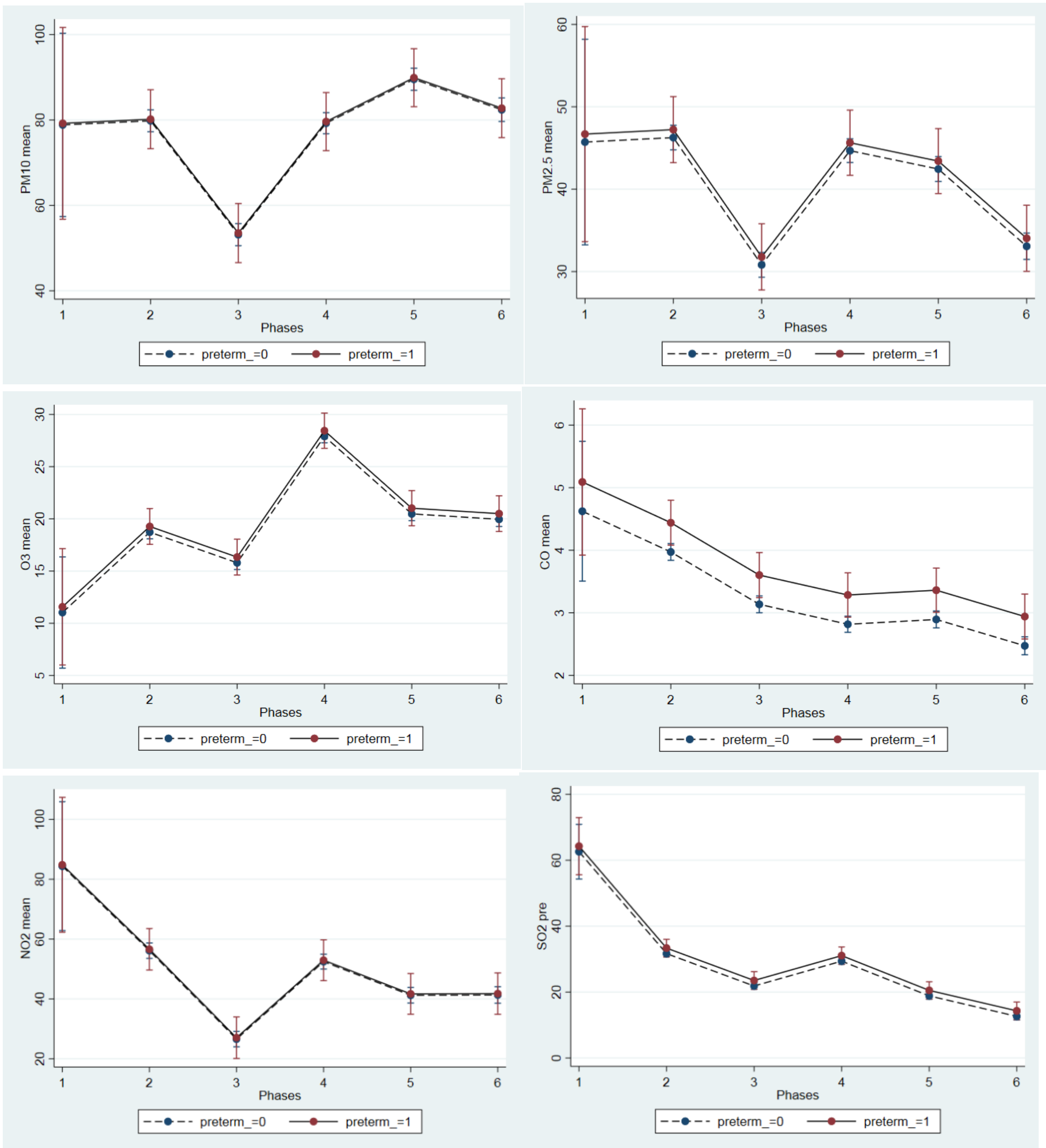

Fig. 3. Trend of mean exposure to pollutants during different phases of TLGS pregnancy based on the incidence or non-incidence of preterm birth

