Trimester-specific association of maternal exposure to fine particulate matter and its components with birth and placental weight in Japan

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Conflict of interest

The authors declare no conflict of interest.

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Ethical Approval of Studies

The study protocol was approved by the Ethics Committee of the Faculty of Medicine, Toho University (A20024_A18049).

Running Head Title

Fine particulate matter and birth/placental weight

Abstract

Objective: We investigated which trimester of exposure to $PM_{2.5}$ and its components was associated with birth and placental weight, and the fetoplacental weight ratio.

Methods: The study included 63,990 women who delivered singleton term births within 23 Tokyo wards between 2013 and 2015. Each day, we collected fine particles on a filter, and analyzed their chemical constituents, including carbons and ions. Trimester-specific exposure to each pollutant was estimated based on the average daily concentrations.

Results: Over the third trimester, sulphate exposure tended to be inversely associated with birth weight, and decreased placental weight (difference for highest *vs.* lowest quintile groups = -6.7g, 95% confidence interval = -12.5 to -0.9). For fetoplacental weight ratio, there was no relationship.

Conclusions: Sulphate exposure over the third trimester may reduce birth weight, particularly placental weight.

Keywords

Fine particulate matter

Chemical components

Birth weight

Placental weight

Third trimester

INTRODUCTION

Though many studies have reported an association between exposure to fine particulate matter during pregnancy and birth weight as an important marker of foetal growth,[1-3] there is, at present, insufficient evidence to determine whether specific components of $PM_{2.5}$ are associated with birth weight.[4-6] In addition, different studies have indicated different exposure windows (e.g., first, second, or third trimester, or entire gestation period) as sensitive periods for birth weight,[7-9] and the findings for specific windows of birth-weight sensitivity to $PM_{2.5}$ exposure are inconsistent. Elucidation of the specific components and sensitive exposure windows which have adverse effects on birth weight may contribute to the elucidation of the mechanisms involved in the foetal toxicity of $PM_{2.5}$ exposure.

The placenta is an organ with a role in all maternal-foetal oxygen and nutrient exchange,[10,11] and placental weight is used as a marker of placental function and an important determinant of birth weight.[12] There have been relatively few studies of air pollution and placental weight.[13-17] One study in Japan reported the residential proximity to major roads, as a surrogate index of air pollutant exposure, was associated with a decrease in placental weight.[13] Other studies reported an inverse relationship between exposure to particulate matter during gestation and placental weight.[14,15] Further, there is evidence that $PM_{2.5}$ exposure leads to placental inflammation and oxidative stress.[18,19] The above

evidence suggests that exposure to $PM_{2.5}$ in the pregnancy affects birth weight via disturbance of the placental oxygen and nutrient transport function. To the authors' knowledge, no studies have investigated the association between specific $PM_{2.5}$ components and placental weight, or the exposure-sensitivity windows for placental weight.

The present study, then, investigated the association between exposure to total $PM_{2.5}$ and its chemical components during gestation, with birth and placental weight, and the fetoplacental weight ratio (the ratio of birth weight divided by placental weight). In our investigation of sensitive windows for exposure to $PM_{2.5}$, for birth and placental weight, we focused on trimester-specific exposure.

METHODS

The study protocol was approved by the Ethics Committee of the Faculty of Medicine, Toho University (A20024_A18049).

Measurement of $PM_{2.5}$ and its chemical components

Details of our study area and measurement of $PM_{2.5}$ are available elsewhere.[20,21] In brief, the study area (Fig. S1) was comprised of 23 Tokyo wards on the east side of Tokyo, which have a total area of roughly 627 km^2. We measured the $PM_{2.5}$ chemical component

levels between April 2013 and December 2015, at the Tokyo Metropolitan Research Institute for Environmental Protection, in the study area in southeast Tokyo (35.7°N, 139.8°E). The institute's location is considered suitable for measuring the typical ambient air pollutant concentrations in the 23 wards. Using an FRM-2000 sampler (Rupprecht & Patashnick, Albany, NY, USA), fine particles were collected daily (from 10:00 a.m. to 9:00 a.m. of the next day) on a quartz-fiber filter (47 mm diameter; 2500 QAT-UP, Pall Life Sciences, Port Washington, NY, USA), following the Federal Reference Methods of the US Environmental Protection Agency.[22] A dual optical carbon analyzer (OCEC Carbon Aerosol Analyzer, Sunset Laboratory Inc., Tigard, OR, USA) was used to measure organic carbon (OC) and elemental carbon (EC); and an ion chromatograph (Dionex ICS-5000, Thermo Fisher Scientific Inc., Waltham, MA, USA) was used to measure the ions, including nitrate, sulphate, ammonium, chloride, sodium, potassium, and calcium. In the chemical analysis, we followed the standardized protocol of the Japanese Ministry of the Environment.[23]

The daily mean concentrations of total $PM_{2.5}$, and the maximum 8-h mean concentrations of ozone, measured at an urban background monitoring station (Harumi monitoring station (Fig. S1), 35.4°N, 139.5°E, approximately 5 km west of the Tokyo Metropolitan Research Institute for Environmental Protection) were collected from the Japan National Institute for Environmental Studies' atmospheric environment database.

The $PM_{2.5}$ concentrations were measured using the β-ray absorption method, and the ozone concentrations were measured using the ultraviolet absorption method. Our previous study confirmed that the urban background concentrations of $PM_{2.5}$ and ozone were spatially homogeneous within the 23 Tokyo wards.[24] The daily mean ambient temperatures were obtained from the database of the Japan Meteorological Agency.

Study participants

The Japan Society of Obstetrics and Gynecology provided the data on all the live births and stillbirths after 22 weeks of gestation, at 39 cooperating hospitals within the 23 Tokyo wards, between January 2013 and December 2015. The data was extracted from the Japan Perinatal Registry Network database, details of which are available elsewhere.[25] The database included roughly two-fifths of the total births in the 23 wards during the study period. The attending physicians inputted the data using a standardized electronic form, and the Perinatal Committee monitored the data quality. In the data, there was anonymised information on maternal age, height, weight, parity, gestational age, smoking habits and alcohol drinking, infertility treatment, medical history, diagnosis of obstetric complications (such as hypertensive disorders of pregnancy and gestational diabetes), mode of delivery, neonatal records, and the hospital at which the woman delivered. The data did not include information on the residential addresses of the participants.

Of all births registered (n = 89,417), which included multiple births, we first limited to 85,513 singleton births (85,513 women). In addition, in Japan, some women return to their hometown in the late pregnancy, and deliver at a hospital near their parents' home (a custom known as *satogaeri* in Japanese). Therefore, as such women may not have resided in the study area during pregnancy, we also excluded 1,677 women, to avoid misclassification of exposure. The further narrowing of participants is presented in Fig. 1. In the end, 63,990 women who delivered term singleton births (37-41 weeks of gestation) were included in our analysis. As the $PM_{2.5}$ component measurements only began on 1 April, 2013 (three months after the beginning of the study), the $PM_{2.5}$ component analysis only included the 48,417 women whose first trimester fell within this later period.

Exposure assessment

From the viewpoint of data availability, we assumed that the concentrations of $PM_{2.5}$ and ozone were homogeneous within the 23 Tokyo wards, and assessed only temporal variability in the pollutant concentrations. On the basis of the birth date and gestational age calculated by ultrasound results in the early pregnancy, we estimated exposure to each pollutant by averaging the daily concentrations of that pollutant over the first trimester (0-13 weeks of gestation), second trimester (14-27 weeks), third trimester (28-36 weeks), and entire gestation period (0-36 weeks).

