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

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ABSTRACT

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

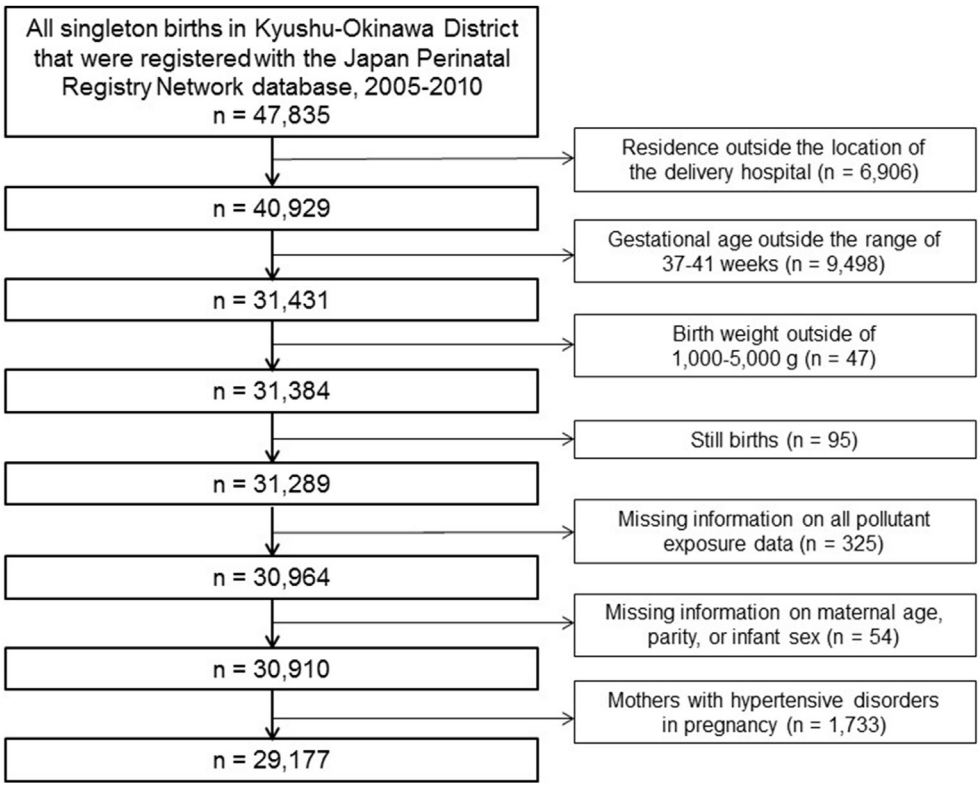

Fig. 1. The narrowing process for births targeted for analysis.

Windows (Stata Corporation, College Station, TX, USA). The strength of the association between exposure to air pollutants and foetal growth was presented as an odds ratio (OR) per 10 units increase in the concentrations of each pollutant, with a 95% confidence interval (CI). With regard to the association with adverse birth weight, we treated normal birth weight (no LBW and no SGA) as the reference. The ORs were estimated after adjustment for maternal age at delivery (<25, 25–29, 30–34, ≥35 years), birth year (2005, 2006, 2007, 2008, 2009, 2010), season of conception (spring, summer, autumn, winter), and the known factors associated with birth weight, including smoking during pregnancy (no, yes, missing) (Suzuki et al., 2016), alcohol consumption during pregnancy (no, yes, missing) (Patra et al., 2011), and prepregnancy body mass index (<18.5, 18.5–24.9, ≥25.0 kg/m^2, missing) (Yu et al., 2013). We did not include gestational age, infant sex, or parity in the models, because our outcomes captured these factors in the SGA definition. When we analysed for trimester-specific exposure, we included exposure during the three trimesters simultaneously (multi-trimester model).

