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Investigation of the relationship between air pollution and gestational diabetes

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ABSTRACT

Background: Gestational diabetes mellitus (GDM) can have negative effects on both the pregnancy and perinatal outcomes, as well as the long-term health of the mother and the child. It has been suggested that exposure to air pollution may increase the risk of developing GDM. This study investigated the relationship between exposure to air pollutants with gestational diabetes.

Methods: The present study is a retrospective cohort study. We used data from a randomised community trial conducted between September 2016 and January 2019 in Iran. During this period, data on air pollutant levels of five cities investigated in the original study, including 6090 pregnant women, were available. Concentrations of ozone (O_3), nitric oxide (NO), nitrogen dioxide (NO_2), nitrogen oxides (NOx), sulphur dioxide (SO_2), carbon monoxide (CO), particulate matter < 2.5 ($PM_{2.5}$) or <10 µm (PM_{10}) were obtained from air pollution monitoring stations. Exposure to air pollutants during the three months preceding pregnancy and the first, second and third trimesters of pregnancy for each participant was estimated. The odds ratio was calculated based on logistic regression in three adjusted models considering different confounders. Only results that had a $p < .05$ were considered statistically significant.

Results: None of the logistic regression models showed any statistically significant relationship between the exposure to any of the pollutants and GDM at different time points (before pregnancy, in the first, second and third trimesters of pregnancy and 12 months in total) ($p > .05$). Also, none of the adjusted logistic regression models showed any significant association between PM_{10} exposure and GDM risk at all different time points after adjusting for various confounders ($p > .05$).

Conclusions: This study found no association between GDM risk and exposure to various air pollutants before and during the different trimesters of pregnancy. This result should be interpreted cautiously due to the lack of considering all of the potential confounders.

PLAIN LANGUAGE SUMMARY

The health of pregnant women and their children can be impacted by gestational diabetes mellitus (GDM), one of the prevalent pregnancy complications. Some of studies showed that the incidence of gestational diabetes can be influenced by genetic or environmental factors. Air pollution is an environmental stimulus that may predispose pregnant women to GDM. This research explored whether air pollution could increase the risk of developing gestational diabetes. Over 6000 pregnant women in five cities of Iran participated in the study and were screened for gestational diabetes. Their exposure to the various air pollutants during the three months preceding pregnancy and total pregnancy period was measured. In this study, we found no clear association between air pollution and gestational diabetes. However, this finding needs to be interpreted cautiously since all the influential factors were not assessed.

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KEYWORDS
Gestational diabetes; pollutant; air pollution; $PM_{2.5}$; PM_{10}

Introduction

Hyperglycaemia during pregnancy that does not reach the levels of overt diabetes is called gestational diabetes mellitus (GDM) (American Diabetes Association 2021). This condition affects 1–30% of all pregnancies and is a common complication (McIntyre *et al.* 2019).

Some studies showed that GDM is associated with adverse perinatal outcomes such as preeclampsia and gestational hypertension, macrosomia, shoulder dystocia, maternal and neonatal trauma, miscarriage, stillbirth and jaundice (Buchanan *et al.* 2012), as well as GDM can also increase the risk of developing type 2 diabetes, obesity, dyslipidaemia, metabolic

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syndrome, hypertension and cardiovascular disease in the future (Sheiner 2020).

Although the cause of GDM is unknown, previous research has suggested several risk factors (Farahvar *et al.* 2019). Recent studies show that environmental factors, including air pollution, may play a more important role in the occurrence of this metabolic disorder than previously thought.

The association between air pollution exposure and GDM in pregnancy has been investigated by many epidemiological studies, but the findings are not consistent (Lin *et al.* 2020, Rammah *et al.* 2020, Yao *et al.* 2020, Ye *et al.* 2020, Yu *et al.* 2020, Zhang *et al.* 2020a).

Pollutants in studies mainly included particles with an aerodynamic diameter < 2.5 μm ($PM_{2.5}$) or <10 μm (PM_{10}), sulphur dioxide (SO_2) and nitrogen dioxide (NO_2).

Exposure to air pollution could be linked to a higher risk of GDM, according to some epidemiological studies in the United States (Hu *et al.* 2015, Robledo *et al.* 2015, Choe *et al.* 2019, Jo *et al.* 2019a, Rammah *et al.* 2020) and Europe (Pedersen *et al.* 2017). On the other hand, no such link was found by other studies even when the pollution was high (Fleisch *et al.* 2014, Fleisch *et al.* 2016, Zhang *et al.* 2020a). Several meta-analyses have also been performed to elucidate the effect of air pollutant exposure on GDM incidence but the results of them were inconsistent (Elshahidi 2019, Bai *et al.* 2020, Zhang *et al.* 2020b).

Given that understanding the risk factors for GDM is crucial to developing appropriate care guidelines and interventions in pregnancy, we conducted this study to assess the association between GDM with exposure to air pollutants (pre-pregnancy and different trimesters of pregnancy).