Birth and placental weight data

The birth weight (g) was measured, and the placental weight (g), recorded immediately following the birth, included the membrane and umbilical cord (after manual removal of any blood clots by the midwife). The fetoplacental weight ratio, as a surrogate parameter for placental efficiency,[26] was calculated by dividing the birth weight by the placental weight.[11]

Statistical methods

We used Stata 16 for Windows (Stata Corporation, College Station, TX, USA) for all analyses. The participants were categorized into five groups, based on the respective quintiles of pollutant concentrations. For the association between maternal exposure to pollutants and the outcomes (birth weight, placental weight, and fetoplacental weight ratio), we considered the participants to be nested within hospitals, and applied a multilevel linear regression model with the hospital as a random effect. The difference and 95% confidence intervals (CIs) of the outcomes were estimated for each pollutant, with the lowest-concentration group as the reference. As potential confounding factors, we adjusted for maternal age at delivery (< 25, 25-34, ≥ 35 years), gestational weeks, infant sex, parity (nulliparous, multiparous), and season of conception (spring, summer, autumn,

winter). As in our previous studies, we estimated the difference per interquartile range increase (IQR) in the pollutant concentrations. In determining which trimester was the sensitive period for the outcomes, we constructed not only single-trimester models that included each trimester-specific exposure, but also multi-trimester models that simultaneously included exposure over the first, second, and third trimesters.

When we found an association between maternal exposure to a pollutant and the outcomes in both the single-trimester and multi-trimester models, we determined whether the observed association was affected by the factors associated with birth weight; that is, we adjusted, in the multi-trimester models, for smoking habits,[27] alcohol drinking (yes, no, missing),[28] pre-pregnancy body mass index (< 18.5, 18.5-24.9, ≥ 25 kg/m^2, missing),[29] gestational weight gain (GWG: poor, normal, excessive gain, missing),[30] exposure to total $PM_{2.5}$,[31] and ambient temperature.[5,32] Hypertensive disorder of pregnancy[33,34] and diabetes/gestational diabetes[35] are related to both $PM_{2.5}$ exposure and birth weight. As these obstetric complications might be intermediate factors for the association between pollutant exposure and outcomes, we performed the sensitivity analysis after excluding women with these complications. Finally, given the assumption of spatial homogeneity in the $PM_{2.5}$ concentrations, we performed a further sensitivity analysis, restricting to women who delivered at hospitals within 10 km of the monitoring sites.

RESULT

Table 1 presents the background information of the 63,990 women. The mean maternal age was 33.8 years, and the proportion of ≥ 35 years accounted for 46.7%. The mean birth weight was 3,033.5 g (standard deviation (SD) = 373.4), the mean placental weight was 570.0 g (SD = 103.3), and the mean fetoplacental weight ratio was 5.422 (SD = 0.771). Table S1 shows the distribution of characteristics among the five groups, according to the average $PM_{2.5}$ concentrations over the entire gestation period.

Table 2 presents the aggregated results of the environmental factors. The average exposure to total $PM_{2.5}$ over the entire gestation period was 16.9 (SD = 1.4) $\mu g/m^3$. The correlation coefficient among pollutant exposures during the entire gestation period is shown in Table S2.

Table S3 presents the association of exposure to total $PM_{2.5}$ and its components over the entire gestation period, with birth weight, placental weight, and fetoplacental weight ratio. We observed no association between such exposure and the outcomes.

Table 3 and Table S4 show the trimester-specific association between exposure to total $PM_{2.5}$ and its components, and birth weight. Total $PM_{2.5}$ and sulphate over the third trimester tended to be inversely associated with birth weight in the single-trimester model. When we compared with the lowest group of total $PM_{2.5}$ and sulphate exposure over the

third trimester in the multi-trimester model, the adjusted differences in the fourth group were -14.4 g for total $PM_{2.5}$ (95% CI = -24.4 to -4.4, p for IQR increase = 0.38, p for inter-quintiles pattern = 0.08) and -19.0 g for sulphate (95% CI = -34.2 to -3.8, p for IQR increase = 0.08, p for inter-quintiles pattern = 0.03).

Table 4 and Table S5 show the trimester-specific association between exposure to total $PM_{2.5}$ and its components, and placental weight. We observed that exposure to sulphate over the third trimester was inversely associated with placental weight. In the multi-trimester model, exposure to sulphate was related to a -6.7 g decrease in placental weight (for highest *vs.* lowest group: 95% CI = -12.5 to -0.9, p for IQR increase = 0.07, p for inter-quintiles pattern = 0.01). We also found an inverse association between exposure to ammonium over the third trimester and placental weight.

Tables S6 and S7 show the trimester-specific association between exposure to total $PM_{2.5}$ and its components, and the fetoplacental weight ratio. Although the association with sulphate over the third trimester was somewhat positive, pollutant exposures were not associated with the fetoplacental weight ratio.

We then aimed at exposure to sulphate over the third trimester, and performed a sensitivity analysis of the association between sulphate exposure and the outcomes (Fig. S2). Overall, the inverse association persisted. For example, after further adjustment for smoking, alcohol drinking, pre-pregnancy body mass index, GWG, total $PM_{2.5}$, and

temperature, the respective adjusted differences per IQR increase in sulphate exposure were -18.6 g for birth weight (95% CI = -32.0 to -5.3) and -4.8 g for placental weight (95% CI = -8.8 to -0.8).

DISCUSSION

The present study investigated the effect of gestation-period exposure to $PM_{2.5}$ and its chemical components, on birth weight, placental weight, and the fetoplacental weight ratio, in Tokyo. Over the entire gestation period, exposure to $PM_{2.5}$ and its components was not associated with any outcome. However, in the third trimester, there was a weak inverse relationship between exposure to total $PM_{2.5}$ and sulphate, and birth weight; and sulphate exposure was associated with a decline in placental weight.

Although past studies presented that maternal exposure to total $PM_{2.5}$ was inversely associated with birth weight,[1-3,7,36,37] there was not sufficient evidence to clarify whether specific exposure windows were responsible for the adverse effects. A review article reported that exposure in the first trimester was marginally associated, and exposure in the second and third trimester was significantly associated, with lower birth weight.[38] In the present study, a suggestive inverse association was observed for exposure to total $PM_{2.5}$ over the third trimester, and only then. Some studies have noted that the third trimester

was a sensitive period in this respect. An analysis based on 572,272 births in Massachusetts in 2000-2008 demonstrated that exposure to total $PM_{2.5}$ over the third trimester (mean = 9.6 $\mu g/m^3$) was associated with a -9.2 g reduction in birth weight (per 10 $\mu g/m^3$ increase; 95% CI = -15.0 to -3.3).[36] A natural experimental study (83,672 births) in Beijing during the 2008 Beijing Olympics, when air pollutant concentrations declined, showed an inverse association between total $PM_{2.5}$ over the 8^{th} gestational month and birth weight (adjusted difference per IQR (19.8) $\mu g/m^3$ increase = -18 g, 95% CI = -32 to -3).[39] Although we could not here confirm whether birth weight is vulnerable to $PM_{2.5}$ exposure during specific time windows, we hope in time to identify these periods, in order to understand the pathways underlying the association between exposure to $PM_{2.5}$ and birth weight. If the mid- or late-gestational periods are determined to be the relevant periods for birth weight as a marker of fetal growth, we may seek to prevent adverse fetal health via risk communication regarding $PM_{2.5}$ exposure.[40]

A novel aspect of this study was the observation of an inverse association between sulphate exposure, as a $PM_{2.5}$ component, over the third trimester, and placental weight as well as birth weight. Compared with the lowest quintile exposure group, placental weight decreased 6.7 g (95% CI = -12.5 to -0.9), roughly 1% of the average placental weight, in the highest group. Although this difference was less than the placental weight difference related to maternal smoking (for example, -18.2 g for the smoker *vs.* the non-smoker group

