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Maternal exposure to air pollutants during the first trimester and foetal growth in Japanese term infants☆

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A B S T R A C T

Evidence supporting an inverse association between maternal exposure to air pollutants and foetal growth has been accumulating. However, the findings from Asian populations are limited, and the question of critical windows of exposure remains unanswered. We examined whether maternal exposure to air pollutants, in particular exposure during the first trimester (an important period of placental development), was associated with foetal growth in Japanese term infants. From the Japan Perinatal Registry Network database, we received birth data for 29,177 term singleton births in western Japan (Kyushu-Okinawa Districts) between 2005 and 2010. Exposure was expressed in terms of average concentrations of air pollutants (ozone, suspended particulate matter, nitrogen dioxide, and sulphur dioxide), as measured at the nearest monitoring stations to the respective delivery hospitals of the pregnant women, during the entire pregnancy and each trimester. As proxy markers of foetal growth restriction, we used small for gestational age (SGA), and adverse birth weight (low birth weight in addition to SGA). For pollutant exposure during the entire pregnancy, we did not observe the association with SGA and adverse birth weight. In the single-trimester model for the first trimester, however, we found a positive association between ozone exposure, and SGA (odds ratio [OR] per 10 ppb increase = 1.07, 95% confidence interval [CI] = 1.01–1.12) and adverse birth weight (OR = 1.07; 95% CI = 1.01–1.14). This association persisted in the multi-trimester model, and no association for exposure during the second or third trimester was observed. Exposure to other pollutants during each trimester was not associated with these outcomes. In conclusion, maternal exposure to ozone during the first trimester was independently associated with an elevated risk of poor foetal growth.

1. Introduction

After Williams et al. reported that air pollution in the Los Angeles Basin was associated with a reduction in birth weight (Williams et al., 1977), evidence supporting an inverse association between maternal exposure to air pollutants and foetal growth has been accumulating (Li et al., 2017; Stieb et al., 2012; Sun et al., 2016). Pollutant exposure over the entire pregnancy might be a risk factor for foetal growth restriction (FGR), which is associated not only with near-term health issues such as neonatal mortality, but also long-term health issues such as lifestyle-related diseases in adults (Chernausek, 2012). However, past studies were mainly performed in the Western countries. There is limited related evidence regarding Asian populations, as compared to the evidence for Western populations (Li et al., 2017; Stieb et al., 2012; Sun et al., 2016). Given the geographical variation in the association between air pollution and foetal growth (Hao et al., 2016), and the influence of race and ethnicity on this association (Darrow et al., 2011), data from Asian populations is desirable for discussions of

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epidemiological causal inference.

Although past studies revealed the effects of pollutant exposure during the pregnancy on foetal growth (Li et al., 2017; Stieb et al., 2012; Sun et al., 2016), we had a question which gestational windows are important to poor foetal growth related to pollutant exposure in utero. Recent meta-analyses suggested that pooled-effect estimate of fine particulate matter ($PM_{2.5}$) during the third trimester appeared higher than that during the first and second trimester (Li et al., 2017; Sun et al., 2016). However, there was a lack of statistical evidence beyond the approach of meta-analysis. Therefore, the investigative research into the critical windows of exposure to air pollutants remained incomplete. To further understanding of foetal growth in association with pollutant exposure during the pregnancy, we paid particular attention to exposure to air pollutants during the first trimester. The first trimester is a crucial period in placental development (James et al., 2012). Inadequate placental development and consequent placental dysfunction are associated with FGR (Burton et al., 2009). Placental development is disturbed by certain factors, such as inflammation (Saito and Nakashima, 2014), suggesting that systemic inflammation due to maternal exposure to air pollutants (Lee et al., 2011; van den Hooven et al., 2012) has potential to influence foetal growth, through interference with placental development. Therefore, we hypothesised that the first trimester is the key period in terms of the association between air pollution and foetal growth.

The aim of this study was to examine whether maternal exposure to air pollutants, in particular the first trimester exposure, was associated with foetal growth in the Japanese population.