Methods

Study design

The present study is a retrospective cohort study assessing the association between exposure to outdoor air pollution and GDM among pregnant women. For the present study, we used data from a randomised community trial conducted between September 2016 and January 2019 in Iran (Ramezani Tehrani and Gulf Study Cooperative Research Group 2019). During the period of study, the data on air pollutants' values of five cities that participated in the original study were available including a total number of 6090 pregnant women.

Study participants

All pregnant women < 14 weeks of gestation, who received prenatal care from governmental health care systems, from the first trimester of pregnancy until delivery, were eligible for enrolment, except those who met the exclusion criteria.

Inclusion and exclusion criteria

The study excluded those with pre-existing diabetes, age < 18 years, unknown date of last menstrual period (LMP), no ultrasound estimation from 6 to 14 weeks of pregnancy, chronic hypertension or asthma, current treatment with oral glucocorticoids, oral β-mimetics, β-blockers, antiretroviral agents, Dilantin or history of bariatric surgery. For the purpose of the present study, we also excluded those without information on the address of the place of residence and/or those data on air pollutants before and during pregnancy. Finally, a total number of 6090 pregnant women remained for the present study (Figure 1).

All participants received routine prenatal standard care, as suggested by the American College of Obstetricians and Gynecologists (ACOG) 2013 (AAP and ACOG 2012), and underwent two phases of GDM screening in the first and second trimesters of pregnancy. The screening was based on FPG in the first trimester and either a one-step or a two-step method in the second trimester, depending on the city they were in. GDM in women who were exposed to different air pollutants were compared with non-GDM pregnant women.

Outcome assessment

Each city had a pre-specified protocol for screening all pregnant women for GDM. Protocol A adhered to the IADPSG[1] recommendations for GDM screening, and the other protocols were also the most prevalent ones nationally and internationally, as advised by a scientific committee of research and maternal health in the Ministry of Health of Iran. Definitions of the five protocols for GDM screening are obtainable in Table S1. GDM screening was performed in five selected cities, Bushehr and Gorgan according to protocol A, Sanandaj according to protocol B, Yazd according to protocol C and Birjand according to protocol D.

The first trimester of pregnancy involved early screening of GDM using FPG from the venous sample, with a specific threshold depending on each screening protocol. Moreover, those who did not have diabetes (overt or gestational) before were screened for GDM again at 24–28 weeks of gestation, based on the pre-specified protocol criteria for that city. Plasma glucose was measured using an enzymatic colorimetric method with glucose oxidase; inter- and intra-assay coefficients of variation were smaller than 2.3%.

Exposure assessment

We obtained concentrations of ozone (O_3), nitric oxide (NO), NO_2, nitrogen oxides (NOx), SO_2, carbon monoxide (CO), $PM_{2.5}$ and PM_{10} from the five urban air pollution monitoring stations. Pollutant data were available in each city at different intervals and on an hourly basis each day (24 records for 24 hours per day). Using these data in the first stage of analysis, daily mean concentrations were calculated for each air pollutant in each city.

Exposure to air pollutants during the three months preceding pregnancy and the first, second and third trimesters of pregnancy for each participant was estimated. Prediction models for different pollutants were developed using the average value for trimesters. For this, for each pregnant woman, according to the city where he lives and using the daily mean of exposure to pollutants in that city, the means of exposure to pollutants in the 90 days before the LMP (pre-pregnancy trimester), the first 90 days (first