Main findings and interpretation

Descriptive comparisons across the study period suggested a higher frequency of recorded pregnancy complications in later years than in the early years of follow-up; however, this pattern should be interpreted cautiously because quantitative trend estimates were not available and improved case reporting over time may have contributed to the observed increase. Specifically, the percentage of pregnancies with any adverse outcome was higher in the later years of the study period (2016–2020) compared to the early 2000s. This increase may be partly due to improvements in the healthcare system and better case reporting in recent years, but it may also reflect a real rise in certain complications, such as gestational diabetes and hypertension.

In parallel, changes in air pollution levels were also observed during the study period. Data from monitoring stations indicated that concentrations of pollutants like CO and SO_2 declined significantly in the late 2010s compared to the early 2000s, likely due to initiatives such as the phase-out of leaded gasoline, improvements in fuel quality, and the expansion of public transportation in Tehran[29]. For example, the annual mean CO concentration decreased from about 11 ppm in 2000 to 3.6 ppm in 2009, and the mean annual NO_2 level dropped from 102 ppb to 66 ppb over the same period. Conversely, the mean ozone concentration showed an upward trend, increasing from around 22 ppb in 2000 to over 80 ppb by the late 2000s.

Additionally, despite annual fluctuations, concentrations of Particulate Matter (PM_{10} and $PM_{2.5}$) remained above the permissible limits for sensitive groups in many years. For instance, the annual mean $PM_{2.5}$ level in the 2010s was reported to be approximately 3 to 4 times higher than the World Health Organization's standard. Consistent with this pattern, the daily monitoring data summarized in Table 2 showed median PM_{10} and $PM_{2.5}$ concentrations of 81.21 µg/m³ and 26.13 µg/m³, respectively.

Thus, the study population experienced varying levels of exposure over different years, which was accounted for in the final analysis. The mean maternal exposure to air pollutants throughout pregnancy was also calculated. The results showed that, across all pregnancies, PM_{10} had the highest mean concentration (approximately 77 µg/m³), followed by NO_2 (~44 ppb) and $PM_{2.5}$ (~40 µg/m³). Ozone had the lowest mean concentration (~21 ppb), although it typically reaches significant levels only during the warmer months. Figure 4 shows how levels of key air pollutants in East Tehran have changed over the 20-year study period.

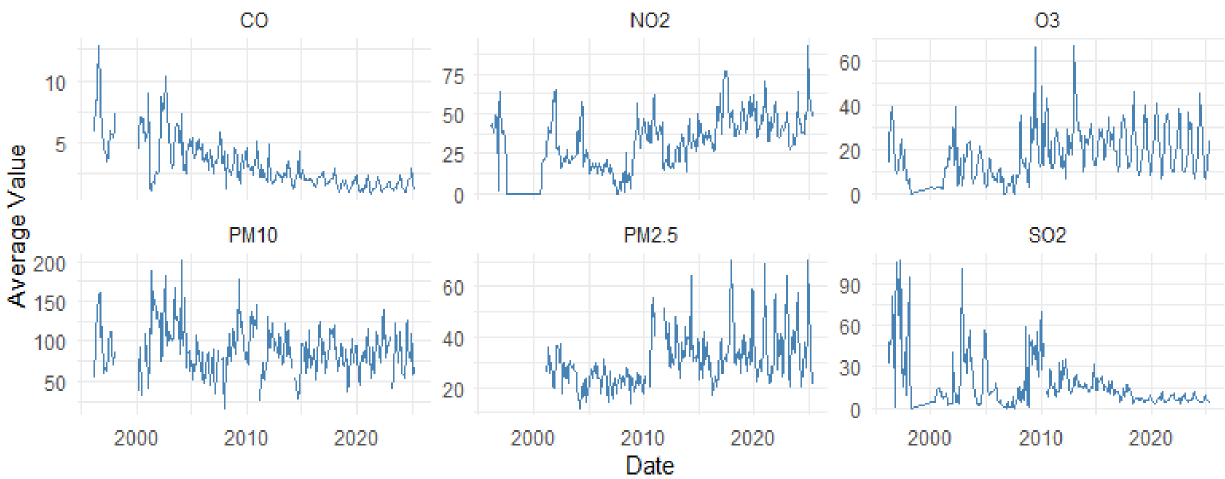

Fig. 4. Temporal trends in ambient air pollutant concentrations in east Tehran (2000–2020)