[95% CI = -16.6 to -19.7]),[41] and the clinical implications of the disparity were unclear, we observed a clear difference. Sulphate, one of the major components of $PM_{2.5}$, mainly arises from sulphur dioxide, due to a chemical reaction caused by sunlight.[42] Few epidemiological studies have found an association between sulphate exposure and birth outcome. One such study, based on 3,673,224 live singleton births in California between 2000 and 2006, demonstrated that sulphate exposure over the entire gestation period (mean = 2.6 $\mu g/m^3$) was associated with decreased birth weight (difference per 1.9 $\mu g/m^3$ increase = -22.0 g, 95% CI = -25.0 to -18.0).[43] Another study, based on 406,627 full-term births in Atlanta from 1994 through 2004, found an inverse association between sulphate exposure over the third trimester (mean = 4.9 $\mu g/m^3$) and birth weight (difference per 2.9 $\mu g/m^3$ increase = -8.5 g, 95% CI = -19.1 to 2.0).[7] To the authors' knowledge, no studies have found an inverse association between sulphate exposure, particularly exposure over the third trimester, and placental weight. Exposure to sulphate was, however, associated with an increase in serum concentrations of vascular cell adhesion molecule-1,[44] interleukin-6,[45] and tumor necrosis factor-alpha,[46] which are inflammatory markers. These markers seem likely to be related to maternal exposure to second-hand smoke,[47,48] which is a causal factor for low birth weight.[48] Therefore, it seems likely that the inflammation induced by sulphate exposure affects not only birth weight but also placental weight, which is strongly related to birth weight. We know that the villous of the placenta actively

arborizes during the third trimester.[10] Sulphate exposure over the third trimester leads to chorioamnionitis via stimulation of inflammation, and may lead to placental insufficiency. The association between ammonium and placental weight seems likely to reflect sulphate toxicity, because sulphate and ammonium combine to form ammonium salt.[42]

The fetoplacental weight ratio is known as a marker of placental efficiency, with a low ratio seemed to be the result of hypertrophy in placenta under the compensatory response to hypoxia[49] or under-nutrition.[50] In this study, we did not show the association of sulphate exposure over the third trimester with this ratio. Therefore, further investigations are needed with respect to our hypothesis that pollutant exposure affects birth weight via functional disturbance of the placenta.

The present study had a number of limitations. First, given its assumption of spatial homogeneity in the $PM_{2.5}$ concentrations, some measure of exposure misclassification could not be avoided. Although we confirmed that this assumption was not violated in the case of the total $PM_{2.5}$ concentrations,[24] the case of $PM_{2.5}$ components was unclear. However, the aforementioned California study between 2000 and 2006 (n = 3,673,224 live singleton births), investigating the relationship of $PM_{2.5}$ components with birth weight, demonstrated that the results of a 10-km buffer were similar to those of a 20-km buffer.[43] In the present study, the 23 Tokyo wards all fell within a roughly 20-km radius of their center (Fig. S1). One study in the U.S. reported that sulphate was relatively spatially

homogeneous.[51] In addition, in the present study's sensitivity analysis restricted to participants who delivered at hospitals within 10 km of the measurement sites, the inverse association of sulphate exposure over the third trimester with birth and placental weight was basically unchanged.

Second, there may have been a measure of exposure misclassification due to deviation in the gestational age, because ultrasound measurements were used for estimation of this factor. If $PM_{2.5}$ exposure affects early foetal growth, gestational age based on ultrasound measurements would be underestimated. However, given that we estimated trimester-specific exposure (3-month average of pollutant concentrations), the influence of underestimation of gestational age, on the 3-month average of pollutant concentrations, was likely to be small.

Third, we could not avoid some misclassification of placental weight, because the measurement procedure regarding placental weight was not standardized nationwide, and thus was likely to differ among the studied hospitals. Finally, the results of this study might chance findings caused by the large number of analyses.

Despite the above limitations, we found evidence of a trimester-specific association of exposure to $PM_{2.5}$ components with birth weight, and this is the first study, as far as we know, to find adverse effects of sulphate in $PM_{2.5}$ on placental weight. Among the study's strengths, fine particles were collected according to the Federal Reference Methods, and

the Perinatal Registry database included all term births in the cooperating hospitals. In addition, we adjusted for several potential confounding factors, and observed a robust association for sulphate exposure. Finally, as we restricted our study area to 23 Tokyo wards, the potential confounding of regional-level variables was unlikely.

CONCLUSION

In this Japanese study, sulphate exposure over the third trimester was weakly associated with birth-weight reduction, and associated with a decline in placental weight. The study, which focused on specific components of $PM_{2.5}$ and specific exposure windows, provided further evidence regarding the adverse birth effects of $PM_{2.5}$ exposure.

REFERENCES

1. Hyder A, Lee HJ, Ebisu K, Koutrakis P, Belanger K, Bell ML. $PM_{2.5}$ exposure and birth outcomes: use of satellite- and monitor-based data. Epidemiology. 2014;25:58-67.

2. Stieb DM, Chen L, Beckerman BS, Jerrett M, Crouse DL, Omariba DW, et al. Associations of Pregnancy Outcomes and $PM_{2.5}$ in a National Canadian Study. Environ Health Perspect. 2016;124:243-9.

3. Erickson AC, Ostry A, Chan LH, Arbour L. The reduction of birth weight by fine particulate matter and its modification by maternal and neighbourhood-level factors: a multilevel analysis in British Columbia, Canada. Environ Health. 2016;15:51.

4. Ebisu K, Bell ML. Airborne $PM_{2.5}$ chemical components and low birth weight in the northeastern and mid-Atlantic regions of the United States. Environ Health Perspect. 2012;120:1746-52.

5. Ha S, Zhu Y, Liu D, Sherman S, Mendola P. Ambient temperature and air quality in relation to small for gestational age and term low birthweight. Environ Res. 2017;155:394-400.

6. Qiao P, Zhao Y, Cai J, van Donkelaar A, Martin R, Ying H, et al. Twin growth discordance in association with maternal exposure to fine particulate matter and its chemical constituents during late pregnancy. Environ Int. 2019;133:105148.

7. Darrow LA, Klein M, Strickland MJ, Mulholland JA, Tolbert PE. Ambient air pollution

and birth weight in full-term infants in Atlanta, 1994-2004. Environ Health Perspect. 2011;119:731-7.

8. Ha S, Hu H, Roussos-Ross D, Haidong K, Roth J, Xu X. The effects of air pollution on adverse birth outcomes. Environ Res. 2014;134:198-204.
9. Laurent O, Hu J, Li L, Cockburn M, Escobedo L, Kleeman MJ, et al. Sources and contents of air pollution affecting term low birth weight in Los Angeles County, California, 2001-2008. Environ Res. 2014;134:488-95.
10. Salafia CM, Charles AK, Maas EM. Placenta and fetal growth restriction. Clin Obstet Gynecol. 2006;49:236-56.
11. Matsuda Y, Itoh T, Okada E, Sasaki K, Itoh H, Kanayama N. Difference in Z scores of placental weight and fetal/placental weight ratio by mode of delivery. J Obstet Gynaecol Res. 2019;45:2377-85.
12. Hjortebjerg D, Andersen AM, Ketzel M, Pedersen M, Raaschou-Nielsen O, Sorensen M. Associations between maternal exposure to air pollution and traffic noise and newborn's size at birth: A cohort study. Environ Int. 2016;95:1-7.
13. Yorifuji T, Naruse H, Kashima S, Murakoshi T, Tsuda T, Doi H, et al. Residential proximity to major roads and placenta/birth weight ratio. Sci Total Environ. 2012;414:98-102.
14. Rahmalia A, Giorgis-Allemand L, Lepeule J, Philippat C, Galineau J, Hulin A, et al.

Pregnancy exposure to atmospheric pollutants and placental weight: an approach relying on a dispersion model. Environ Int. 2012;48:47-55.

15. van den Hooven EH, Pierik FH, de Kluizenaar Y, Hofman A, van Ratingen SW, Zandveld PY, et al. Air pollution exposure and markers of placental growth and function: the generation R study. Environ Health Perspect. 2012;120:1753-9.

16. Ghasemi-Tehrani H, Fallah S, Mozafarian N, Miranzadeh S, Sadeghi S, Azidhak A. Effect of Exposure to Air Pollution on Placental Weight in Isfahan-Iran. J Family Reprod Health. 2017;11:90-96.

17. Giovannini N, Schwartz L, Cipriani S, Parazzini F, Baini I, Signorelli V, et al. Particulate matter (PM10) exposure, birth and fetal-placental weight and umbilical arterial pH: results from a prospective study. J Matern Fetal Neonatal Med. 2018;31:651-655.

