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Gestational diabetes mellitus was related to ambient air pollutant nitric oxide during early gestation

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ABSTRACT

Background: Ambient air pollution has been linked to the risk of gestational diabetes mellitus (GDM). However, evidence of this association is limited, and no study has examined the effects of nitric oxide (NO).
Objective: This study investigated the association between air pollution exposure during gestation and GDM.
Methods: The Taiwan Birth Cohort Study database was used to examine the association between the risk of GDM and all routinely monitored air pollutants among 21,248 women who were pregnant during 2004–2005. We further employed a two-pollutant model for confirming the effect of each pollutant on GDM.
Results: After the exclusion criteria were applied, 19,606 women were included in the final analysis. Among them, 378 (1.9%) had been diagnosed as having GDM. These women were older and had higher BMIs than the women without GDM. The risks of GDM onset were significantly associated with NO exposure during the first [adjusted OR (aOR): 1.05, 95% confidence interval (CI): 1.02–1.08] and second (aOR: 1.05, 95%CI: 1.02–1.08) trimesters. Under the two-pollutant model, the effect of NO exposure was also significant during the first (aOR: 1.05, 95%CI: 1.02–1.08) and second (aOR: 1.05, 95%CI: 1.02–1.09) trimesters.
Conclusion: The results indicated that exposure to higher NO levels during pregnancy increases the risk of GDM.

1. Introduction

Diabetes mellitus (DM) has become a highly prevalent disease and a major cause of death in most developed countries. The global prevalence of diabetes among adults over 18 years of age has increased from 4.7% in 1980 to 8.5% in 2014. In 2012, an estimated 1.5 million deaths were directly caused by diabetes, and another 2.2 million deaths were attributable to high blood glucose (World Health Organization, 2016). During pregnancy, women are particularly vulnerable to diabetogenesis. Women who have no previous history of DM, and are diagnosed as having diabetes during gestation are considered to have gestational diabetes mellitus (GDM). GDM has adverse effects on both mother and fetus. For mothers, increased risks of preeclampsia during pregnancy, and type 2 DM after pregnancy have been reported (Bellamy et al., 2009; Lai et al., 2016). For fetuses, risks of malformations (Fadl et al., 2010), still birth (Smith and Fretts, 2007), excessive size for gestational age (fetal macrosomia) (Group et al., 2008; Naylor et al., 1997), and growth abnormalities are increased.

Air pollution, is a ubiquitous source of exposure for the general population and is known to negatively affect health. Exposing mice to air pollution engenders systemic inflammation, oxidative stress, and insulin resistance (Lei et al., 2005; Sun et al., 2009). Humans exposed to air pollution exhibit elevated fasting glucose and HbA1c (Chuang et al., 2011; Tamayo et al., 2014), as well as increased insulin resistance (Brook et al., 2013; Kelishadi et al., 2009; Kim and Hong, 2012), and impaired glucose tolerance (IGT) (Teichert et al., 2013). In addition, living near major roads is associated with a higher prevalence of type 2 DM. (Kramer et al., 2010; Puett et al., 2011).

Although pregnant women may be more susceptible to potential air pollution effects on diabetes onset, the association between air pollution and GDM remains controversial. A prospective cohort study conducted in the Netherlands, detected no association between air pollution and GDM (van den Hooven et al., 2009). However, other studies have indicated that exposure to $PM_{2.5}$ during pregnancy was associated with IGT, but not GDM (Fleisch et al., 2014). Moreover, exposure to NOx and SO_2 have been associated with increased risk of GDM

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(Malmqvist et al., 2013; Robledo et al., 2015). Critical periods of exposure have not been clearly documented.

The present study investigated the association between exposure to air pollution during different periods of gestation and the risk of GDM. To assess this relationship, a nation-wide representative survey in women giving birth in 2005 was combined with air-monitoring data from the Taiwan Environmental Protection Administration (EPA).

2. Materials and methods

2.1. Study population and sampling

The Taiwan Birth Cohort Study was conducted in 2005 and involved sampling from the Birth Registration Database in Taiwan. In 2005, 206,741 live births occurred. A two-stage systematic random sampling design was employed to obtain representative samples. First, 359 townships in Taiwan were ranked into 12 strata, according to their urbanization level (four strata: county, town, city, and area) and total fertility rate (three strata: high, medium, and low). Subsequently, 85 of the 359 townships were designated as the primary sampling units (PSUs), and final samples were randomly sampled by probability proportional to size. A total of 24,200 birth samples were obtained from the 85 PSUs (sampling rate = 12%). The studies were approved by the Institutional Review Board of the Bureau of Health Promotion, Taiwan.