2. Materials and methods

2.1. Study population

The study protocol was approved by the Institutional Review Board of Kyushu University, Japan, and the Japan National Institute for Environmental Studies. Data on a total of 47,835 singleton births in 28 hospitals of western Japan (Kyushu-Okinawa District), including 8 prefectures (Fukuoka, Saga, Nagasaki, Kumamoto, Oita, Miyazaki, Kagoshima, and Okinawa), between 2005 and 2010, were obtained from the Japan Perinatal Registry Network database, after receiving permission from the Japan Society of Obstetrics and Gynaecology. This database included all the live births and stillbirths after 22 weeks of gestation at cooperating hospitals (mainly university hospitals and local general hospitals). Details of the database have been published elsewhere (Matsuda et al., 2011). From this database, we obtained information on maternal age, height, and weight, parity, gestational age (basically determined by ultrasound findings during early pregnancy), smoking and alcohol consumption during pregnancy, medical history, diagnoses of obstetric complications, and neonatal records, such as birth weight and sex.

Out of the 47,835 singleton births, we excluded 6906 because the prefecture of the mother's residence differed from that of the delivery hospital; 9498 because of gestational age (<37 weeks or > 41 weeks); and 47 because of weight (<1000 g or > 5000 g); as well as 95 still births, 325 births with missing information on all pollutant exposure data, and 54 births with missing data for maternal age, parity, or infant sex; leaving a total of 30,910 births. We also excluded 1733 births before which the mothers had experienced hypertensive disorders in pregnancy, including chronic hypertension, gestational hypertension, and/or pre-eclampsia (Brown et al., 2001), because we disregarded the effect of air pollution on foetal growth via hypertensive disorders that had been linked to ozone exposure in this population (Michikawa et al., 2015). Fig. 1 outlines the narrowing process for births targeted for analysis in the present study. In the end, we analysed data for 29,177 singleton births at term (37–41 weeks of gestation).

2.2. Environmental data

The Japan Perinatal Registry Network database is composed of anonymous information, and thus did not, in this case, include residential addresses information, such as postal codes, for the pregnant women. In our previous study (Michikawa et al., 2017), we validated the assumption that the pregnant women resided near their delivery hospitals. Therefore, we linked individual birth data and background pollutant concentrations measured at the closest monitoring stations to the respective delivery hospitals of the pregnant women. The specific locations of the monitoring stations and hospitals may be found elsewhere (Michikawa et al., 2015). Each monitoring station and the respective hospital were located within the same administrative area, and the median linear distance between them was 1.8 km (1.1 miles), except in the case of one hospital in Okinawa prefecture (13.6 km (8.5 miles)). We obtained background pollutant concentrations, including daily mean concentrations of suspended particulate matter [SPM], nitrogen dioxide [NO_2], sulphur dioxide [SO_2], and the maximum 8-h mean concentrations of ozone, from the Japan National Institute for Environmental Studies' atmospheric environment database. SPM is a marker of particulate matter in Japan, and is defined as airborne particles with a 100% cut-off level of 10 μm in aerodynamic diameter under the Japan Air Quality Standards (Japan Ministry of the Environment, 2009). When we apply the definition of $PM_{2.5}$ (particles with a 50% cut-off level of 2.5 μm in aerodynamic diameter), SPM is roughly presented as PM_7. In Japan, ozone has traditionally been measured in terms of photochemical oxidants, including ozone and other secondary oxidants generated by photochemical reactions (Japan Ministry of the Environment, 2009); however, as the concentrations of photochemical oxidants are known to nearly equal those of ozone, this study treated photochemical oxidants as ozone.

In the present study, we defined exposure to air pollutants during the entire pregnancy as the average of pollutant concentrations from 0 to 36 weeks of gestation. We also estimated the exposure during the first trimester (0–13 weeks of gestation), the second trimester (14–27 weeks of gestation), and the third trimester (28–36 weeks of gestation) (Japan Society of Obstetrics and Gynaecology, 2014).

2.3. Definition of outcomes

In earlier studies, low birth weight (LBW, birth weight < 2500 g) at term, and small for gestational age (SGA, birth weight < 10 percentile for gestational age), were used as proxy markers of FGR. However, due to differences in genetic background, birth weight is typically lower in Asian than in European infants (Janssen et al., 2007). In Japan, the range of appropriate birth weight includes LBW, even for term pregnancies (Itabashi et al., 2014). In this study, therefore, we used SGA defined as birth weight below the 10th percentile according to gestational age, infant sex, and parity (primiparous, multiparous), based on the Japanese neonatal anthropometric chart (Itabashi et al., 2014). In addition, with the intention to exclude naturally small infants included in SGA classification, we defined adverse birth weight (LBW in addition to SGA) as an additional outcome.

2.4. Statistical methods

We performed multilevel logistic regression with hospital-level random effects, using the melogit command in Stata13 for