18. Nachman RM, Mao G, Zhang X, Hong X, Chen Z, Soria CS, et al. Intrauterine Inflammation and Maternal Exposure to Ambient $PM_{2.5}$ during Preconception and Specific Periods of Pregnancy: The Boston Birth Cohort. Environ Health Perspect. 2016;124:1608-15.

19. Saenen ND, Vrijens K, Janssen BG, Madhloum N, Peusens M, Gyselaers W, et al. Placental Nitrosative Stress and Exposure to Ambient Air Pollution During Gestation: A Population Study. Am J Epidemiol. 2016;18:442-9.

20. Saito S, Hoshi J, Ikemori F, Osada K. Comparison ofwater-soluble organic carbon in

$PM_{2.5}$ obtained by filter analysis and continuous dichotomous aerosol chemical speciation analyzer. J Jpn Soc Atmos Environ. 2020;55:150–8 (In Japanese with English abstract).

21. Michikawa T, Morokuma S, Yamazaki S, Takami A, Sugata S, Yoshino A, et al. Exposure to chemical components of fine particulate matter and ozone, and placenta-mediated pregnancy complications in Tokyo: a register-based study. J Expo Sci Environ Epidemiol. 2021. https://doi.org/10.1038/s41370-021-00299-4.
22. United States Environmental Protection Agency. Integrated science assessment for particulate matter. https://www.epa.gov/isa/integrated-science-assessment-isa-particulate-matter. Accessed 19 March 2021.
23. Ministry of the Environment, Japan. Measurement manual of fine particulate matter in ambient atmosphere. http://www.env.go.jp/air/osen/pm/ca/manual.html. Accessed 19 March 2021.
24. Michikawa T, Yamazaki S, Ueda K, Yoshino A, Sugata S, Saito S, et al. Effects of exposure to chemical components of fine particulate matter on mortality in Tokyo: A case-crossover study. Sci Total Environ. 2021;755:142489.
25. Matsuda Y, Hayashi K, Shiozaki A, Kawamichi Y, Satoh S, Saito S. Comparison of risk factors for placental abruption and placenta previa: case-cohort study. J Obstet Gynaecol Res. 2011;37:538-46.
26. Hayward CE, Lean S, Sibley CP, Jones RL, Wareing M, Greenwood SL, et al. Placental Adaptation: What Can We Learn from Birthweight:Placental Weight Ratio? Front

Physiol. 2016;7:28.

27. Steyn K, de Wet T, Saloojee Y, Nel H, Yach D. The influence of maternal cigarette smoking, snuff use and passive smoking on pregnancy outcomes: the Birth To Ten Study. Paediatr Perinat Epidemiol. 2006;20:90-9.

28. Larroque B, Kaminski M, Lelong N, Subtil D, Dehaene P. Effects of birth weight of alcohol and caffeine consumption during pregnancy. Am J Epidemiol. 1993;137:941-50.

29. Zhao R, Xu L, Wu ML, Huang SH, Cao XJ. Maternal pre-pregnancy body mass index, gestational weight gain influence birth weight. Women Birth. 2018;31:e20-e5.

30. Rasmussen K, Yaktine AL (eds). Weight Gain During Pregnancy: Reexamining the Guidelines. National Academies Press. Institute of Medicine; National Research Council. Washington, DC. 2009.

31. Mostofsky E, Schwartz J, Coull BA, Koutrakis P, Wellenius GA, Suh HH, et al. Modeling the association between particle constituents of air pollution and health outcomes. Am J Epidemiol. 2012;176:317-26.

32. Zhang Y, Yu C, Wang L. Temperature exposure during pregnancy and birth outcomes: An updated systematic review of epidemiological evidence. Environ Pollut. 2017;225:700-12.

33. Pedersen M, Stayner L, Slama R, Sorensen M, Figueras F, Nieuwenhuijsen MJ, et al. Ambient air pollution and pregnancy-induced hypertensive disorders: a systematic review

and meta-analysis. Hypertension. 2014;64:494-500.

34. Ibrahimou B, Salihu HM, Aliyu MH, Anozie C. Risk of preeclampsia from exposure to particulate matter $PM_{2.5}$ speciation chemicals during pregnancy. J Occup Environ Med. 2014;56:1228-34.

35. Robledo CA, Mendola P, Yeung E, Mannisto T, Sundaram R, Liu D, et al. Preconception and early pregnancy air pollution exposures and risk of gestational diabetes mellitus. Environ Res. 2015;137:316-22.

36. Kloog I, Melly SJ, Ridgway WL, Coull BA, Schwartz J. Using new satellite based exposure methods to study the association between pregnancy $PM_{2.5}$ exposure, premature birth and birth weight in Massachusetts. Environ Health. 2012;11:40.

37. Gehring U, Tamburic L, Sbihi H, Davies HW, Brauer M. Impact of noise and air pollution on pregnancy outcomes. Epidemiology. 2014;25:351-8.

38. Sun X, Luo X, Zhao C, Zhang B, Tao J, Yang Z, et al. The associations between birth weight and exposure to fine particulate matter ($PM_{2.5}$) and its chemical constituents during pregnancy: A meta-analysis. Environ Pollut. 2016;211:38-47.

39. Rich DQ, Liu K, Zhang J, Thurston SW, Stevens TP, Pan Y, et al. Differences in Birth Weight Associated with the 2008 Beijing Olympics Air Pollution Reduction: Results from a Natural Experiment. Environ Health Perspect. 2015;123:880-7.

40. Rajagopalan S, Brauer M, Bhatnagar A, Bhatt DL, Brook JR, Huang W, et al.

Personal-Level Protective Actions Against Particulate Matter Air Pollution Exposure: A Scientific Statement From the American Heart Association. Circulation. 2020;142:e411-e31.

41. Larsen S, Haavaldsen C, Bjelland EK, Dypvik J, Jukic AM, Eskild A. Placental weight and birthweight: the relations with number of daily cigarettes and smoking cessation in pregnancy. A population study. Int J Epidemiol. 2018;47:1141-50.
42. Sagai M. Toxic Components of $PM_{2.5}$ and Their Toxicity Mechanisms-On the Toxicity of Sulfate and Carbon Components. Nihon Eiseigaku Zasshi. 2019;74:1-11 (In Japanese with English abstract).
43. Basu R, Harris M, Sie L, Malig B, Broadwin R, Green R. Effects of fine particulate matter and its constituents on low birth weight among full-term infants in California. Environ Res. 2014;128:42-51.
44. Bind MA, Lepeule J, Zanobetti A, Gasparrini A, Baccarelli A, Coull BA, et al. Air pollution and gene-specific methylation in the Normative Aging Study: association, effect modification, and mediation analysis. Epigenetics. 2014;9:448-58.
45. Bind MA, Baccarelli A, Zanobetti A, Tarantini L, Suh H, Vokonas P, et al. Air pollution and markers of coagulation, inflammation, and endothelial function: associations and epigene-environment interactions in an elderly cohort. Epidemiology. 2012;23:332-40.
46. Zhang Q, Niu Y, Xia Y, Lei X, Wang W, Huo J, et al. The acute effects of fine

particulate matter constituents on circulating inflammatory biomarkers in healthy adults. Sci Total Environ. 2020;707:135989.

47. Salmasi G, Grady R, Jones J, McDonald SD, Knowledge Synthesis G. Environmental tobacco smoke exposure and perinatal outcomes: a systematic review and meta-analyses. Acta Obstet Gynecol Scand. 2010;89:423-41.

48. Niu Z, Xie C, Wen X, Tian F, Yuan S, Jia D, et al. Potential pathways by which maternal second-hand smoke exposure during pregnancy causes full-term low birth weight. Sci Rep. 2016;6:24987.

49. Macdonald EM, Natale R, Regnault TR, Koval JJ, Campbell MK. Obstetric conditions and the placental weight ratio. Placenta. 2014;35:582-6.