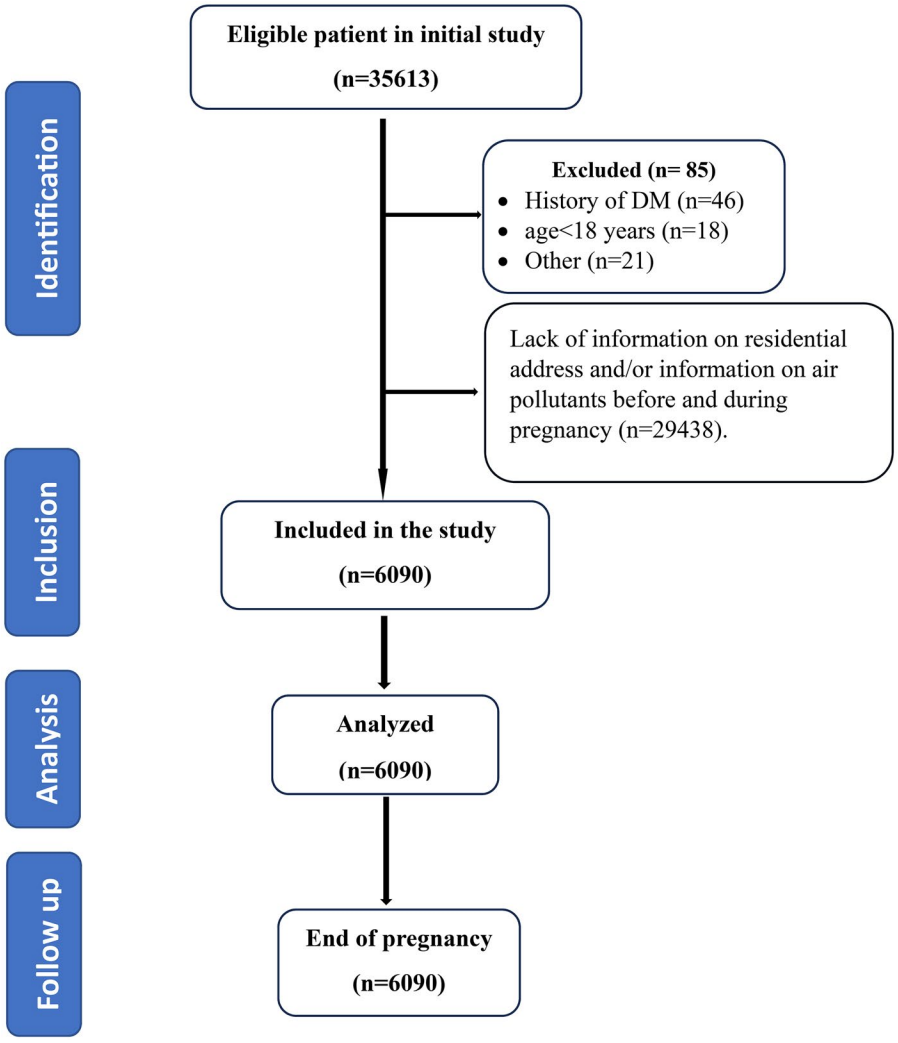

Figure 1. STROBE flowchart.

trimester), the second 90 days (second trimester) and the third 90 days (third trimester) after the LMP date were calculated.

Also, the mean exposure of the pregnant women to the pollutants during 360 days (from three months before to 9 months after the LMP date) was calculated. Calculations were done using coding in R statistical software (R Foundation for Statistical Computing, Vienna, Austria).

However, these means were applicable to samples for which contaminant levels were available in all required 360 days. Therefore, these values were not calculated for the samples in which pollutant registration data related to their city were not available in the study period, or a large part of which was missing data. Accordingly, the pregnant women with complete data on the available pollutants from each city were entered into the final calculations.

Confounding variables

Potential confounders in this study included maternal age, BMI, GDM history, family history of type 2 diabetes, and the protocol used for GDM. A composite risk score was calculated by the sum of scores obtained from the following variables: maternal age (< or ≥35 years), BMI (< or ≥30), history of pre-eclampsia/eclampsia, intrauterine growth restriction (IUGR), GDM, foetal malformation, macrosomia (foetal weight >4000 g), multiple pregnancies, recurrent miscarriage, stillbirth, polycystic ovarian syndrome and family history of type 2 diabetes. This composite risk score has a range of 0–12.

Statistical analysis

For continuous variables, we used mean (standard deviation) if they followed a normal distribution and median, interquartile range otherwise. We expressed categorical variables as numbers (%) and compared them with the Chi-squared test or Fisher's exact test (when some cells had low frequencies).

Multiple logistic regression was used for analysing the effects of pollutants exposures on the odds of GDM and considering adjustment variables' effects. Three adjustment models were developed including model 1 (adjustment based on age, BMI), model 2 (adjustment based on age, BMI, previous GDM history, family history of type 2 diabetes) and model 3 (adjustment based on the composite risk score for GDM). Since PM_{10} was the only pollutant, whose data were available in all studied cities, for evaluating the relationship between

GDM and PM_{10} exposure, the screening protocol for GDM was also added to all of the above-mentioned models. The variable of the screening protocol (taking into account the city Sanandaj as the reference) was added in all those three mentioned models. Predicted and observed mean PM_{10} exposure in GDM/non-GDM subjects is shown by a Box plot in the different trimesters (before pregnancy, 1st, 2nd and 3rd trimesters of pregnancy, and a total of 12 months of exposure).

We performed data analysis using R version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria) and IBM SPSS Statistics version 21 (IBM Corp., Armonk, NY). We considered $p < .05$ as the threshold for statistical significance for all the tests.

Ethical statement and approval number

The Ethics Committee of the Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences approved this study (code: IR.SBMU.ENDOCRINE.REC.1399.149). Written informed consent was obtained from all study participants.

Results

The event of GDM was observed in 1144 women out of 6090 participants. Tables 1 and 2 show the descriptive statistics of predictors and characteristics of women in non-GDM and GDM groups.

Table 3 demonstrates the daily average air pollution concentrations at various time intervals including before and during each trimester of pregnancy. The results of various adjusted logistic regression models are presented in Supplementary Tables 1–3. To calculate the odds ratio of GDM based on PM_{10}, three models (considering different confounding factors) were used. None of these models shows any statistically significant association between exposure to

Table 1. Descriptive statistics of predictors and characteristics of women in GDM and non-GDM groups.