Comparison with previous research

The most significant finding was a statistically significant association between Carbon monoxide (CO) exposure and an increased risk of preterm birth. This finding is also biologically plausible: CO binds to hemoglobin, replacing oxygen in the blood, and can lead to tissue hypoxia [30]. During pregnancy, insufficient oxygen supply to the fetus can disrupt fetal development and activate mechanisms that may trigger preterm labor [31] .This result is consistent with both international and domestic studies, which have similarly reported a link between elevated maternal CO exposure and higher rates of preterm delivery.

The absence of statistically significant associations for $PM_{2.5}$, PM_{10}, NO_2, SO_2, and O_3 should not be interpreted as definitive evidence of no effect. The number of preterm birth cases was small, which limited statistical power and may have reduced the ability to detect modest associations. In addition, exposure assignment based on fixed-site monitoring stations and residential proximity may have introduced non-differential exposure misclassification, particularly for pollutants with substantial spatial or temporal variability. Such misclassification would generally be expected to bias associations toward the null. Therefore, the non-significant findings for these pollutants should be interpreted cautiously.

The limited number of preterm birth cases warrants particular emphasis in interpreting all findings reported here, including the positive association observed for CO. Only 26 of the 697 analysed pregnancies (3.7%) ended in preterm birth. With so few events, the effective information available to estimate each association is small, the resulting coefficients are statistically unstable, and the confidence intervals are correspondingly wide. Point estimates derived under these conditions should not be regarded as precise, and modest changes in model specification or in the composition of the sample could shift them appreciably. Because multiple pollutants were examined, the possibility of chance findings was also considered; formal correction for multiple comparisons was not applied, as such procedures would have been overly conservative given the small number of events and the exploratory aim of the analysis. Findings were therefore interpreted on the basis of effect direction, confidence intervals, biological plausibility, and consistency with previous evidence. For all of these reasons, the present results are best regarded as hypothesis-generating, and replication in a cohort with a substantially larger number of preterm birth events is required before any of these associations can be considered established.

While our results showed a significant association between Carbon monoxide (CO) exposure and preterm birth, this finding is not consistently supported across all studies. For example, a systematic review by Stieb et al found mixed evidence—some individual studies reported links between CO and preterm birth, but overall, the pooled analysis did not show a clear association [32]. This suggests that the impact of CO may vary by setting, and highlights the importance of context-specific research like ours, particularly in highly polluted cities.

Ming et al in a study of 515,498 pregnant women in Chengdu, China, found that air pollution—particularly carbon monoxide—was associated with an increased risk of preterm birth. The study, using advanced statistical models, showed that while short-term exposure to low levels of CO might have a protective effect, prolonged exposure to high levels significantly increased the risk of preterm birth. Maternal age and different stages of pregnancy also played a role in this relationship, underscoring the importance of air pollution control for maternal and neonatal health [33].

A study by Partha et al in Bangladesh also found that air pollution, especially $PM_{2.5}$, Ozone (O_3), and CO, was a major factor contributing to increased rates of preterm birth. This research, which used satellite data and advanced models to precisely measure pollution across different regions, reported that $PM_{2.5}$ accounted for about 45% of the disease burden [34].