50. Lumey LH. Compensatory placental growth after restricted maternal nutrition in early pregnancy. Placenta. 1998;19:105-11

51. Bell ML, Ebisu K, Peng RD. Community-level spatial heterogeneity of chemical constituent levels of fine particulates and implications for epidemiological research. J Expo Sci Environ Epidemiol. 2011;21:372-384.

Figure legend

Fig. 1

The narrowing process for births targeted for analysis.

List of Supplemental Digital Content

Table S1

Characteristics of the 63,990 studied women, based on the quintiles of $PM_{2.5}$ concentrations over the entire gestation period, in 23 Tokyo wards, between 2013 and 2015.

Table S2

Pearson's correlation coefficients among pollutant exposures over the entire gestation period.

Table S3

Association of exposure to total $PM_{2.5}$ and its components with birth weight, placental weight, and the fetoplacental weight ratio, over the entire gestation period.

Table S4

Trimester-specific association between exposure to $PM_{2.5}$ components and birth weight.

Table S5

Trimester-specific association between exposure to $PM_{2.5}$ components and placental weight.

Table S6

Trimester-specific association between exposure to total $PM_{2.5}$ and its components, and the fetoplacental weight ratio, in the single-trimester model.

Table S7

Trimester-specific association between exposure to total $PM_{2.5}$ and its components, and the fetoplacental weight ratio, in the multi-trimester model.

Fig. S1

Locations of monitoring stations and hospitals.

Fig. S2

Sensitivity analysis of the association between exposure to sulphate over the third trimester and the outcomes.

Figure

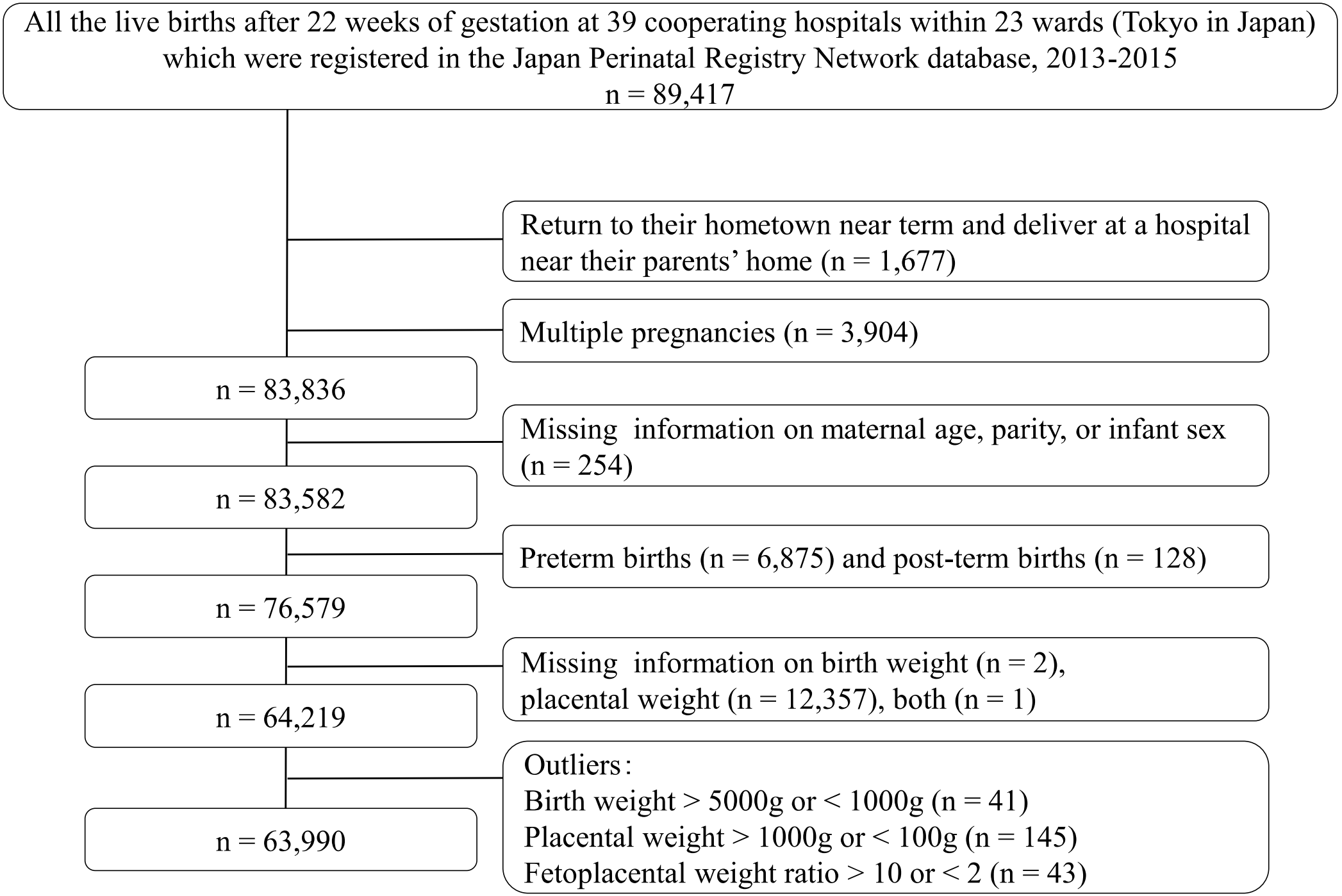

Figure 1

Table

Table 1. Characteristics of the 63,990 studied women; distribution of birth weight and placental weight.

	Number of women n (%)	Birth weight (g) mean (SD)	Placental weight (g) mean (SD)
Total	63990	3033.5 (373.4)	570.0 (103.3)
Maternal age			
< 25	2248 (3.5)	3022.9 (372.6)	577.1 (102.2)
25-34	31880 (49.8)	3029.9 (370.0)	568.6 (101.5)
≥ 35	29862 (46.7)	3038.0 (377.1)	570.9 (105.3)
Parity			
Nulliparous	38850 (60.7)	3021.5 (374.1)	565.8 (101.9)
Multiparous	25140 (39.3)	3051.9 (371.7)	576.4 (105.1)
Smoking status			
Yes	54405 (85.0)	3032.2 (372.8)	569.2 (103.4)
No	1917 (3.0)	3023.2 (370.1)	559.6 (103.9)
Missing	7668 (12.0)	3051.5 (376.7)	577.3 (101.7)
Alcohol drinking habits			
Yes	47209 (73.8)	3025.4 (373.1)	566.8 (103.2)
No	2115 (3.3)	3023.7 (371.7)	576.3 (106.3)
Missing	14666 (22.9)	3060.9 (373.4)	579.2 (102.5)
Pre-pregnancy body mass index (kg/m^2)			
< 18.5	7245 (11.3)	2931.1 (352.0)	542.3 (96.9)
18.5-24.9	47611 (74.4)	3044.8 (371.4)	572.9 (103.0)
≥ 25.0	4147 (6.5)	3191.4 (435.6)	625.9 (118.2)
Missing	4987 (7.8)	3038.3 (384.4)	570.5 (104.0)
Gestational week			
37	8343 (13.0)	2764.9 (340.3)	547.8 (106.7)
38	16996 (26.6)	2932.2 (336.2)	556.1 (102.6)
39	17606 (27.5)	3057.3 (339.4)	569.6 (99.8)
40	15323 (24.0)	3172.4 (347.6)	585.4 (100.3)
41	5722 (8.9)	3280.6 (356.4)	603.3 (104.3)
Infant sex			
Male	32457 (50.7)	3082.5 (372.3)	574.0 (103.5)
Female	31533 (49.3)	2983.0 (367.9)	565.9 (103.0)
Season of conception			
Spring (March–May)	15503 (24.2)	3032.8 (376.5)	570.4 (103.8)
Summer (June–August)	15496 (24.2)	3034.1 (373.7)	571.7 (103.3)
Autumn (September–November)	16578 (25.9)	3031.2 (371.5)	569.7 (103.1)
Winter (December–February)	16413 (25.7)	3035.7 (372.2)	568.2 (103.1)
Gestational weight gain[a]			
Poor gain	32808 (51.3)	2968.2 (354.7)	555.4 (99.2)
Normal gain	14309 (22.4)	3115.3 (366.2)	584.6 (103.4)
Excessive gain	11886 (18.6)	3113.1 (392.3)	592.2 (107.6)
Missing	4987 (7.7)	3038.2 (384.4)	570.5 (104.0)
Hypertensive disorders of pregnancy			
Yes	3190 (5.0)	2909.3 (410.2)	547.0 (106.2)
No	60800 (95.0)	3040.0 (370.3)	571.2 (103.0)
Diabetes/gestational diabetes			
Yes	3281 (5.1)	3050.0 (408.1)	580.6 (110.3)
No	60709 (94.9)	3032.6 (371.5)	569.4 (102.9)
Mode of delivery			
Vaginal delivery	49183 (76.9)	3052.8 (361.4)	568.2 (100.0)
Caesarean section	14807 (23.1)	2969.2 (404.4)	575.7 (113.5)

