Nitrogen Dioxide Exposure During Pregnancy and Risk of Spontaneous Abortion: A Case-control Study in China

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Research

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Abstract

Background

Evidence on the relationship between prenatal exposure to NO_2 and CO and spontaneous abortion (SAB) is insufficient. We investigated whether there is an association between maternal exposure to nitrogen dioxide (NO_2) and carbon monoxide (CO) before and during pregnancy and SAB.

Methods

We conducted a case-control study using medical records of 2445 pregnant women who admitted for abortion prior to 20 weeks of gestational age from January 2014 to December 2019 at a tertiary-care hospital in Shanghai, China. Of the 2445 participants, 1075 were SAB cases and 1370 were healthy controls (underwent elective abortions). Maternal exposure to NO_2 and CO before and during pregnancy was estimated using daily air pollution concentration data. Multivariable logistic regression models were constructed to quantify the relationships between maternal exposure to NO_2 or CO and the risk of SAB while controlling for potential confounders.

Results

NO_2 exposure levels during pregnancy were significantly higher in SAB cases than in healthy controls (42.26 vs 40.67, $P < 0.01$). NO_2 exposure during pregnancy was positively associated with the risk of SAB. An interquartile range (16 $\mu g/m^3$) increase in NO_2 exposure was associated with 67% increase in the odds of SAB (OR = 1.67, 95% CI, 1.28, 2.18). Analyses of associations by quartile of NO_2 exposure showed that elevated NO_2 exposure during pregnancy was associated with increased odds of SAB in linear dose-response manners. Compared with the lowest quartile of NO_2 exposure, the odds of SAB in the fourth quartile of NO_2 exposure increased 60% (OR = 1.60, 95% CI, 1.03–2.49). No associations of CO exposure with SAB risk were observed.

Conclusion

Our study suggested that exposure to NO_2 during early pregnancy was associated with increased risk of SAB. Further studies are need to confirm our results and explore the potential biological mechanism underlying these associations.

Introduction

Ambient air pollution is the most serious environmental threat and represents a major mortality risk factor worldwide [1]. According to a recent global diseases burden estimates, exposure to ambient air pollution from particulate matter caused about 4.2 million deaths and 103.1 million disability-adjusted life-years (DALYs) in 2015 [2].

The cardiovascular and respiratory effects of air pollution have been well documented [3, 4]. Recently, its reproductive and developmental toxicity has raised concern. Numerous epidemiological studies have reported significant associations between prenatal exposure to air pollution and increased risk of adverse pregnancy outcomes [5]. Those adverse pregnancy outcomes included low birth weight (LBW), fetal growth restriction (FGR), preterm birth (PTB) and birth defects [6–8].

Spontaneous abortion (SAB) or miscarriage, a common and serve complication of pregnancy, defined as the spontaneous loss of a pregnancy before 20 weeks of pregnancy [9]. At least 25% of all women experience one or more sporadic miscarriages [10]. Detrimental effects of air pollution on SAB have been previously suggested with exposure to particulate matter (PM) and some gaseous pollutants [11. Most of the previous studies reported strong associations of high PM [12–15], sulfur dioxide (SO_2) [16, 17] and ozone (O_3) [12, 15, 18] exposure with increased risk of SAB. However, evidence regarding nitrogen dioxide (NO_2) and carbon monoxide (CO) are insufficient and less inclusive, suggesting more studies are warranted to better understand their associations with SAB risk [11].

In this study, using clinal records of abortions in a tertiary hospital in Shanghai, China, we conducted a case-control study to examine whether maternal exposure to NO_2 and CO before and during pregnancy was associated with increased risk of SAB.

Methods

Study Design and Subjects

A retrospective review of the medical records of abortions was conducted at Shanghai First Maternity and Infant Hospital, which is a tertiary-care hospital serving approximately 45,000 inpatients per year in Shanghai, China. The electronic medical record system of our hospital was used for data collection. From January 2014 to December 2019, a total of 2445 singleton pregnant women, aged between 14 to 48 years, admitted for abortion prior to 20 weeks of gestational age (GA). Of the 2445 pregnant women, 1075 were diagnosed as having missed abortion and were enrolled as SAB cases. While 1370 women with normal pregnancies who requested induced abortion due to unplanned or unwanted pregnancy were enrolled as healthy controls.