In addition to carbon monoxide, fine particulate matter, particularly $PM_{2.5}$, has been identified as a strong and consistent risk factor for preterm birth in multiple studies. This association is biologically plausible given $PM_{2.5}$'s ability to penetrate deep into the respiratory tract and induce systemic inflammation and oxidative stress, which can interfere with normal pregnancy progression. A cross-sectional study conducted in Wuhan, China by Zhang et al found that a 10 μg/m³ increase in $PM_{2.5}$ during pregnancy was significantly associated with elevated odds of preterm birth, especially during the first trimester. The study also noted a stronger effect on very preterm births (28–32 weeks) compared to moderate preterm births [35]. Similarly, Li et al. performed a large-scale analysis in Beijing and observed that maternal exposure to $PM_{2.5}$ was significantly associated with increased risk of preterm birth, particularly among women with lower education or in cold seasons, highlighting both biological and sociodemographic vulnerability [36]. These findings reinforce the growing consensus that $PM_{2.5}$ exposure poses a substantial risk to pregnancy outcomes and warrant continued attention in urban health research.

Strengths of the study

One of the strengths of this study is its long 20-year timeframe and the use of data from a well-established cohort study (TLGS), which allowed for the tracking of pregnancy outcomes over time. Additionally, the integration of environmental and health data at the individual level enabled, for the first time, the assessment of $PM_{2.5}$ effects before 2010 in the country. The reconstruction of historical air pollution data using alternative sources, such as JICA (Japan International Cooperation Agency) documents and the Environmental Organization's archives was an innovative aspect of this research and could serve as a model for future studies. Moreover, the use of the GEE analytical method—a robust model resistant to violations of classical assumptions and accounting for data correlation—enhanced the accuracy of our inferences.

In this context, it is worth noting that other similar studies in Iran have primarily used the Land Use Regression (LUR) method to assess maternal exposure to air pollutants [37, 38]. However, in the present study, due to the high population density of participants' residential areas and the limited number of monitoring stations in that region, the LUR model was not deemed suitable. This necessitated the use of alternative exposure estimation methods, a decision that was logical and based on the available data structure.

Limitations

This study has some limitations. First, the sample size was insufficient for certain rare outcomes; the low numbers of preterm birth cases likely reduced the ability to detect significant associations. Second, despite efforts to collect exposure data from multiple monitoring stations, there remains a possibility of exposure misclassification. We used the mean concentration from local stations as a proxy for individual maternal exposure, which may differ from actual personal exposure (e.g., depending on outdoor activities, workplace location, or indoor air quality). This imprecision could attenuate true associations. Third, the adjusted models included maternal age and BMI; however, information on several important potential confounders was not available, including socioeconomic status, maternal education, smoking or second-hand smoke exposure, occupational exposures, nutrition, access to prenatal care, and residential mobility during pregnancy. Therefore, residual confounding cannot be ruled out. This limitation is particularly important because both air pollution exposure and preterm birth risk may be socially patterned. Accordingly, the observed association between CO exposure and preterm birth should be interpreted as an adjusted association rather than definitive evidence of causality. The lack of access to these data is a limitation that may have led to residual confounding. Fourth, air pollution data had some missing gaps in certain years and stations, necessitating overall averaging and data integration. This could have obscured fine spatiotemporal variations and reduced the observable impact of exposures. Nevertheless, the trend analyses and seasonal mean comparisons conducted in this study showed that exposure patterns between case and control groups were somewhat distinct, providing supporting evidence of a real effect—even if not statistically significant in tests.

Fifth, exposure was assigned by linking each participant to the nearest active monitoring station within a 5 km radius of the geocoded residential centroid. This approach treats every woman assigned to a given station as having experienced an identical ambient concentration, and therefore ignores within-neighbourhood spatial gradients, differences between residential and workplace or commuting microenvironments, indoor-outdoor concentration differences, and individual time-activity patterns. For pollutants with steep spatial gradients close to their sources, most notably CO and NO_2, this is a meaningful source of exposure misclassification. Because the assignment procedure was applied identically to preterm and term pregnancies and was independent of outcome status, the resulting misclassification is expected to be non-differential and would, on average, bias associations toward the null. It nevertheless adds uncertainty to every effect estimate reported here.