2.2. Questionnaire

A structured questionnaire was implemented by 89 well-trained interviewers when infants were six months of age. Maternal demographics were obtained, namely, medical history, weight and height before pregnancy, maximum weight gain, residential township, parity, and gestational age. The following question was used to determine the prevalence of GDM among the pregnant women: “Have you been diagnosed as having gestational diabetes by your obstetrician during this pregnancy?” In Taiwan, the National Health Insurance (NHI) coverage rate was approximately 98% in 2005. Maternal health screening, including routine urinary analyses, was provided at no cost to all insured pregnant women at approximately the 17th gestational week and beyond. A total of ten times of screening tests were provided. Among all pregnant women with health insurance coverage, 98.3% had at least one screening test by an obstetrician. GDM was diagnosed according to the American Diabetes Association criteria; pregnant women were classified as having GDM if they had two of the following abnormal values on the OGTT: blood glucose > 95 mg/dL at baseline, > 180 mg/dL at 1 h, > 155 mg/dL at 2 h, or > 140 mg/dL at 3 h (American Diabetes, 2008).

2.3. Exposure assessment

Air pollution data were collected from 77 fixed-site air monitoring stations in Taiwan during 2004–2006. We excluded four industrial stations, four stations located on outlying islands, and three stations not enabled until 2005. The remaining 66 stations were located on main island of Taiwan and nearby participant's resident townships (Huang et al., 2015). At each station, automatic hourly monitoring of the following pollutants occurred: PM_{10} (particles with a diameter of 10 μm or less, $\mu g/m^3$) through the β-ray attenuation method; carbon monoxide (CO, parts per million, ppm) through nondispersive infrared; NO, NO_2, and NOx through chemiluminescence; SO_2 through ultraviolet fluorescence; and O_3 through ultraviolet absorption (ppb [parts per billion]). The daily average for each pollutant was calculated on the basis of at least 18 hourly measurements; fewer data points than 18 hourly measurements would result in a missing value for that day. The missing data for any specific air pollutant were estimated by multiplying the daily ratio (average daily concentration at a station compared with that of the other stations during 2004–2006) by the average concentration of the other stations on that day.

The calculated monthly average of each pollutant was used for further spatial interpolation. Spatial interpolation and cross-validation have been previously detailed (Huang et al., 2015). Briefly, we used ArcGIS Desktop v.10 (ESRI Inc., Redlands, CA, U.S.A.) with ordinary kriging to interpolate exposure concentration to a regular grid (250 × 250 m) across Taiwan. Then, we performed cross-validation by removing one of the 66 stations and using remaining 65 stations to predict the exposure level at the removed station, and compared the measured to the predicted values. The mean prediction errors and standardized prediction errors were approximated to zero. The root mean squares standardized were ranged from 0.93 to 0.98 with SDs between 0.03 and 0.05. Finally, we geocoded every participant's home address to the township level and linked to the exposure concentration as their personal exposure. Exposure periods were defined as (1) first trimester (from last menstrual period to 12th week of gestational age, whereas the last menstrual period was estimated by subtracting the participants' gestational age from infant's birth date), (2) second trimester (13th–26th week of gestational age), and (3) third trimester (from 27th week of gestational age to birth date).

2.4. Covariates

Maternal characteristics such as age, body mass index (BMI), weight gain during pregnancy, socioeconomic status (SES), tobacco, alcohol and betel use, parity, and fetal gender were used as covariates. Maternal BMI before pregnancy was categorized into four groups, < 18.5, 18.5–24, 24–27, and ≥ 27. Annual household income (U.S. dollar) as SES was partitioned into ≤ 20000, 20000–40000, > 40000. Parity was divided into 0, 1, and ≥ 2, whereas use of tobacco, alcohol, and betel during pregnancy were categorized into two groups (yes and no).

2.5. Statistical analysis

The demographics and potential covariates were compared between women with gestational diabetes and those without by using the chi-squared test (for categorical variables) and *t*-test (for continuous variables). We performed separate logistic regressions for each pollutant during each exposure period (first trimester, second trimester, or third trimester). For air pollutants significantly associated with GDM, other pollutants were added one at a time to form a two-pollutant model, thus excluding the effects of the second pollutant. All models were adjusted for potential confounders, namely, maternal age, BMI, weight gain during pregnancy, parity, annual household income, and fetal gender. Furthermore, sensitivity analyses were done, stratified by maternal age, BMI, parity, fetal gender and season of conception. Maternal age was categorized into < 30 and ≥ 30; season of conception categorized as spring (March-May), summer (June-August), autumn (September-November) and winter (December-February). Odds ratios (ORs) and 95% confidence Intervals (95% CIs) were estimated for each 10 $\mu g/m^3$ increment in PM_{10}, 0.1 ppm in CO, and 1 ppb in NO, NO_2, NOx, SO_2, and O_3. All analyses were performed using SAS (version 9.3; SAS Institute Inc., Cary, NC).

3. Results

Among the 24,200 sampled participants, 21,248 (87.8%) completed the first interview when their babies were 6 months old. Reasons for exclusion from the study included incorrect address (n = 358), refusal to interview (n = 1734), moving abroad (n = 351), repeated absence from home following multiple visits (n = 104), death of the infant (n = 67), and other factors (n = 338). We further excluded participants according to the following criteria: missing data for maternal age, tobacco use, betel use, alcohol use, gestational age and gestational diabetes (n = 81), multiple births (n = 558), preexistent diabetes (n = 87), missing data for maternal weight, height and weight gained during