Demographic and current pregnancy status				
Variables	Total (N = 6090)	Non-GDM (N = 4946)	GDM (N = 1144)	p Value
Age, median, IQR (years)	30 (26–34)	29 (25–33)	31 (26–35)	$p < .001$
BMI, kg/m^2, median, IQR (kg/m^2)	24.91 (22–28.05)	24.65 (21.84–27.90)	26.02 (23.00–29.22)	$p < .001$
Gravidity, mean ± SD	2 (1–3)	2 (1–3)	2 (1–3)	$p = .581$
Number of abortions, mean ± SD	0 (0–1)	0 (0–1)	0 (0–0)	$p = .001$
Number of deliveries, mean ± SD	1 (0–1)	1 (0–1)	1 (0–2)	$p = .185$
Number of vaginal deliveries, mean ± SD	0 (0–1)	0 (0–1)	0 (0–1)	$p = .558$
Number of caesarean deliveries, mean ± SD	0 (0–1)	0 (0–1)	0 (0–1)	$p = .301$
Number of children, mean ± SD	1 (0–1)	1 (0–1)	1 (0–1)	$p = .164$

GDM: gestational diabetes mellitus; IQR: interquartile range; BMI: body mass index.
Definition of all GDM screening protocol is presented in Table S1.

Table 2. Descriptive statistics of predictors and characteristics of women with previous pregnancy history in GDM and non-GDM groups.

Previous history					
Variables		Total (N = 4829)	Non-GDM (N = 3998)	GDM (N = 831)	p Value
Pre-eclampsia	No	4787 (99.1)	3968 (99.2)	819 (98.6)	$p = .050$
	Yes	42 (0.9)	30 (0.8)	12 (1.4)	
Gestational diabetes	No	4752 (98.4)	3947 (98.7)	805 (96.9)	$p < .001$
	Yes	77 (1.6)	51 (1.3)	26 (3.1)	
Multiple pregnancy	No	4806 (99.5)	3980 (99.5)	826 (99.4)	$p = .578$
	Yes	23 (0.5)	18 (0.5)	5 (0.6)	
Recurrent abortion	No	4718 (97.7)	3911 (97.8)	807 (97.1)	$p = .213$
	Yes	111 (2.3)	87 (2.2)	24 (2.9)	
IUGR	No	4826 (99.9)	3995 (99.9)	831 (100)	$p = 1.00$
	Yes	3 (0.1)	3 (0.1)	0 (0)	
Foetal abnormality	No	4807 (99.5)	3977 (99.5)	830 (99.9)	$p = .154$
	Yes	22 (0.5)	21 (0.5)	1 (0.1)	
Macrosomia (>4000 g)	No	4782 (99)	3959 (99)	823 (99)	$p = .973$
	Yes	47 (1)	39 (1)	8 (1)	
Stillbirth	No	4797 (99.3)	3971 (99.3)	826 (99.4)	$p = .519$
	Yes	32 (0.7)	27 (0.7)	5 (0.6)	
Oligo-anovulation	No	4780 (99)	3958 (99)	822 (98.9)	$p = .829$
	Yes	49 (1)	40 (1)	9 (1.1)	
Hirsutism	No	4797 (99.3)	3972 (99.3)	825 (99.3)	$p = .817$
	Yes	32 (0.7)	26 (0.7)	6 (0.7)	
PCOs history	No	4760 (98.6)	3939 (98.5)	821 (98.8)	$p = .547$
	Yes	69 (1.4)	59 (1.5)	10 (1.2)	
Type 2 diabetes in first degree relatives	No	4323 (90)	3582 (89.6)	741 (89.2)	$p = .716$
	Yes	506 (10)	416 (10.4)	90 (10.8)	
Composite GDM risk score[a]		0 (0–1)	1 (1–1)	0 (0–1)	$p < .001$

GDM: gestational diabetes mellitus; IUGR: intrauterine growth restriction.
[a]The composite GDM risk score was created based on 12 confounding variables (0–12) including maternal age (≤35 years), BMI (≤30), history of preeclampsia/eclampsia, intrauterine growth restriction (IUGR), gestational diabetes, foetal malformation, macrosomia (foetal weight >4000 g), multiple pregnancy, recurrent miscarriage, stillbirth, polycystic ovarian syndrome (PCOs) and family history of type 2 diabetes.
Definition of all GDM screening protocol is presented in Table S1.

Table 3. Daily average air pollution concentrations during before and each trimester of pregnancy in the study population.