Sixth, the models were not adjusted for season or for meteorological covariates such as ambient temperature and relative humidity. Exposure was averaged over the full 280-day gestational window, which spans all seasons for most pregnancies and therefore attenuates but does not eliminate seasonal confounding, since conception and delivery dates were not uniformly distributed across the calendar year. Ambient pollutant concentrations in Tehran vary markedly by season, with CO and particulate matter peaking in the cold months and ozone in the warm months, and both season and temperature extremes are themselves recognised risk factors for preterm birth. Residual confounding by season and by meteorological conditions therefore cannot be excluded. Future analyses in this cohort should incorporate season and temperature as covariates and should examine trimester-specific exposure windows.

Future directions

Alongside these limitations, it is essential for future studies to include more monitoring stations and categorize them based on criteria such as measurement accuracy, proximity to mothers' residences, and the range of pollutants measured. It is also worth noting that assessing the accuracy of pollutant measurements is only possible by reviewing the technical documentation of the equipment, such as JICA reports. These measures could enhance exposure data quality and improve the precision of analyses in future research.

In light of this study's findings, several health implications and practical recommendations can be proposed. First, confirming the association between pollutants like CO and preterm birth suggests that reducing emissions of these pollutants at the city level could help decrease pregnancy complications. This can be pursued through policies such as improving vehicle efficiency, expanding clean public transportation, and restricting the movement of high-emission vehicles in densely populated areas. Second, recognizing air pollution as a pregnancy risk factor should be integrated into prenatal care programs. Educating pregnant women on how to avoid unnecessary exposure to polluted air (e.g., on high pollution index days or during peak traffic hours) and recommending the use of appropriate masks when necessary can help reduce individual exposure. Additionally, improving air pollution alert systems and implementing pollution reduction laws (such as low-emission zones and expansion of controlled areas) in Tehran and other polluted cities can indirectly benefit the health of mothers and future newborns.

Ultimately, the results of this study highlight the significance of air pollution as a health-related issue that affects not only patients with cardiac or respiratory conditions but also pregnant women and future generations. It is hoped that with continued large-scale research and the application of these findings in urban and health policymaking, we will witness a reduction in the burden of air pollution on maternal and child health in our society.

Conclusion

In this 20-year cohort study in East Tehran, maternal exposure to ambient CO during pregnancy showed a positive and statistically significant association with preterm birth. In the adjusted GEE model, CO exposure remained associated with preterm birth (coefficient = 0.537; 95% CI: 0.158 to 0.917; P=0.005), whereas $PM_{2.5}$, PM_{10}, NO_2, SO_2, and O_3 did not show statistically significant associations in the adjusted models.

Given the small number of preterm birth cases and the potential for exposure misclassification and residual confounding, these findings should be interpreted cautiously and considered hypothesis-generating rather than definitive causal evidence. Nevertheless, the observed CO association is biologically plausible and has important public health implications, particularly for traffic-related air pollution control, prenatal risk assessment, and targeted protection of pregnant women during high-pollution periods. Future studies with larger sample sizes, improved exposure assessment, and broader confounder adjustment are needed to validate these findings.

Financial supports

No funding was received from any organization in this study.

Competing interests

The author declares that there are no conflicts of interest regarding the publication of this article.

Acknowledgements

We would like to express our sincere gratitude to all participants of the Tehran Lipid and Glucose Study (TLGS) for their invaluable contributions and cooperation. We also thank the Air Quality Control Company and the Environmental Protection Organization for providing the air pollution data essential to this research. We further acknowledge Somayeh Farhang Dehghan for her valuable scientific support in the development of this study. AI-assisted language editing tools were used solely to improve grammar and readability. The authors reviewed and take full responsibility for the scientific content of the manuscript.

Ethical considerations

The ethical approval was granted under the code [IR.SBMU.PHNS.REC.1403.211] from Ethics Committee of the School of Public Health and Neuroscience Research Center, Shahid Beheshti University of Medical Sciences. Ethical issues (Including plagiarism, Informed Consent, misconduct, data fabrication and/or falsification, double publication and/ or submission, redundancy, etc) have been completely ob-served by the authors.

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