To confirm the robustness of our findings, several sensitivity analyses were performed. Firstly, we additionally adjusted for exposure to another pollutant (two-pollutant model). Secondly, we additionally adjusted for ambient temperature, because birth weight was potentially affected by temperature (Lawlor et al., 2005). The ambient temperature data were obtained from the Japan Meteorological Agency. Thirdly, births in Okinawa prefecture were excluded, due to the geographical difference and exposure misclassification resulting from the great distance between the respective hospital and its monitoring station. Fourthly, gestational weight gain was included in the model, because an association between gestational weight gain and birth weight was indicated (Viswanathan et al., 2008). Finally, to avoid residual confounding, we repeated the analysis for the respective subgroups of non-smokers, non-drinkers, and mothers with a BMI range of 18.5–24.9 kg/m^2. We also performed a subgroup analysis after excluding mothers who suffered from chronic diseases, including heart disease, respiratory disease, diabetes and gestational diabetes (Yessoufou and Moutairou, 2011), thyroid disease (Krassas et al., 2010), and autoimmune disease (Baer et al., 2011), each of which may have an impact on birth weight. In addition, we explored whether the association between pollutant exposure and birth weight varied according to maternal age (<35, ≥35 years), parity (primiparous, multiparous), or infant sex (boy, girl). Statistical effect modification by these factors was tested using a likelihood ratio test.

3. Results

Among 29,177 term singleton births (14,937 boys and 14,240 girls), the percentage of SGA and adverse birth weight was 11.6% and 8.0%, respectively. The mean mother's age at delivery was 30.9 years old (standard deviation [SD] = 5.5), and 46.6% of the mothers were primiparous. Other characteristics of this population are presented in Supplementary Table 1.

Table 1 shows descriptive statistics for the average pollutant concentrations over each trimester and the entire pregnancy. The mean exposures during the first trimester were 41.2 (SD = 9.6) ppb for ozone, 27.5 (7.9) μg/m^3 for SPM, 12.0 (6.1) ppb for NO_2, and 3.2 (1.5) ppb for SO_2. Ozone exposure during the first trimester had a −0.10 Pearson's correlation coefficient with exposure during the second trimester, −0.15 with exposure during the third trimester, and 0.49 with exposure during the entire pregnancy. In the case of the other pollutants, we observed moderate to strong correlations between exposure during the first trimester, and exposure during

Table 1
Average concentration of various air pollutants according to pregnancy period, and Pearson's correlations among exposures to pollutants within the different pregnancy periods.

Pollutant	n	Mean (SD)	Percentile			Pearson's correlation			
			25	50	75	First trimester (0–13 weeks)	Second trimester (14–27 weeks)	Third trimester (28–36 weeks)	Entire pregnancy (0–36 weeks)
Ozone (ppb)						Ozone			
First trimester (0–13 weeks)	26,577	41.2 (9.6)	34.5	40.0	47.8	1			
Second trimester (14–27 weeks)	26,577	41.3 (9.4)	34.7	40.1	48.0	−0.10	1		
Third trimester (28–36 weeks)	26,577	41.1 (10.7)	33.5	39.7	48.2	−0.15	0.03	1	
Entire pregnancy (0–36 weeks)	26,577	41.3 (5.4)	37.6	40.9	45.1	0.49	0.66	0.42	1
SPM ($\mu g/m^3$)						SPM			
First trimester (0–13 weeks)	29,158	27.5 (7.9)	22.0	27.7	32.9	1			
Second trimester (14–27 weeks)	29,158	27.3 (7.8)	21.8	27.4	32.5	0.74	1		
Third trimester (28–36 weeks)	29,158	27.2 (8.2)	21.1	27.2	32.4	0.61	0.77	1	
Entire pregnancy (0–36 weeks)	29,158	27.4 (7.1)	22.2	27.8	31.9	0.88	0.94	0.85	1
NO_2 (ppb)						NO2			
First trimester (0–13 weeks)	26,722	12.0 (6.1)	7.6	12.0	16.7	1			
Second trimester (14–27 weeks)	26,722	11.8 (6.1)	7.3	11.7	16.5	0.81	1		
Third trimester (28–36 weeks)	26,722	11.6 (6.2)	6.9	11.6	16.3	0.66	0.85	1	
Entire pregnancy (0–36 weeks)	26,722	11.8 (5.7)	8.2	11.7	16.4	0.90	0.97	0.88	1
SO_2 (ppb)						SO2			
First trimester (0–13 weeks)	28,792	3.2 (1.5)	2.1	3.1	4.2	1			
Second trimester (14–27 weeks)	28,792	3.2 (1.5)	2.0	3.0	4.1	0.79	1		
Third trimester (28–36 weeks)	28,792	3.1 (1.5)	2.0	2.9	4.0	0.66	0.83	1	
Entire pregnancy (0–36 weeks)	28,792	3.2 (1.4)	2.1	3.1	4.1	0.90	0.96	0.88	1

NO_2: nitrogen dioxide, SD: standard deviation, SO_2: sulphur dioxide, SPM: suspended particulate matter.

either of the other two trimesters and during the entire pregnancy. For each trimester and the entire pregnancy, correlations among pollutants were not strong, except for the correlation between SPM and NO_2 during the entire pregnancy (coefficient = 0.68) (Supplementary Table 2).