Pollutant	Trimester	Mean	SD	Median	Min	Max	Q1	Q3
PM_{10}	Pre-pregnancy	78.78	49.52	59.30	23.54	266.67	42.04	104.37
	1	81.13	52.90	69.23	23.10	305.63	41.53	108.33
	2	84.31	61.89	67.44	23.10	309.53	42.15	105.53
	3	82.12	58.67	63.52	23.46	309.53	40.35	110.21
$PM_{2.5}$	Pre-pregnancy	65.07	35.62	48.98	9.57	154.25	39.33	78.15
	1	65.90	23.00	67.86	6.88	154.03	42.95	80.60
	2	78.26	33.20	78.43	6.54	153.78	49.19	106.97
	3	69.20	30.91	65.73	6.96	153.80	57.71	94.01
CO	Pre-pregnancy	3.39	0.44	3.24	2.48	4.08	3.05	3.80
	1	3.65	0.32	3.73	2.51	4.09	3.54	3.84
	2	3.75	0.16	3.77	2.97	4.03	3.66	3.86
	3	3.75	0.15	3.79	3.32	4.00	3.62	3.88
O_3	Pre-pregnancy	27.86	5.29	28.24	15.07	34.29	24.53	33.02
	1	30.35	3.58	30.75	17.96	36.25	29.32	32.65
	2	31.51	4.61	32.02	17.63	41.36	27.47	35.64
	3	35.92	6.13	36.02	20.19	46.15	32.31	40.67
NO	Pre-pregnancy	13.87	2.74	13.72	5.97	50.79	13.72	13.72
	1	13.72	4.47	13.72	5.03	50.81	12.98	13.72
	2	12.34	2.57	11.83	4.68	30.79	11.83	12.15
	3	15.93	5.68	12.33	5.16	24.91	12.04	23.86
NO_2	Pre-pregnancy	19.37	0.20	19.37	14.42	20.96	19.37	19.37
	1	19.38	0.55	19.37	13.10	26.60	19.37	19.41
	2	19.28	0.49	19.26	14.33	23.99	19.26	19.48
	3	19.38	0.46	19.34	16.48	21.35	19.32	19.63
NOX	Pre-pregnancy	30.46	1.61	30.37	19.95	52.81	30.37	30.37
	1	30.39	2.63	30.37	20.12	52.82	30.01	30.37
	2	29.72	1.18	29.46	23.07	40.82	29.46	29.77
	3	31.86	3.25	29.78	26.20	37.30	29.69	36.24
SO_2	Pre-pregnancy	17.96	5.46	18.57	9.38	29.94	13.19	20.34
	1	17.74	5.64	18.99	9.38	29.94	12.53	21.37
	2	15.72	3.72	16.24	10.41	29.80	12.99	17.17
	3	14.55	2.64	14.38	11.29	29.94	11.92	16.27

The measurement of PM_{10} was available for all five cities (Bushehr and Gorgan: protocol A, Sanandaj: protocol B, Yazd: protocol C, Birjand: protocol D); the measurement of $PM_{2.5}$ was available for Gorgan (protocol A) and Sanandaj (protocol B); the measurement of CO was available for Yazd (protocol C); the measurement of O_3 was available for Birjand (protocol D); the measurement of NO, NO_2 and NOX were available for Sanandaj (protocol B); the measurement of SO_2 was available for Gorgan (protocol A) and Sanandaj (protocol B). Definition of all GDM screening protocol is presented in Table S1.

Table 4. Results of multiple logistic regression model for assessing the odds ratio of GDM according to PM_{10} and various time points after adjustment for potential confounders.

Trimester		Pre-pregnancy	First trimester	Second trimester	Third trimester	Total[a]
Model 1						
PM_{10}		1.00 (0.99–1.00)	1.00 (0.99–1.00)	1.00 (1.00–1.00)	1.00 (0.99–1.00)	1.00 (1.00–1.00)
Age		1.03 (1.01–1.04)	1.03 (1.01–1.04)	1.03 (1.01–1.04)	1.03 (1.01–1.04)	1.03 (1.01–1.04)
BMI		1.07 (1.05–1.09)	1.07 (1.05–1.09)	1.07 (1.05–1.09)	1.07 (1.05–1.09)	1.07 (1.05–1.09)
Protocol [reference = Sanandaj (B)]	Boushehr (A)	6.69 (4.44–10.49)	6.46 (4.22–10.25)	6.96 (4.61–10.93)	6.13 (4.06–9.63)	6.07 (3.92–9.74)
	Bijand (D)	6.09 (3.97–9.69)	5.86 (3.76–9.46)	6.36 (4.17–10.08)	5.79 (3.81–9.14)	5.59 (3.58–9.04)
	Gorgan (A)	6.21 (2.91–13.29)	6.29 (3.33–12.01)	4.95 (2.58–9.54)	8.52 (4.50–16.32)	8.82 (3.63–21.24)
	Yazd (C)	2.40 (1.49–3.99)	2.38 (1.52–3.86)	2.23 (1.42–3.60)	2.70 (1.70–4.41)	2.66 (1.63–4.47)
Model 2						
PM_{10}		1.00 (0.99–1.00)	1.00 (0.99–1.00)	1.00 (1.00–1.00)	1.00 (0.99–1.00)	1.00 (1.00–1.000)
Age		1.03 (1.01–1.04)	1.03 (1.01–1.04)	1.02 (1.01–1.04)	1.03 (1.01–1.04)	1.03 (1.01–1.04)
BMI		1.07 (1.05–1.09)	1.07 (1.05–1.09)	1.07 (1.05–1.09)	1.07 (1.05–1.09)	1.07 (1.05–1.09)
History of GDM		1.79 (1.04–3.02)	1.79 (1.03–3.01)	1.79 (1.04–3.02)	1.78 (1.03–3.01)	1.79 (1.04–3.02)
Family history of type 2 diabetes (first degree relatives)		1.45 (1.10–1.90)	1.45 (1.10–1.90)	1.45 (1.10–1.90)	1.45 (1.10–1.90)	1.46 (1.10–1.91)
Protocol [reference = Sanandaj (B)]	Boushehr (A)	7.05 (4.65–11.10)	6.82 (4.43–10.87)	7.31 (4.82–11.53)	6.47 (4.26–10.20)	6.38 (4.10–10.28)
	Bijand (D)	6.06 (3.95–9.65)	5.84 (3.74–9.43)	6.31 (4.13–1.00)	5.76 (3.78–9.10)	5.54 (3.54–8.97)
	Gorgan (A)	6.43 (3.01–13.80)	6.47 (3.41–12.38)	5.20 (2.70–10.05)	8.80 (4.64–16.90)	9.27 (3.80–22.39)
	Yazd (C)	2.35 (1.45–3.90)	2.32 (1.48–3.76)	2.18 (1.39–3.53)	2.63 (1.66–4.30)	2.61 (1.59–4.38)
Model 3						
PM_{10}		1.00 (0.99–1.01)	1.00 (0.99–1.00)	1.00 (1.00–1.00)	1.00 (0.99–1.00)	1.00 (1.00–1.00)
Score[b]		1.40 (1.24–1.57)	1.39 (1.24–1.57)	1.40 (1.24–1.57)	1.39 (1.24–1.57)	1.40 (1.24–1.57)
Protocol [reference = Sanandaj (B)]	Boushehr (A)	6.42 (3.86–11.32)	6.28 (3.70–11.28)	6.51 (3.90–11.52)	6.17 (3.70–10.92)	6.18 (3.60–11.22)
	Bijand (D)	5.23 (3.10–9.33)	5.11 (2.96–9.30)	5.30 (3.16–9.42)	5.10 (3.05–9.03)	5.06 (2.93–9.21)
	Gorgan (A)	4.14 (1.60–10.70)	4.30 (1.89–9.88)	3.84 (1.64–9.00)	4.82 (2.11–11.11)	4.76 (1.55–14.35)
	Yazd (C)	1.91 (1.06–3.60)	1.93 (1.11–3.51)	1.86 (1.07–3.40)	2.02 (1.14–3.74)	1.99 (1.09–3.80)