Maternal demographic characteristics including maternal age (MA), menstrual cycles, weight and height, the use of assisted reproduction technology (ART) and reproductive history were collected. GA was calculated based on the last menstrual period (LMP) of pregnant women and confirmed by ultrasound. The study protocol was approved and monitored by the medical Ethics Committee of the Shanghai First Maternity and Infant Hospital (NO. KS2008). Since all data were from medical record and used anonymously, there was no informed consent.

Air Pollution Exposure Assessment

Daily (24-h) NO_2 and CO concentration data for each of the 16 administrative districts in Shanghai city, from May 1, 2013 to December 30, 2019, were obtained from the database of the Shanghai Environmental Monitoring Center (SEMC). The daily concentrations of NO_2 and CO in each district were averaged from the available data of all fixed-site monitoring stations. Ambient NO_2 and CO measurements in each monitoring stations relied on a chemiluminescence detection method (API 200e, Thermo 42i) and a gas filter correlation method (API 300e, Thermo 48i), respectively. All ambient measurements of NO_2 and CO were operated under the China National Quality Control Automated methods [(GB3095-2012) and (HJ/T 193–2005)] for ambient air quality monitoring. In order to adjust for the potential confounding effects of weather on SAB, we also obtained daily 24-h mean temperature and relative humidity from the database of the Shanghai Meteorological Bureau.

To explore the critical exposure time windows of NO_2 and CO on SAB, we examined four exposure time windows for each subject (Phases 1–4). The four exposure windows were defined as follows: Phase 1, from the first day of LMP to the date of abortion; Phase 2, 30 days before the first day of the LMP; Phase 3, 60 days before the first day of the LMP; Phase 4, 90 days before the first day of the LMP. The phase-averaged values of daily concentrations of NO_2 and CO during various phases in the district where the subject's residence is located were calculated.

Statistical Analyses

In descriptive analysis, the demographic characteristics of all participants were shown as mean ± standard deviation (SD) or percent (%). Parametric t-tests and χ^2 tests were used to compared the difference in demographic characteristics between SAB cases and healthy controls. As NO_2 and CO exposure levels were not normally distributed, medians (25th -75th percentile) were presented to characterize their distribution in descriptive analysis. Mann-Whitney U-test was used to examine the potential differences in NO_2 and CO exposure between SAB cases and healthy controls.

Multivariate logistic regression models were used to examine the association between SAB risk and exposure to NO_2 and CO with adjustment for potential confounders. According to the data accessibility and literature studies [15, 19], we denoted the following factors to be covariates: GA, MA, body mass index (BMI), maternal parity, the use of ART, temperature and relative humidity. We first conducted single pollutant model with only NO_2 or CO in the multivariate logistic regression models. Then we conducted two-pollutants model to examine the joint effects of NO_2 and CO exposure on SAB. We reported the odd ratio (OR) and 95% confidence interval (CI) in association with an interquartile range (IQR) increase in NO_2 or CO concentrations.

In order to explore the potential dose-response relationships between NO_2 exposure and risk of SAB, the distribution of NO_2 exposure levels was divided into quartiles and an OR and 95% CI was calculated for each higher quartile compared with the lowest quartile using multivariate logistic regression analysis. All statistical analysis was performed by using SPSS16.0 software (SPSS Inc., Chicago, IL, USA) and a two-sided $p < 0.05$ was considered statistically significant.

Result

Population Characteristics

Table 1 presents the demographic characteristics of all study participants (N = 2445). The average MA of all participants was 33.18 (5.34) years at enrollment. The average GA and BMI was 72.73 (23.29) days and 22.20 (3.31) kg/m^2, respectively. Of the 2445 participants, 1075 were SAB cases and 1370 were health controls. SAB cases and healthy controls differed with regard to GA, BMI, menstrual cycles, parity and the use of ART. SAB cases and health controls did not differ by MA (33.15 ± 4.98 vs 33.20 ± 5.60, P = 0.819).