For pollutant exposure during the entire pregnancy, we did not observe the association with SGA and adverse birth weight (Table 2). However, exposure to ozone during the first trimester was associated with SGA (covariates adjusted OR per 10 ppb increase = 1.07, 95% CI = 1.01–1.12) and adverse birth weight (OR = 1.07, 95% CI = 1.01–1.14). Even after mutual adjustment for ozone exposure during the other two trimesters, the OR estimate showed little change (multi-trimester adjusted OR = 1.07, 95% CI = 1.01–1.13 for SGA; OR = 1.07, 95% CI = 1.00–1.14 for adverse birth weight). There was no association between proxy markers of FGR and pollutant exposures during either of the other two trimesters (Supplementary Table 3). For example, the multi-trimester adjusted ORs of SGA for ozone exposure were 1.00 (95% CI = 0.95–1.06) in the second trimester and 0.99 (0.95–1.04) in the third trimester.

We performed several sensitivity analyses for the association of exposure to ozone during the first trimester with SGA and adverse birth weight, and observed that the OR estimate did not change substantially (range from 1.05 to 1.08) (Table 3). With regard to the stratified analyses by maternal age at delivery, parity, and infant sex, there was no evidence for effect modification.

4. Discussion

In the present study, we examined whether maternal exposure to ozone, SPM, NO_2, and SO_2 was associated with proxy markers of FGR, including SGA and adverse birth weight (LBS in addition to SGA), in Japanese population. There was no association between exposure during the entire trimester, and SGA and adverse birth weight. For the trimester-specific analysis, however, an association of maternal exposure to ozone during the first trimester with outcomes was observed.

By assessing pollutant effects on three trimesters simultaneously, we found that only pollutant exposure during the first trimester was associated with foetal growth. Since the average concentrations of air pollutants are highly correlated within the different pregnancy periods, it is not easy to extract the exposure effects on foetal growth with respect to each trimester. In this study, however, ozone exposure during the first trimester was not correlated with that during the second or third trimester. Hence, we could confirm that an independent association between ozone exposure during the first trimester and proxy markers of FGR. As we estimated exposure on the basis of the mothers' delivery hospitals, and did not consider residential mobility during pregnancy, the exposure estimates for the first trimester might be misclassified more than those for the third trimester. Although this misclassification would weaken the strength of the association between pollutant exposure and outcome, only ozone exposure during the first trimester was associated with adverse birth weight. Additionally, all the subgroup and sensitivity analyses provided consistent results suggesting the positive association observed.

An association between maternal exposure to ozone during the first trimester and poor foetal growth has been reported in earlier studies. One California study, from 1996 to 2006, concluded that ozone exposure was inversely associated with birth weight at term (Morello-Frosch et al., 2010); and another, from 2001 to 2008, estimated that the OR of term LBW per interquartile range increase (= 10.8 ppb) in ozone concentrations was 1.009 (95% CI = 1.001–1.018) (Laurent et al., 2016). A Texas study from 1998 to 2004 suggested that increases in ozone concentration were related to decreases in term birth weight (Geer et al., 2012). A study conducted in Detroit from 1990 to 2001 found elevated odds for term SGA in the high ozone season (OR = 1.13 for highest *vs.* lowest quartile of ozone concentrations, 95% CI = 1.01–1.27) (Le et al., 2012). In addition, an association of ozone exposure with SGA and term LBW was observed in Ontario, Canada between 2005 and 2012 (Lavigne et al., 2016). Although these studies also reported an association with ozone exposure during other trimesters, a multi-trimester model was not constructed. In Asia, however, a study based on Seoul birth certificates from the Korean National Birth Register, from 1996 to 1997, showed no association between ozone

Table 2
Association of exposure to air pollutants during the entire pregnancy and the first trimester with foetal growth in western Japan, 2005–2010.