GDM: gestational diabetes mellitus; BMI: body mass index; model 1: age, BMI and protocol adjusted; model 2: age, BMI, history of GDM, family history of type 2 diabetes and protocol adjusted; model 3: score and protocol adjusted.
Definition of all GDM screening protocol is presented in Table S1.
[a]Sum of pre pregnancy, first, second and third trimester of pregnancy.
[b]The composite GDM risk score was created based on 12 confounding variables (0–12) including maternal age (≤35 years), BMI (≤30), history of preeclampsia/eclampsia, intrauterine growth restriction (IUGR), gestational diabetes, foetal malformation, macrosomia (foetal weight >4000 g), multiple pregnancy, recurrent miscarriage, stillbirth, polycystic ovarian syndrome (PCOs) and family history of type 2 diabetes.

each of the pollutants and GDM at various time points including before pregnancy, in the 1st, 2nd and 3rd trimesters of pregnancy, and a total of 12 months.

All adjusted logistic regression models revealed no significant association between exposure to PM_{10} and risk of GDM in all of the various time points including pre-pregnancy, in the 1st, 2nd and 3rd trimesters of pregnancy, and a total of 12 months, after adjustment for different confounding factors.

The multiple logistic regression models, considering Sanandaj city (with the simplest screening protocol (B)) as the reference, showed that this association was the highest in screening protocol A (as the most conservative approach) and the lowest in protocol C (using the same FBS cut-off value as protocol B) (Table 4).

Figure 2 illustrates a comparison of predicted and observed mean PM_{10} exposure in the different trimesters (before pregnancy, first, second and third) in GDM/non-GDM subjects. As this figure shows, there is no appreciable difference in the level of PM_{10} exposure in both GDM and non-GDM groups and in all trimesters, and a total of 12 months of exposure.

Tables S2, S3 and S4 show the odds ratio for GDM risk from logistic regression models.

Discussion

The current study revealed no significant difference in the prevalence of GDM in women exposed to various air pollutants compared to non-exposed pregnant women.

Over the last two decades, the association between GDM and air pollutants has attracted considerable debate and original studies reported inconsistent results. Zhang *et al.* (2020a, 2020b) based on a meta-analysis including 13 epidemiological studies reported no significant association between GDM with exposure to $PM_{2.5}$, PM_{10} and NO_2 (Zhang *et al.* 2020b). Bai *et al.* (2020), in another meta-analysis including 33 cohort studies, also did not observe a significant association between PM_{10}, CO, O_3 and NO_2 with GDM (Bai *et al.* 2020). However, Nazarpour *et al.* (2023) conducted a meta-analysis that included 13 studies and revealed a positive association between air pollutants $PM_{2.5}$, PM_{10}, O_3 and SO_2 and the risk of GDM (Nazarpour *et al.* 2023). Additionally, Liang *et al.* (2023) conducted a meta-analysis of 31 cohort studies. Their findings indicated that exposure to NO_2, SO_2, $PM_{2.5}$ and PM_{10} significantly increases the risk of GDM (Liang *et al.* 2023). Another meta-analysis found that only NO and SO_2 (especially SO_2 exposure) exposure from air pollution was associated with a higher risk of GDM (Elshahidi 2019).