Table 1
Selected characteristics of case and control subjects

Characteristics [a]	Total (N = 2445)	Case (N = 1075)	Control (N = 1370)	P-value [b]
Maternal age (years)	33.18 ± 5.34	33.15 ± 4.98	33.20 ± 5.60	0.819
Gestational age (days)	72.73 ± 23.29	78.22 ± 19.31	68.43 ± 25.17	< 0.001**
BMI (kg/m^2)	22.20 ± 3.31	22.36 ± 3.27	22.08 ± 3.34	< 0.001**
Menstrual cycles				
Regular	2139 (87.5%)	921 (85.7%)	1218 (88.9%)	0.017*
Irregular	306 (12.5%)	154 (14.3%)	152 (11.1%)	
Parity				
Nulliparous	1005 (41.1%)	669 (62.2%)	336 (24.5%)	< 0.001**
Multiparous	1440 (58.9%)	406 (37.8%)	1034 (75.5%)	
ART				
Yes	24 (1.0%)	24 (2.2%)	0 (0.0%)	< 0.001**
No	2421 (99.0%)	1051 (97.8%)	1370 (100.0%)	

[a] Values were shown as mean ± standard deviation (SD) or percent (%).

[b] p Values were calculated using Student's t-test or χ^2-test.

*P < 0.05, **P < 0.01.

No And Co Exposure Levels

Table 2 presents the distribution of NO_2 and CO exposure levels during each specific exposure window (Phases 1–4). The median (25th -75th percentile) NO_2 exposure levels for phases 1–4 were 41.46 (33.52, 49.52), 40.34 (31.85, 50.81), 41.00 (32.24, 50.76) and 41.65 (32.73, 50.11) μg/m^3, respectively. The median CO exposure levels were 0.68 (0.60, 0.78), 0.69 (0.59, 0.80), 0.69 (0.60, 0.80) and 0.69 (0.61, 0.79) mg/m^3, respectively. Exposure levels of NO_2 were moderately correlated with CO during each phase, with the correlation coefficients ranging from 0.633 to 0. 680 (Fig. 1).

Table 2
Exposure Characteristics of NO_2 and CO

Pollutants	Total (N = 2445) (P_{50}, P_{25}-P_{75})	Case (N = 1075) (P_{50}, P_{25}-P_{75})	Control (N = 1370) (P_{50}, P_{25}-P_{75})	P-value [a]
NO_2 ($\mu g/m^3$)				
Phase 1	41.46 (33.52, 49.52)	42.26 (34.31, 50.12)	40.67 (32.74, 48.93)	< 0.001**
Phase 2	40.34 (31.85, 50.81)	40.00 (31.35, 51.25)	40.48 (32.39, 50.42)	0.758
Phase 3	41.00 (32.24, 50.76)	40.40 (31.38, 51.10)	41.28 (32.57, 50.42)	0.472
Phase 4	41.65 (32.73, 50.11)	41.55 (32.18, 50.36)	41.80 (33.38, 49.81)	0.280
CO (mg/m^3)				
Phase 1	0.68 (0.60, 0.78)	0.69 (0.60, 0.78)	0.68 (0.60, 0.78)	0.488
Phase 2	0.69 (0.59, 0.80)	0.69 (0.59, 0.79)	0.69 (0.59, 0.80)	0.484
Phase 3	0.69 (0.60, 0.80)	0.69 (0.59, 0.79)	0.69 (0.61,0.80)	0.363
Phase 4	0.69 (0.61, 0.79)	0.69 (0.60, 0.80)	0.69 (0.62, 0.79)	0.446

[a] p Values were calculated using Mann-Whitney U-test.

Phase 1: form the last menstrual period to the date of missed abortion, Phase 2: 30 days before pregnancy, Phase 3: 60 days before pregnancy, Phase 4: 90 days before pregnancy.

**P < 0.01.

Analyses of potential differences in NO_2 and CO exposure levels during each exposure window between SAB cases and health controls were conducted using the Mann-Whitney U-test. As shown in Table 2, NO_2 exposure levels during phase 1 (from the first day of LMP to the date of abortion) were significantly higher in SAB cases than in healthy controls (42.26 vs 40.67, $P < 0.01$). While there was no significant difference in CO exposure during each exposure window.