	SGA		Adverse birth weight (LBW in addition to SGA)[a]	
	OR[b]	95% CI	OR[b]	95% CI
Ozone (ppb), n = 26,577				
Number of outcomes	n = 3074		n = 2114	
Exposure during the entire pregnancy (0–36 weeks of gestation)				
Model 1[c]	1.06	(0.96–1.16)	1.06	(0.94–1.19)
Exposure during the first trimester (0–13 weeks of gestation)				
Model 1[c]	1.07	(1.01–1.12)	1.07	(1.01–1.14)
Model 2[d]	1.07	(1.01–1.13)	1.07	(1.00–1.14)
SPM (μg/m^3), n = 29,158				
Number of outcomes	n = 3384		n = 2327	
Exposure during the entire pregnancy (0–36 weeks of gestation)				
Model 1[c]	0.98	(0.89–1.07)	0.93	(0.83–1.05)
Exposure during the first trimester (0–13 weeks of gestation)				
Model 1[c]	1.00	(0.93–1.07)	0.98	(0.89–1.07)
Model 2[d]	1.01	(0.92–1.10)	0.99	(0.89–1.11)
NO_2 (ppb), n = 26,722				
Number of outcomes	n = 3116		n = 2145	
Exposure during the entire pregnancy (0–36 weeks of gestation)				
Model 1[c]	1.09	(0.94–1.27)	1.11	(0.90–1.37)
Exposure during the first trimester (0–13 weeks of gestation)				
Model 1[c]	1.05	(0.92–1.19)	1.06	(0.89–1.26)
Model 2[d]	1.00	(0.85–1.18)	1.02	(0.83–1.25)
SO_2 (ppb), n = 28,792				
Number of outcomes	n = 3362		n = 2299	
Exposure during the entire pregnancy (0–36 weeks of gestation)				
Model 1[c]	0.94	(0.63–1.42)	0.73	(0.44–1.22)
Exposure during the first trimester (0–13 weeks of gestation)				
Model 1[c]	1.02	(0.71–1.45)	0.83	(0.54–1.27)
Model 2[d]	1.05	(0.67–1.65)	0.89	(0.52–1.53)

CI: confidence interval, LBW: low birth weight, NO_2: nitrogen dioxide, OR: odds ratio, SGA: small for gestational age, SO_2: sulphur dioxide, SPM: suspended particulate matter.

[a] Using normal birth weight (no LBW and no SGA) as the reference.

[b] OR per 10 units increase.

[c] Model 1 included maternal age at delivery (<25, 25–29, 30–34, ≥35 years), birth year (2005, 2006, 2007, 2008, 2009, 2010), season of conception (spring, summer, autumn, winter), smoking during pregnancy (no, yes, missing), alcohol consumption during pregnancy (no, yes, missing), and prepregnancy body mass index (<18.5, 18.5–24.9, ≥25.0 kg/m^2, missing).

[d] In addition to Model 1, Model 2 simultaneously included exposure during the second and third trimester.

exposure during the first trimester and LBW (Ha et al., 2001). This inconsistency may be partly explained by the area ozone concentrations, as those observed in the Korean study were lower than those observed, for example, in the present study.