Our findings are consistent with some prior population-based studies that found no associations with exposure to air pollutants (Fleisch *et al.* 2014, 2016) and contrary to some other studies that showed a significant positive relationship between different air pollutants and GDM (Hu *et al.* 2015, Robledo *et al.* 2015, Choe *et al.* 2019, Lin *et al.* 2020, Zhang and Zhao 2021).

In agreement with the present study, several studies reported no associations between exposure to PM_{10} and GDM (Robledo *et al.* 2015, Pan *et al.* 2017, Jo *et al.* 2019a, 2019b, Zhang *et al.* 2020a, Zhang and Zhao 2021); while Lin *et al.* (2020) showed that the risk of GDM is significantly increased among those highly been exposed to PM_{10} (Lin *et al.* 2020).

The WHO guidelines state that annual average concentrations of $PM_{2.5}$ and PM_{10} should not exceed 5 and 15 μg/m^3, while 24-h average exposures of $PM_{2.5}$ and PM_{10} should not exceed 15 and 45 μg/m^3, respectively (WHO 2021).

Exposure to $PM_{2.5}$ appears to be a risk factor for hyperglycaemia. According to some epidemiological studies, exposure to $PM_{2.5}$ for any duration (short, medium or long) may play a role in increased glycosylated haemoglobin A1c (HbA1c), FBG and type 2 diabetes in non-pregnant adults (Lucht *et al.* 2018, Qiu *et al.* 2018, Liu *et al.* 2019).

Previous studies have shown that endoplasmic reticulum stress, oxidative stress and inflammation may play important roles in GDM development paths. Particulate matter is believed to be an inflammatory stimulant that can increase inflammatory cytokines (Tamagawa *et al.* 2008). Insulin signalling or insulin secretion by beta cells can be disturbed by these inflammatory cytokines, which results in lower insulin receptor tyrosine kinase activity and insulin resistance (Barbour *et al.* 2007, Kim *et al.* 2009, Haberzettl *et al.* 2016).

Exposure to $PM_{2.5}$ appears to impair endothelial function, reduce peripheral glucose uptake and induce diabetes mellitus (Rajagopalan and Brook 2012). All these mechanisms make women vulnerable to developing insulin resistance and GDM. Several studies reported that exposure to $PM_{2.5}$ before and during pregnancy was associated with an increased risk of GDM (Rammah *et al.* 2020, Ye *et al.* 2020, Yu *et al.* 2020, Zhang *et al.* 2020c, Hu *et al.* 2021, Zheng *et al.* 2021). We did not find an association between GDM and $PM_{2.5}$, which may be due to the lack of many variations in air pollutants among study participants.

The WHO guidelines state that annual average concentrations of O_3 should not exceed 100 μg/m^3, eight-hour daily maximum (WHO 2021). Data on O_3 were only available for one city with a daily average of 27–35 μg/m^3. We found no significant association between GDM and O_3 in our data set. According to research from the US and China, pregnant women who were exposed to O_3 in the first and second trimesters of their pregnancy had a higher chance of developing GDM (Hu *et al.* 2015, Robledo *et al.* 2015). In contrast, the results of other studies did not show a significant association (Pan *et al.* 2017, Abdo *et al.* 2019, Lin *et al.* 2020).

According to the current WHO guideline, the 24-hour mean value of 25 μg/m^3 and 40 μg/m^3 was recommended to be considered for the prevention of adverse health effects of NO_2 and SO_2, respectively (WHO 2021). The levels of these pollutants were below these thresholds in the present study and we found no association between NO_2 and SO_2 and GDM. While some studies have reported an association between exposure to GDM and SO_2 (Robledo *et al.* 2015, Pan *et al.* 2017, Choe *et al.* 2019, Zhang *et al.* 2020a, 2020b, Zhang and Zhao 2021).

Some studies have shown an association between exposure to NO_2 and GDM (Pedersen *et al.* 2017, Choe *et al.* 2019, Jo *et al.* 2019a, Hehua *et al.* 2021, Zhang and Zhao 2021). However, the association of NO_2 exposure in the first and/or second trimester was not significant in some studies (Pan *et al.* 2017, Lin *et al.* 2020, Zhang *et al.* 2020a).