Associations Of No And Co Exposure With Sab Risk

The associations of NO_2 and CO exposure with SAB risk were investigated. ORs and 95% CIs for the risk of SAB in relation to NO_2 or CO exposure are presented in Table 3. Higher NO_2 exposure during phase 1 was significantly associated with increased risk of SAB. In single-pollutant model, an IQR (16 $\mu g/m^3$) increase in NO_2 exposure during was associated with 52% (OR = 1.52, 95% CI, 1.19–1.95) increase in the odds of SAB. A similar result was observed in two-pollutant models with 67% (OR = 1.67, 95% CI, 1.28, 2.18) increase in the odds of SAB per IQR increase in NO_2 exposure during phases 1. However, no significant association was found between SAB risk and CO exposure during any phases.

Table 3
Associations of NO_2 and CO exposure with spontaneous abortion risk

Pollutants	Single pollutant model [a] OR (95% CI)	Two-pollutants models [b] OR (95% CI)
NO_2		
Phase 1	1.52 (1.19, 1.95) **	1.67 (1.28, 2.18) **
Phase 2	0.98 (0.79, 1.22)	0.99 (0.77, 1.26)
Phase 3	1.00 (0.77, 1.30)	1.01 (0.76, 1.35)
Phase 4	0.94 (0.71, 1.25)	0.96 (0.70, 1.31)
CO		
Phase 1	0.99 (0.86, 1.14)	0.88 (0.76, 1.03)
Phase 2	0.99 (0.87, 1.13)	1.00 (0.86, 1.15)
Phase 3	0.99 (0.86, 1.13)	0.98 (0.84, 1.15)
Phase 4	0.97 (0.85, 1.11)	0.98 (0.85, 1.14)

[a] Adjusted for GA, MA, BMI, maternal parity, ART, temperature and relative humidity.

Phase 1: form the last menstrual period to the date of missed abortion, Phase 2: 30 days before pregnancy, Phase 3: 60 days before pregnancy, Phase 4: 90 days before pregnancy.

**P < 0.01.

Given NO_2 exposure during phase 1 was found to be significantly associated with increased risk of SAB, we examined the dose-response associations between NO_2 exposure during phase 1 and the risk of SAB. As shown in Fig. 2, higher NO_2 exposure was associated with increased odds of SAB in linear dose-response manners.

In both single-pollutant model, compared with the lowest quartile of NO_2 exposure, being in the fourth quartile of NO_2 exposure was significantly associated with increased odds of having SAB (OR = 1.54, 95% CI, 1.01–2.34). Similar results were observed in two-pollutants model. Compared with the lowest quartile of NO_2 exposure, the odds of SAB in the fourth quartile of NO_2 exposure increased 60% (OR = 1.60, 95% CI, 1.03–2.49). The trend tests for the above dose-response relationships were statistically significant (single pollutant model, p-trend = 0.053; Two-pollutants model, p-trend = 0.038).

Discussion

SAB is one of the most frequent traumatic life events a woman may encounter. It is associated with various negative psychological outcomes including depression, grief, anxiety and marital conflict [20]. The causes of SAB are likely to be multifactorial [9, 21, 22]. Along with genetic and socioeconomic factors, environmental pollution, including air pollution, may possibly play a role in the development of SAB.

In this study, on the basis of a case-control study design, we investigated the adverse effects of NO_2 and CO exposure on SAB. We found that exposure to NO_2 during pregnancy was associated with increased risk of SAB. Moreover, we observed significantly linear dose-response relationships between NO_2 exposure and SAB risk. However, we did not find any association between CO exposure and SAB. Our findings indicate that pregnant women who exposed to higher levels of NO_2 during pregnancy might be at higher risk for SAB.

Some studies have investigated the associations between maternal exposure to NO_2 and SAB. Most of those reported studies used fixed air monitoring station data to estimate individual NO_2 exposure and reported significant positive associations between NO_2 exposure and SAB risk [18, 19, 23, 24]. Our findings were consistent with the results of those previous studies. Moreover, one prospective cohort study found that pregnant women living within 50 m of a road with higher annual average daily traffic was statistically significantly associated with increased risk of SAB [25]. The results of this prospective cohort study also supported our findings since vehicle emissions is a major source of ambient NO_2.