NOTE: SD, standard deviation

[a] Gestational weight gain (GWG) was defined as follows: poor gain (GWG < 5.0 kg for obesity, < 7.0 kg for overweight, < 11.5 kg for normal weight, < 12.5 kg for underweight); normal gain (5.0 ≤ GWG < 9.0 kg for obesity, 7.0 ≤ GWG < 11.5 kg for overweight, 11.5 ≤ GWG < 16.0 kg for normal weight, 12.5 ≤ GWG < 18.0 kg for underweight); and excessive gain (GWG ≥ 9.0 kg for obesity, GWG ≥ 11.5 kg for overweight, GWG ≥ 16.0 kg for normal weight, GWG ≥ 18.0 kg for underweight).

Table 2. Summary statistics of environmental factors.

		Entire gestation period						Trimester					
		Percentile						First		Second		Third	
		25th	50th	75th	IQR	mean	SD	mean	SD	mean	SD	mean	SD
Total $PM_{2.5}$	$\mu g/m^3$	16.2	16.7	17.8	1.6	16.9	1.4	16.9	2.6	16.9	2.6	16.9	3.0
$PM_{2.5}$ components[a]													
EC	$\mu g/m^3$	1.3	1.4	1.4	0.1	1.3	0.1	1.3	0.1	1.3	0.2	1.3	0.2
OC	$\mu g/m^3$	2.6	2.7	2.8	0.2	2.7	0.2	2.7	0.3	2.7	0.3	2.7	0.5
Nitrate	$\mu g/m^3$	1.1	1.5	1.7	0.6	1.4	0.3	1.4	0.8	1.5	0.8	1.4	0.9
Sulphate	$\mu g/m^3$	2.5	2.9	3.1	0.6	2.8	0.4	2.8	1.1	2.7	0.9	2.7	1.0
Ammonium	$\mu g/m^3$	1.4	1.5	1.5	0.2	1.5	0.1	1.5	0.3	1.5	0.3	1.4	0.4
Sodium	$\mu g/m^3$	0.14	0.15	0.16	0.02	0.15	0.01	0.15	0.04	0.15	0.04	0.15	0.04
Chloride	$\mu g/m^3$	0.17	0.22	0.26	0.09	0.22	0.06	0.22	0.14	0.22	0.13	0.22	0.15
Potassium	$\mu g/m^3$	0.07	0.07	0.08	0.01	0.07	0.01	0.08	0.02	0.08	0.02	0.08	0.02
Calcium	$\mu g/m^3$	0.06	0.07	0.08	0.02	0.07	0.01	0.08	0.03	0.08	0.03	0.08	0.03
O_3[b]	ppb	33.6	36.2	39.6	6.0	36.5	3.2	35.9	7.4	36.8	7.6	37.0	8.3

NOTE: EC, elemental carbon; IQR, interquartile range; OC, organic carbon; O_3, ozone; SD, standard deviation.

[a] As the $PM_{2.5}$ component measurements only began on 1 April, 2013 (three months after the beginning of the study), we only assigned these measurements to the 48,417 women whose first trimester fell within this later period.

[b] Daily maximum 8-h mean concentrations.

Table 3. Trimester-specific association between exposure to total $PM_{2.5}$ and its components, and birth weight.

Trimester	Single-trimester model						Multi-trimester model[b]		
	First		Second		Third		First	Second	Third
Category	Birth weight (g)	Adjusted difference[a] (95% CI)	Birth weight (g)	Adjusted difference[a] (95% CI)	Birth weight (g)	Adjusted difference[a] (95% CI)	Adjusted difference[a] (95% CI)	Adjusted difference[a] (95% CI)	Adjusted difference[a] (95% CI)
Total $PM_{2.5}$									
1st	3030.9	ref	3027.0	ref	3038.9	ref	ref	ref	ref
2nd	3035.8	-3.6 (-12.0, 4.9)	3035.9	-0.2 (-8.7, 8.3)	3027.4	-5.1 (-13.4, 3.3)	-3.3 (-11.8, 5.3)	2.8 (-6.1, 11.7)	-6.8 (-15.4, 1.7)
3rd	3035.6	-3.1 (-12.5, 6.4)	3032.9	-1.4 (-11.6, 8.8)	3031.8	-5.9 (-14.3, 2.6)	-2.2 (-12.0, 7.5)	3.0 (-7.7, 13.7)	-7.8 (-17.3, 1.7)
4th	3030.5	-9.3 (-19.3, 0.8)	3030.1	-4.1 (-14.3, 6.2)	3031.8	-10.3 (-19.7, -1.0)	-11.4 (-22.3, -0.6)	1.5 (-9.9, 12.9)	-14.4 (-24.4, -4.4)
5th	3034.6	-4.4 (-14.9, 6.1)	3041.3	6.6 (-4.3, 17.5)	3037.5	-3.3 (-13.0, 6.4)	-4.5 (-15.5, 6.5)	11.9 (0.3, 23.4)	-7.8 (-18.2, 2.5)
IQR		-0.6 (-5.5, 4.2)		2.5 (-2.2, 7.3)		-0.2 (-4.6, 4.2)	-0.4 (-5.6, 4.7)	5.4 (0.3, 10.5)	-2.1 (-6.8, 2.6)
EC									
1st	3023.6	ref	3020.9	ref	3033.7	ref	ref	ref	ref
2nd	3032.5	3.5 (-6.3, 13.3)	3036.1	8.8 (-1.6, 19.2)	3041.2	9.4 (-0.9, 19.6)	3.8 (-6.4, 13.9)	5.8 (-6.3, 17.8)	5.7 (-6.8, 18.1)
3rd	3040.6	5.5 (-4.2, 15.2)	3038.1	7.7 (-2.1, 17.5)	3037.6	6.0 (-4.3, 16.2)	2.5 (-8.9, 14.0)	2.3 (-13.0, 17.6)	0.0 (-13.8, 13.8)
4th	3037.8	9.3 (-0.6, 19.1)	3037.8	8.6 (-1.8, 19.0)	3034.9	5.8 (-5.1, 16.7)	7.0 (-5.7, 19.8)	5.2 (-9.8, 20.2)	2.3 (-11.7, 16.2)
5th	3039.5	7.3 (-3.4, 18.0)	3041.1	13.4 (2.3, 24.5)	3026.7	4.8 (-6.9, 16.6)	6.0 (-7.6, 19.6)	11.2 (-4.2, 26.6)	1.1 (-14.6, 16.8)
IQR		3.7 (-1.9, 9.2)		6.1 (0.5, 11.7)		0.5 (-5.2, 6.2)	1.8 (-5.9, 9.4)	6.0 (-1.9, 13.9)	-3.4 (-10.8, 4.0)
OC									
1st	3037.8	ref	3025.7	ref	3039.1	ref	ref	ref	ref
2nd	3034.3	-5.3 (-15.2, 4.6)	3034.7	-0.6 (-10.4, 9.1)	3035.3	1.4 (-8.3, 11.0)	-5.3 (-16.0, 5.3)	-0.5 (-11.5, 10.5)	2.3 (-8.7, 13.3)
3rd	3036.6	3.0 (-7.8, 13.8)	3041.1	2.1 (-8.7, 13.0)	3031.0	-7.0 (-18.7, 4.6)	4.7 (-6.9, 16.3)	3.8 (-8.9, 16.5)	-7.5 (-20.4, 5.4)
4th	3031.5	-2.4 (-13.7, 9.0)	3036.2	-0.5 (-11.7, 10.6)	3041.8	3.1 (-8.6, 14.8)	-3.5 (-15.6, 8.6)	1.7 (-10.5, 13.8)	3.6 (-9.2, 16.4)
5th	3034.0	-7.8 (-19.8, 4.2)	3036.4	0.2 (-11.4, 11.8)	3026.9	-5.5 (-17.6, 6.5)	-8.3 (-21.4, 4.8)	-0.5 (-13.1, 12.1)	-5.6 (-19.5, 8.3)
IQR		-3.4 (-9.4, 2.6)		2.0 (-3.1, 7.1)		0.0 (-5.7, 5.6)	-3.3 (-9.9, 3.3)	2.1 (-3.5, 7.7)	0.9 (-5.6, 7.5)