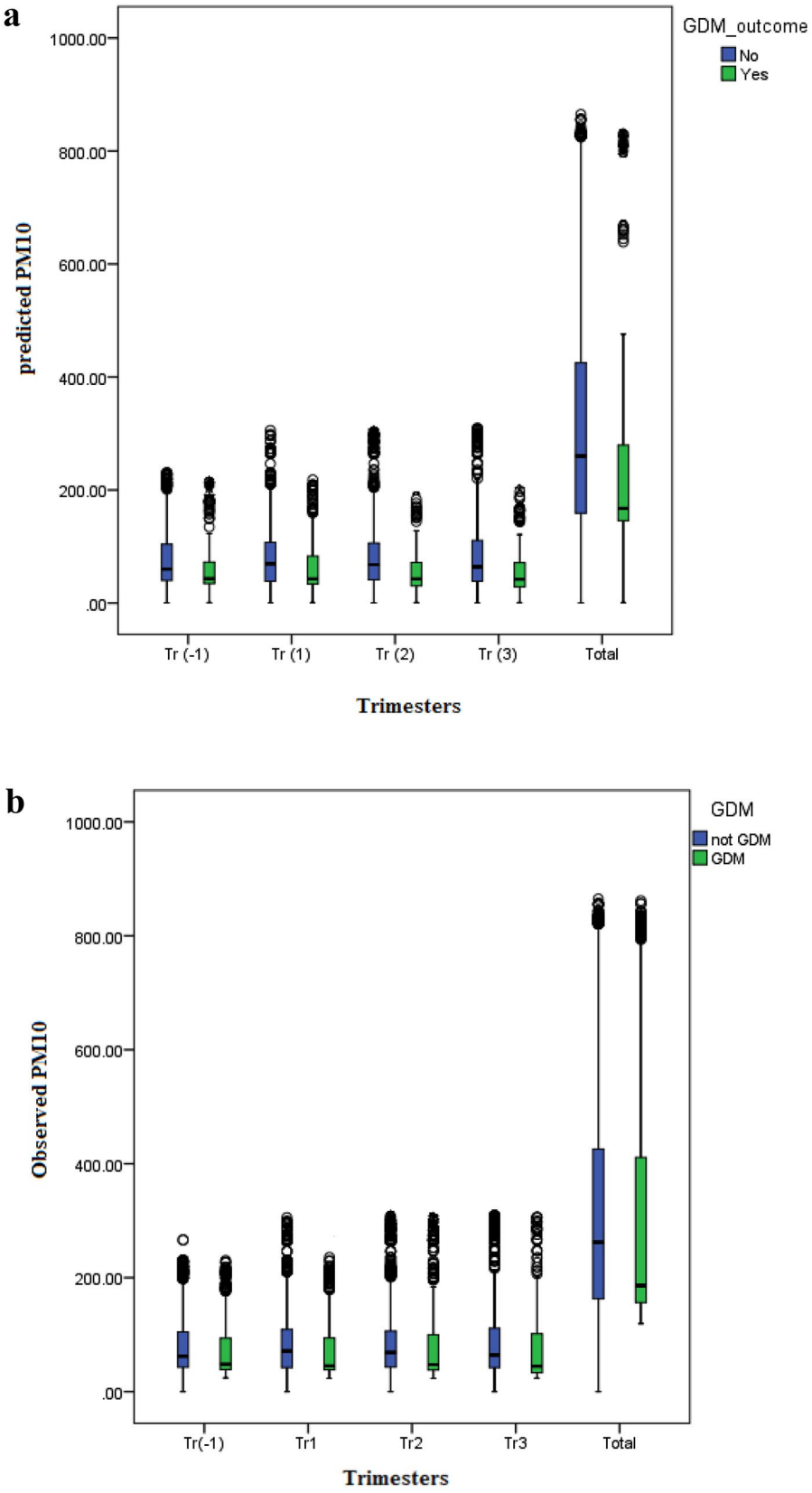

Figure 2. Comparison of predicted (a) and observed (b) mean PM_{10} exposure in the different trimesters (before pregnancy, first, second and third) in GDM/non-GDM subjects.

Different study designs, diverse populations, exposure measurement methods and changing levels of air pollutants in different places and times may explain the causes of differences among different studies.

It should also be noted that the average levels of air pollutants especially O_3, NO_2 and SO_2 levels in our study were lower than in many other studies, which could be the cause of differences in study results.

This study was a large, retrospective population cohort with several measures of air pollution exposure during the pre-pregnancy period and different trimesters of pregnancy. However, several limitations in this study should be noted. First, we did not have enough data about all the pollutant's daily levels in all locations and PM_{10} was the only pollutant whose data were available for all participants. Second, we did not have data about the proximity of where pregnant women live to sources of air pollution. It is clear that habitat and proximity to the source of pollution are factors influencing exposure to pollutants. Third, we have not evaluated the effect of a mixture of contaminants on GDM, while it is possible that there is a cumulative effect of pollutants. Fourth, in the present study, some potential disruptive factors, including place of residence, diet, physical activity and other diseases of the mother, such as hyperlipidaemia, were not considered. Finally, we also did not have information on dietary patterns that might exacerbate the impact of air pollution exposure on GDM. To clarify the cause and effect of pollutant standards and GDM occurrence, more research is necessary to explore how they work. Additionally, big-scale studies with data on multiple variables and pollutants are needed.

Conclusions

Although the results of this study showed that there is no relationship between air pollutants and the risk of GDM, more comprehensive cohort studies considering all those mentioned confounders are highly needed to clarify how air pollution affects GDM.

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Author contributions

S.N.: the conception or design, interpretation of data, drafting preparation, and reviewing it critically for important intellectual content; A. Sh. P.: data curation, interpretation of data, and reviewing it critically for important intellectual content; F.R.T.: the conception or design, interpretation of data, and reviewing it critically for important intellectual content; M.M.: data curation, data analysis and interpretation of data; S.B.G.: the conception or design, interpretation of data, and reviewing it critically for important intellectual content. All authors provided final approval for the submitted final version of the paper. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Data availability statement

The data that support the findings of this study are available upon reasonable request.

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