For air pollutant of CO, only three studies examined the association of maternal exposure to CO with the risk of SAB. In agreement with findings from this presented study, both a time-series study and a prospective cohort study did not find any association between SAB risk and CO exposure [15, 26]. However, a recent study failed to support our findings. Zhang and colleagues examined the records of 255,668 pregnant women from 2009 to 2017 in Beijing, China, and quantified the link between CO exposure and SAB risk. They found long-term exposure to CO before pregnancy was associated with significant increased risk of SAB [17]. Inconsistent results may mainly be ascribed to different study designs and exposure ranges.

The mechanisms of action of NO_2 exposure on SAB are not fully understood. Some studies demonstrated that exposure to NO_2 during pregnancy could induce structural or chromosomal anomalies, which are relevant for SAB [27]. Moreover, some previous studies have shown that NO_2 exposure could induced oxidative stress and inflammatory responses [28–30], which have been hypothesized to play a role in the development of SAB [31].

Some limitations should be acknowledged. Firstly, we estimated maternal exposure to NO_2 and CO based on fixed-site monitoring station data and ignored the spatial distribution of those two pollutants, which may cause exposure misclassification. Secondly, due to the data inaccessibility, we were unable to collect information about some potential risk factors for SAB and thus could not rule out the role of those unmeasured confounders. Thirdly, this is only an exploratory study, we were unable to examine the biological pathways underlying the association between maternal exposure to NO_2 and increased risk of SAB.

In summary, our findings suggest that maternal exposure to NO_2 during early pregnancy is associated with increased risk of SAB. Further studies are needed to confirm our finding and to explore the biologic mechanisms underlying this association.

Abbreviations

NO_2
Nitrogen Dioxide; SAB:spontaneous abortion; CO:carbon monoxide; GA:gestational age; MA:maternal age; ART:assisted reproduction technology; LMP:last menstrual period

Declarations

Competing Interests

The authors have declared that no competinginterest exists.

Consent for publication

Not applicable

Author Contributions

Conceptualization: Beiying Wang, Xiaocui Li*

Data curation: Wei Hong, Qingjing Sheng, Zhiping Wu, Li Li,.