Although some studies have suggested that ozone exposure during the second and/or third trimester, rather than the first trimester, was associated with a proxy marker of FGR (Laurent et al., 2013; Salam et al., 2005; Vinikoor-Imler et al., 2014). Also, there was a possibility of our observation for ozone exposure during the first trimester being a chance finding due to the multiple comparisons performed in the study. However, we believe that our principal conclusion, that the first trimester is the important period of exposure, is reasonable from the viewpoint of the putative mechanisms linking ozone exposure and FGR. The occurrence of FGR is related to placental malperfusion resulting from deficient conversion of the spiral arteries (Burton et al., 2009). Spiral artery remodelling during the first trimester seems to be inhibited by inflammation. Cotechini et al. created an inflammation-induced FGR model that used lipopolysaccharide-treated pregnant rats, and observed impaired spiral artery remodelling in the model of inflammation-induced FGR (Cotechini et al., 2014). An association between elevated levels of C-reactive protein (CRP), as a biomarker of systemic inflammation, during the first trimester and delivery of infants with FGR, has been observed in humans (Tjoa et al., 2003). In pregnant women, ozone exposure in early pregnancy has been linked with elevated levels of CRP (Lee et al., 2011). A positive association between ozone exposure and CRP levels has also been reported in the Japanese general population, though this population did not include pregnant women (Michikawa et al., 2016). Overall, the results suggest that ozone exposure during the first trimester has the potential to interrupt normal placental development via inflammation and oxidative stress linked to inflammation, and lead to the occurrence of FGR. In this study, we excluded infants born from mothers with hypertensive disorders in pregnancy, which was previously associated with exposure to ozone during the first trimester (Michikawa et al., 2015), because FGR occurs in relation to hypertensive disorders. Our findings were in accordance with the theory that FGR and hypertensive disorders share a common aetiology (Burton et al., 2009).

Maternal exposures to SPM, NO_2, and SO_2 were not associated with adverse birth weight. Since exposure to particulate matter, in particular, has been associated with elevated CRP levels in early pregnancy (Lee et al., 2011; van den Hooven et al., 2012), an association between particulate matter exposure and adverse birth weight has been generally presumed. Multi-country studies including Asian countries (Dadvand et al., 2013; Fleischer et al., 2014), and studies in Korea and Taiwan (Seo et al., 2010; Yang et al., 2003), have found an association of particulate matter exposure with LBW and reduced birth weight. Also, recent meta-analyses included the studies in the Western countries suggested the association between $PM_{2.5}$ exposure during the pregnancy and LBW (Li et al., 2017; Sun et al., 2016). However, this association is known to show geographical variation (Hao et al., 2016) depending on different regional factors, such as the sources and elemental constituents of the particulate matter (Laurent et al., 2016; Pedersen et al., 2016; Sun et al., 2016). In the present study, we could not investigate the association with $PM_{2.5}$ that there were growing concern about adverse health effects, because $PM_{2.5}$ measurement expanded throughout Japan after 2009. The studies assessing exposure to $PM_{2.5}$ would be necessary in Japan. Although a systematic review in China reported SO_2 exposure was associated with lower birth weight (Jacobs et al., 2017), SO_2 concentrations in China were quite higher than those in our study.

There were some studies on air pollution and markers of foetal growth in Japan. A nationwide Japanese survey of infants born in 2001 found an association between SPM, NO_2, and SO_2 exposures during pregnancy (particularly in the first trimester) and LBW at term (Yorifuji et al., 2015). As that study was conducted in 2001, the concentrations of SPM, NO_2, and SO_2 tended to be higher than in the present study. On the other hand, there was no association in the case of ozone concentrations that were lower than those in the present study. Among other Japanese studies, one ecological study, from 1973 to 1977, reported that regional concentrations of NO_2 and SO_2 were correlated with LBW rates (Sakai, 1984); while another, using the perinatal database of one hospital from 1997 to 2008, showed that NO_2 exposure (estimated by land-use regression) was not associated with LBW at term or SGA (Kashima et al., 2011). The association between maternal exposure to air pollutants and foetal growth may be affected by changes in the distribution of pollutant concentrations over time. Therefore, the results of the present study were in broad agreement with those of past Japanese studies.

We note some limitations to our study. First, the strength of the association between ozone exposure and adverse birth weight may have been underestimated. One reason for such underestimation could be exposure misclassification, resulting from exposure

Table 3
Sensitivity and subgroup analyses for the association between ozone exposure during the first trimester (0–13 weeks of gestation) and foetal growth.