Nitrate									
1st	3034.9	ref	3022.2	ref	3038.8	ref	ref	ref	ref
2nd	3040.6	1.5 (-8.1, 11.0)	3043.4	9.1 (-0.9, 19.0)	3034.8	-3.2 (-16.1, 9.7)	5.3 (-6.0, 16.5)	9.1 (-3.6, 21.8)	5.3 (-11.8, 22.4)
3rd	3021.7	-7.7 (-20.7, 5.3)	3037.6	-0.2 (-13.4, 13.0)	3025.9	-6.9 (-23.3, 9.4)	3.7 (-18.7, 26.1)	1.5 (-14.1, 17.0)	7.9 (-13.4, 29.2)
4th	3035.3	-0.9 (-16.0, 14.3)	3038.9	-5.2 (-21.6, 11.3)	3038.5	-1.1 (-19.0, 16.8)	8.5 (-17.9, 34.8)	-7.2 (-25.4, 10.9)	11.0 (-16.5, 38.6)
5th	3041.7	4.8 (-11.6, 21.2)	3032.0	-14.0 (-31.6, 2.9)	3036.1	0.3 (-19.8, 20.4)	11.6 (-16.4, 39.5)	-15.0 (-33.3, 4.1)	9.3 (-21.1, 39.7)
IQR		4.6 (-6.5, 15.8)		-9.7 (-20.7, 1.4)		-0.6 (-11.4, 10.3)	16.1 (-3.6, 35.8)	-10.0 (-23.0, 2.1)	-0.3 (-16.7, 16.1)
Sulphate									
1st	3037.0	ref	3038.4	ref	3037.5	ref	ref	ref	ref
2nd	3040.2	6.5 (-4.9, 17.9)	3036.2	-5.9 (-18.6, 6.8)	3027.5	-7.7 (-17.7, 2.3)	7.0 (-5.1, 19.2)	-0.7 (-14.8, 13.4)	-6.6 (-18.5, 5.3)
3rd	3038.6	3.1 (-11.5, 17.6)	3023.0	-10.0 (-25.8, 5.4)	3038.1	-11.0 (-23.5, 0.7)	-1.6 (-17.8, 14.6)	-2.4 (-19.6, 14.7)	-15.0 (-27.6, -1.4)
4th	3022.2	-0.9 (-16.2, 14.5)	3039.4	-6.4 (-22.7, 10.0)	3031.8	-15.0 (-28.3, -2.4)	-7.6 (-25.2, 10.1)	2.4 (-15.8, 20.5)	-19.0 (-34.2, -3.8)
5th	3036.1	5.8 (-10.4, 22.0)	3037.0	-9.6 (-28.2, 8.9)	3039.3	-13.0 (-30.4, 4.2)	-0.8 (-18.8, 17.1)	-1.3 (-21.8, 19.2)	-15.0 (-34.2, 4.7)
IQR		0.4 (-8.5, 9.3)		1.1 (-10.4, 12.7)		-7.7 (-17.2, 1.8)	-3.1 (-13.0, 6.9)	7.5 (-5.2, 20.3)	-10.0 (-21.7, 1.2)
Ammonium									
1st	3039.1	ref	3036.8	ref	3038.9	ref	ref	ref	ref
2nd	3036.0	-5.8 (-15.7, 4.0)	3031.5	-2.9 (-13.1, 7.4)	3026.9	-3.1 (-13.0, 6.9)	-2.4 (-13.6, 8.9)	-6.5 (-19.2, 6.3)	-2.5 (-14.2, 9.1)
3rd	3033.3	-6.4 (-17.9, 5.0)	3044.2	11.9 (-0.2, 24.1)	3030.7	-6.6 (-16.8, 3.7)	-3.4 (-16.5, 9.8)	6.0 (-9.9, 21.9)	-7.8 (-20.8, 5.2)
4th	3034.1	-4.1 (-17.2, 8.9)	3029.9	7.7 (-5.7, 21.2)	3041.5	1.9 (-9.3, 13.1)	-4.6 (-20.1, 10.9)	4.1 (-11.6, 19.7)	-3.2 (-17.5, 11.0)
5th	3031.8	-2.2 (-16.5, 12.3)	3031.9	0.6 (-14.0, 15.2)	3036.3	-2.9 (-15.2, 9.4)	-3.8 (-21.8, 14.2)	-5.1 (-23.7, 13.6)	-7.0 (-23.0, 9.0)
IQR		4.6 (-5.2, 14.5)		-1.9 (-13.8, 10.1)		-4.4 (-15.7, 7.0)	1.5 (-10.4, 13.4)	1.7 (-11.8, 15.3)	-6.9 (-19.5, 5.7)

NOTE: CI, confidence interval; EC, elemental carbon; IQR, interquartile range; OC, organic carbon.

[a] Adjusted for maternal age, parity, gestational week, infant sex, and season of conception.

[b] We simultaneously included exposure over the first, second, and third trimesters.

Table 4. Trimester-specific association between exposure to total $PM_{2.5}$ and its components, and placental weight.