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Figures

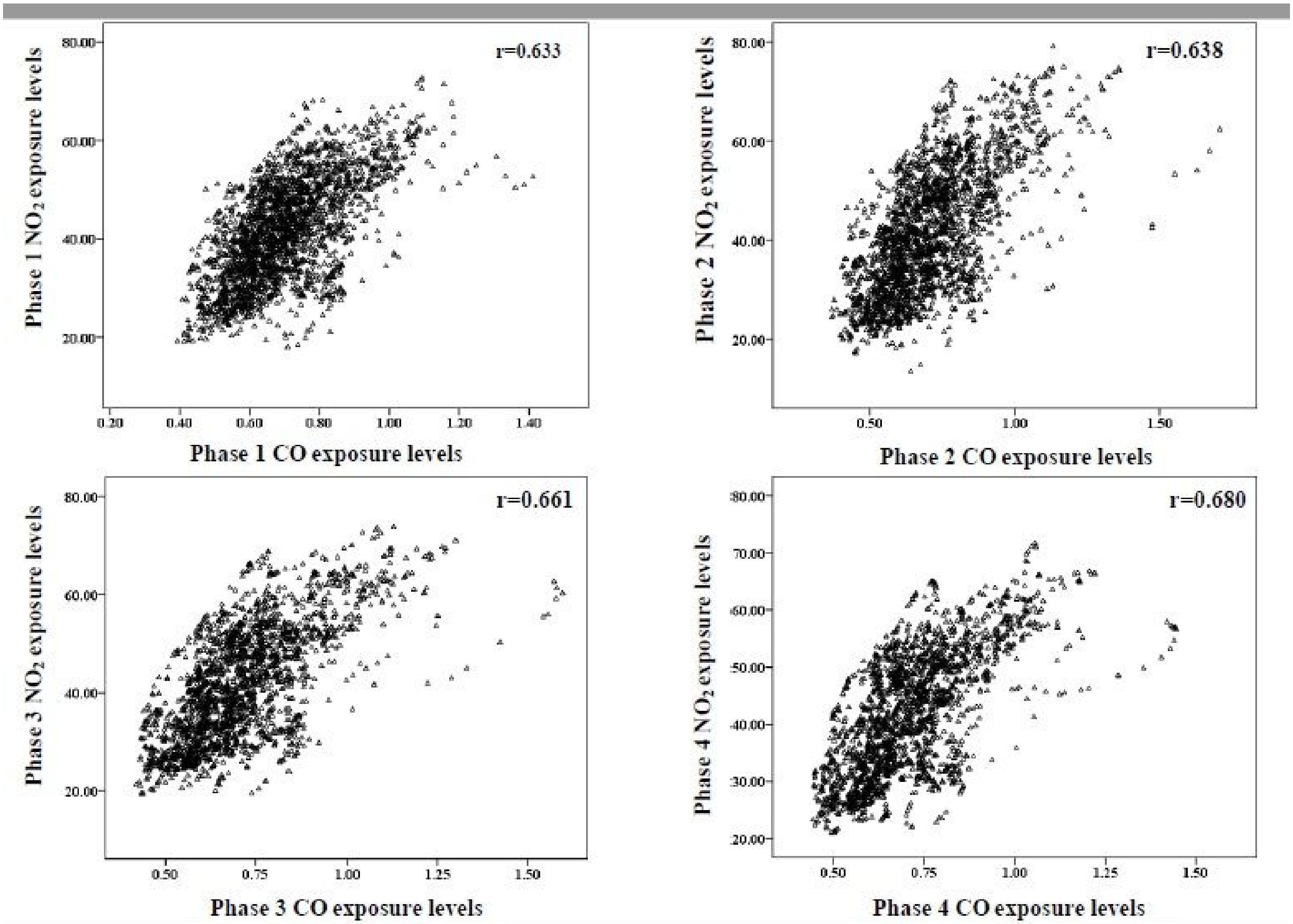

Figure 1

Plots of the correlations between NO2 exposure levels and CO exposure levels. Scatterplots depict the correlation of NO2 exposure levels (Y axis) and CO exposure levels (x axis), with the spearman correlation coefficient (r) provided. All spearman correlation coefficients were significant at $p<0.01$. Phase 1: form the last menstrual period to the date of missed abortion, Phase 2: 30 days before pregnancy, Phase 3: 60 days before pregnancy, Phase 4: 90 days before pregnancy.

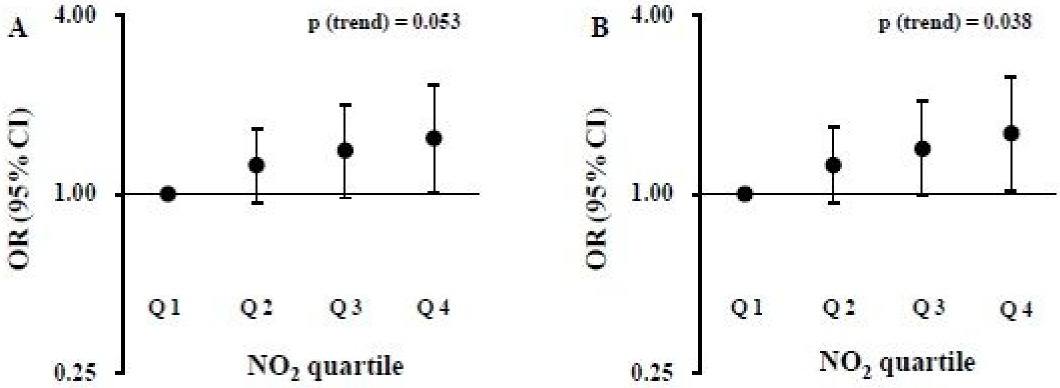

Figure 2

ORs and 95% CI for the associations between NO2 exposure during pregnancy and SAB.(A) Single pollutant model. (B) Two-pollutants model. Q1: <33.52μg/m3; Q2: 33.52-41.46μg/m3; Q3: 41.46-49.52μg/m3; Q4: >49.52μg/m3.First quartile is the reference and models were adjusted for GA, MA, BMI, maternal parity, ART, temperature and relative humidity.