	n	SGA			Adverse birth weight (LBW in addition to SGA)[a]		
		OR[b]	95% CI	p for effect modification[c]	OR[b]	95% CI	p for effect modification[c]
Main results (Model 1 in Table 2)	26,577	1.07	(1.01–1.12)		1.07	(1.01–1.14)	
Two-pollutant model							
Additionally adjusted for SPM during the first trimester	26,577	1.07	(1.01–1.12)		1.07	(1.01–1.14)	
Additionally adjusted for NO_2 during the first trimester	24,451	1.06	(1.01–1.12)		1.06	(1.00–1.13)	
Additionally adjusted for SO_2 during the first trimester	26,336	1.07	(1.01–1.13)		1.07	(1.00–1.14)	
Temperature							
Additionally adjusted for temperature during the first trimester	26,577	1.07	(1.01–1.12)		1.07	(1.01–1.14)	
Additionally adjusted for temperature during the entire pregnancy	26,577	1.08	(1.02–1.14)		1.07	(1.01–1.15)	
Prefecture							
Excluding Okinawa area	24,064	1.06	(1.00–1.12)		1.07	(0.99–1.14)	
Gestational weight gain							
Additionally adjusted for gestational weight gain	21,730	1.08	(1.02–1.15)		1.08	(1.01–1.16)	
Smoking							
Restricting to non-smokers during pregnancy	17,552	1.06	(1.00–1.13)		1.06	(0.98–1.14)	
Alcohol consumption							
Restricting to non-drinkers during pregnancy	18,194	1.06	(1.00–1.13)		1.05	(0.98–1.13)	
Prepregnancy BMI							
Restricting to mothers with a BMI range of 18.5–24.9 kg/m^2	16,112	1.06	(0.99–1.14)		1.06	(0.97–1.15)	
History of chronic diseases[d]							
Excluding to mothers with chronic diseases	22,836	1.06	(1.00–1.12)		1.07	(1.00–1.14)	
Maternal age at delivery							
< 35 years	19,387	1.06	(0.99–1.12)	0.95	1.07	(1.00–1.15)	0.77
≥ 35 years	7190	1.11	(1.00–1.23)		1.08	(0.95–1.22)	
Parity							
Primiparous	12,447	1.03	(0.95–1.11)	0.21	1.04	(0.95–1.14)	0.31
Multiparous	14,130	1.10	(1.03–1.18)		1.10	(1.01–1.20)	
Infant sex							
Boys	13,605	1.06	(0.99–1.14)	0.74	1.05	(0.96–1.15)	0.63
Girls	12,972	1.08	(1.00–1.16)		1.09	(1.00–1.19)	

BMI: body mass index, CI: confidence interval, LBW: low birth weight, NO_2: nitrogen dioxide, OR: odds ratio, SGA: small for gestational age, SO_2: sulphur dioxide, SPM: suspended particulate matter.

[a] Using normal birth weight (no LBW and no SGA) as the reference.

[b] OR per 10 ppb increase was adjusted for birth year (2005, 2006, 2007, 2008, 2009, 2010), season of conception (spring, summer, autumn, winter), maternal age at delivery (<25, 25–29, 30–34, ≥35 years), smoking during pregnancy (no, yes, missing), alcohol consumption during pregnancy (no, yes, missing), and prepregnancy body mass index (<18.5, 18.5–24.9, ≥25.0 kg/m^2, missing).

[c] The difference in the effect estimates was tested by a likelihood ratio test.

[d] Including heart disease, respiratory disease, diabetes/gestational diabetes, thyroid disease, and autoimmune disease.

assignments being based on the measured concentrations of air pollutants at the monitoring stations nearest to the respective hospitals of the pregnant women. Also, since this study used a historical approach, we did not have information on residential mobility during pregnancy and maternal time-activity pattern, which might lead to exposure misclassification. Another reason could be the use of ultrasound-based gestational age. We would estimate the reported gestational age to be less than the real gestational age in infants with FGR (Slama et al., 2008), if exposure to air pollutants has an adverse effect on early foetal growth. Some infants with FGR, exposed to high pollutant concentrations, might not be categorised as showing SGA, resulting in underestimation of the association. Nevertheless, we detected a risk of adverse birth weight related to ozone exposure during the first trimester. Another limitation is that there was a likelihood of residual confounding, e.g., noise exposure (Gehring et al., 2014). Finally, it may be difficult to generalise the results of the study given the characteristics of the cooperative hospitals (mainly university hospitals and local general hospitals).

In conclusion, after adjustment for ozone exposures during the second and third trimester, maternal exposure to ozone during the first trimester was independently associated with an elevated risk of poor foetal growth in Japanese term infants.

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Conflicts of interest

The authors declare that they have no actual or potential competing financial interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.envpol.2017.06.069.

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