Trimester	Single-trimester model						Multi-trimester model[b]		
	First		Second		Third		First	Second	Third
Category	Placental weight (g)	Adjusted difference[a] (95% CI)	Placental weight (g)	Adjusted difference[a] (95% CI)	Placental weight (g)	Adjusted difference[a] (95% CI)	Adjusted difference[a] (95% CI)	Adjusted difference[a] (95% CI)	Adjusted difference[a] (95% CI)
Total $PM_{2.5}$									
1st	569.5	ref	569.5	ref	569.2	ref	ref	ref	ref
2nd	570.0	-0.6 (-3.1, 1.9)	570.6	-0.1 (-2.6, 2.5)	569.6	0.3 (-2.2, 2.8)	-0.6 (-3.1, 2.0)	0.4 (-2.2, 3.1)	-0.2 (-2.7, 2.4)
3rd	569.6	-0.6 (-3.5, 2.2)	568.9	0.6 (-2.5, 3.6)	570.5	0.4 (-2.2, 2.9)	-0.3 (-3.3, 2.6)	1.4 (-1.8, 4.6)	-0.6 (-3.4, 2.2)
4th	569.4	-1.8 (-4.8, 1.2)	570.1	1.3 (-1.8, 4.3)	569.2	-1.7 (-4.5, 1.1)	-2.3 (-5.6, 0.9)	2.1 (-1.4, 5.5)	-2.9 (-5.9, 0.1)
5th	571.4	-0.9 (-4.0, 2.3)	570.7	2.1 (-1.2, 5.3)	571.4	0.7 (-2.3, 3.5)	-1.1 (-4.4, 2.2)	2.8 (-0.7, 6.3)	-0.5 (-3.6, 2.6)
IQR		-0.3 (-1.7, 1.2)		1.1 (-0.3, 2.5)		0.1 (-1.2, 1.4)	-0.5 (-2.0, 1.1)	1.5 (-0.1, 3.0)	-0.3 (-1.7, 1.1)
EC									
1st	569.5	ref	565.9	ref	567.3	ref	ref	ref	ref
2nd	570.3	0.2 (-2.7, 3.2)	571.1	2.9 (-0.2, 6.0)	571.4	2.9 (-0.1, 6.0)	-0.2 (-3.2, 2.8)	3.0 (-0.6, 6.6)	2.5 (-1.2, 6.2)
3rd	571.8	0.4 (-2.5, 3.3)	571.6	2.5 (-0.4, 5.5)	570.9	2.1 (-1.0, 5.1)	-1.0 (-4.4, 2.5)	1.9 (-2.7, 6.4)	1.0 (-3.2, 5.1)
4th	571.1	1.4 (-1.6, 4.3)	572.1	2.9 (-0.2, 6.0)	571.2	2.2 (-1.1, 5.5)	-0.4 (-4.2, 3.4)	2.4 (-2.1, 6.8)	1.2 (-3.0, 5.4)
5th	570.6	0.4 (-2.7, 3.6)	572.7	3.8 (0.5, 7.1)	572.5	3.6 (0.1, 7.1)	-1.1 (-5.2, 2.9)	3.7 (-0.9, 8.3)	2.7 (-2.0, 7.4)
IQR		0.2 (-1.5, 1.8)		1.5 (-0.2, 3.1)		1.4 (-0.4, 3.1)	-1.0 (-3.3, 1.3)	1.3 (-1.0, 3.7)	0.7 (-1.5, 2.9)
OC									
1st	572.9	ref	568.5	ref	569.3	ref	ref	ref	ref
2nd	570.9	-1.8 (-4.7, 1.2)	571.6	1.1 (-1.8, 4.1)	570.3	0.5 (-2.4, 3.4)	-2.5 (-5.6, 0.7)	1.3 (-2.0, 4.6)	1.3 (-2.0, 4.5)
3rd	572.3	1.5 (-1.7, 4.7)	572.1	1.4 (-1.9, 4.6)	570.8	-0.1 (-3.6, 3.4)	1.7 (-1.7, 5.2)	2.6 (-1.2, 6.5)	0.0 (-3.9, 3.8)
4th	569.0	-1.3 (-4.7, 2.1)	570.3	0.0 (-3.3, 3.3)	572.3	1.0 (-2.5, 4.4)	-1.3 (-5.0, 2.3)	1.3 (-2.3, 5.0)	1.4 (-2.5, 5.2)
5th	568.2	-3.4 (-7.0, 0.2)	570.9	-0.2 (-3.7, 3.3)	570.7	0.4 (-3.2, 4.0)	-3.2 (-7.1, 0.8)	0.1 (-3.7, 3.9)	0.5 (-3.7, 4.7)
IQR		-1.8 (-3.6, 0.0)		0.1 (-1.4, 1.6)		0.9 (-0.8, 2.6)	-1.8 (-3.8, 0.1)	0.0 (-1.7, 1.7)	1.2 (-0.7, 3.2)

Nitrate									
1st	572.2	ref	569.0	ref	569.3	ref	ref	ref	ref
2nd	572.6	0.6 (-2.2, 3.5)	571.1	1.3 (-1.7, 4.3)	569.1	-2.1 (-6.0, 1.7)	1.1 (-2.2, 4.5)	0.4 (-3.4, 4.2)	-2.5 (-7.6, 2.6)
3rd	569.4	-0.9 (-4.8, 3.0)	570.9	-1.2 (-5.2, 2.7)	570.5	-2.0 (-6.9, 2.9)	-1.8 (-8.5, 4.9)	-2.1 (-6.7, 2.5)	-2.0 (-8.4, 4.4)
4th	569.1	-0.5 (-5.0, 4.0)	571.4	-2.3 (-7.3, 2.6)	571.7	-2.1 (-7.4, 3.3)	-1.8 (-9.7, 6.1)	-3.3 (-8.7, 2.2)	-4.1 (-12.3, 4.2)
5th	570.0	0.3 (-4.6, 5.2)	571.0	-3.6 (-8.7, 1.6)	572.7	-1.4 (-7.4, 4.7)	-2.5 (-10.8, 5.9)	-4.7 (-10.3, 0.9)	-3.6 (-12.7, 5.5)
IQR		0.5 (-2.8, 3.9)		-2.3 (-5.6, 1.1)		0.2 (-3.1, 3.4)	0.0 (-5.9, 5.9)	-3.3 (-7.0, 0.5)	0.1 (-4.8, 5.0)
Sulphate									
1st	570.0	ref	572.0	ref	573.2	ref	ref	ref	ref
2nd	572.4	2.1 (-1.4, 5.5)	571.9	0.6 (-3.2, 4.3)	568.3	-3.8 (-6.8, -0.8)	1.8 (-1.9, 5.4)	0.7 (-3.5, 5.0)	-4.6 (-8.1, -1.0)
3rd	570.2	1.0 (-3.4, 5.3)	570.2	1.6 (-3.1, 6.2)	569.6	-4.9 (-8.5, -1.3)	-0.3 (-5.1, 4.6)	3.6 (-1.5, 8.7)	-6.5 (-10.4, -2.6)
4th	567.7	-0.9 (-5.5, 3.7)	570.1	1.3 (-3.6, 6.2)	572.0	-3.3 (-7.1, 0.6)	-2.4 (-7.7, 2.9)	3.6 (-1.8, 9.1)	-5.1 (-9.7, -0.6)
5th	573.0	2.1 (-2.7, 7.0)	569.3	1.8 (-3.8, 7.3)	570.3	-5.7 (-10.8, -0.5)	0.4 (-5.0, 5.7)	3.1 (-3.1, 9.2)	-6.7 (-12.5, -0.9)
IQR		-0.1 (-2.8, 2.6)		1.5 (-1.9, 5.0)		-1.7 (-4.5, 1.2)	-0.8 (-3.7, 2.2)	3.2 (-0.7, 7.0)	-3.2 (-6.6, 0.3)
Ammonium									
1st	572.6	ref	571.0	ref	569.8	ref	ref	ref	ref
2nd	570.3	-1.4 (-4.2, 1.5)	571.5	-0.9 (-3.9, 2.1)	569.9	-2.0 (-5.4, 1.5)	-2.6 (-5.7, 0.6)	-1.7 (-5.0, 1.6)	-3.7 (-7.5, 0.1)
3rd	571.3	0.2 (-3.2, 3.6)	569.1	-2.1 (-5.9, 1.8)	570.3	-2.4 (-6.1, 1.4)	-0.7 (-4.4, 3.0)	-2.8 (-7.3, 1.7)	-5.1 (-9.5, -0.7)
4th	569.1	-0.4 (-4.4, 3.6)	570.4	-0.4 (-5.0, 4.3)	571.7	-3.2 (-8.1, 1.8)	-2.8 (-7.4, 1.9)	-0.2 (-5.6, 5.1)	-6.0 (-11.7, -0.4)
5th	570.1	-0.3 (-4.5, 3.8)	571.4	0.7 (-4.2, 5.5)	571.7	-4.1 (-9.1, 0.9)	-2.8 (-7.7, 2.0)	1.1 (-4.4, 6.5)	-7.0 (-12.7, -1.4)
IQR		0.1 (-2.9, 3.0)		1.1 (-2.5, 4.7)		-1.3 (-4.7, 2.1)	-1.6 (-5.1, 2.0)	1.9 (-2.2, 6.0)	-2.5 (-6.2, 1.3)

NOTE: CI, confidence interval; EC, elemental carbon; IQR, interquartile range; OC, organic carbon.

[a] Adjusted for maternal age, parity, gestational week, infant sex, and season of conception.

[b] We simultaneously included exposure over the first, second, and third trimesters.

Clinical Significance

In this study, we focused on trimester-specific exposure, and observed an inverse association of sulphate exposure over the third trimester with birth and placental weight. The result provides valuable insight into the mechanism underlying the association between $PM_{2.5}$ exposure and adverse birth effects.