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Correlation between Exposure to Fine Particulate Matter (PM$_{2.5}$) during Pregnancy and Congenital Anomalies: Its Surgical Perspectives

Eun-jung Koo [ID],[1] Jin-Gon Bae [ID],[2] Eun Jung Kim [ID],[3] and Yong-Hoon Cho [ID] [4]

[1]Division of Pediatric Surgery, Department of Surgery, Keimyung University School of Medicine, Daegu, Korea
[2]Department of Obstetrics & Gynecology, Keimyung University School of Medicine, Daegu, Korea
[3]Department of Urban Planning, Keimyung University, Daegu, Korea
[4]Division of Pediatric Surgery, Department of Surgery, Pusan National University Yangsan Hospital, Gyeongnam, Korea

Address for Correspondence:
Eun Jung Kim, PhD
Department of Urban Planning, Keimyung University, 1095 Dalgubeol-daero, Dalseo-gu, Daegu 42601, Republic of Korea.
E-mail: kimej@kmu.ac.kr

Yong-Hoon Cho, MD, PhD
Department of Surgery, Pusan National University School of Medicine, 49 Busandaehak-ro, Yangsan 50612, Republic of Korea.
E-mail: choyh70@pusan.ac.kr

ORCID iDs
Eun-jung Koo [ID]
https://orcid.org/0000-0002-9982-7037
Jin-Gon Bae [ID]
https://orcid.org/0000-0001-6127-162X
Eun Jung Kim [ID]
https://orcid.org/0000-0003-0896-2389
Yong-Hoon Cho [ID]
https://orcid.org/0000-0003-0170-9997

ABSTRACT

Background: Fine particulate matter (PM$_{2.5}$) can easily penetrate blood vessels and tissues through the human respiratory tract and cause various health problems. Some studies reported that particular matter (PM) exposure during pregnancy is associated with low birth weight or congenital cardiovascular anomalies. This study aimed to investigate the correlation between the degree of exposure to PM $\leq$ 2.5 µm (PM$_{2.5}$) during pregnancy and congenital anomalies relevant to the field of pediatric surgery.

Methods: Mother-infant dyads with registered addresses in the Metropolitan City were selected during 3 years. The electronic medical records of mothers and neonates were retrospectively analyzed, with a focus on maternal age at delivery, date of delivery, gestation week, presence of diabetes mellitus (DM) or hypertension, parity, the residence of the mother and infant, infant sex, birth weight, Apgar score, and presence of congenital anomaly. The monthly PM$_{2.5}$ concentration from the first month of pregnancy to the delivery was computed based on the mothers' residences.

Results: PM$_{2.5}$ exposure concentration in the second trimester was higher in the congenital anomaly group than in the non-congenital anomaly group (24.82 ± 4.78 µg/m³, P = 0.023). PM$_{2.5}$ exposure concentration did not affect the incidence of nervous, cardiovascular, and gastrointestinal anomalies. While statistically insignificant, the groups with nervous, cardiovascular, gastrointestinal, musculoskeletal, and other congenital anomalies were exposed to higher PM$_{2.5}$ concentrations in the first trimester compared with their respective counterparts. The effect of PM$_{2.5}$ concentration on the incidence of congenital anomalies was significant even after adjusting for the mother's age, presence of DM, hypertension, and parity. The incidence of congenital anomalies increased by 26.0% (95% confidence interval of 4.3% and 49.2%) per 7.23 µg/m³ elevation of PM$_{2.5}$ interquartile range in the second trimester.

Conclusions: The congenital anomaly group was exposed to a higher PM$_{2.5}$ concentration in the second trimester than the non-congenital anomaly group. The PM$_{2.5}$ exposure concentration level in the first trimester tended to be higher in groups with anomalies than those without anomalies. This suggests that continuous exposure to a high PM$_{2.5}$ concentration during pregnancy influences the incidence of neonatal anomalies in surgical respects.

Keywords: Air Pollution; Congenital Anomaly; Particulate Matter; Pregnancy; Surgical

INTRODUCTION

Health problems caused by particulate matter (PM) are important societal issues. Particles smaller than 50 μm are referred to as total suspended particles (TSPs), and PM is referred to as very small particles. Particles smaller than 10 μm and 2.5 μm are referred to as PM$_{10}$ and PM$_{2.5}$, respectively.[1] In 2013, the World Health Organization's International Agency for Research on Cancer designated PM as a group 1 carcinogen.[2]

The correlations of PM with various diseases, including cognitive-behavioral disorders, respiratory diseases, cardiovascular diseases, and ocular diseases, have been reported in many studies.[3-7] In particular, exposure to air pollutants during pregnancy is associated with the development of congenital anomalies, low birth weight, stillbirth, and neonatal respiratory diseases.[8-11] A recent study has shown links between PM$_{2.5}$ exposure and the development of congenital cardiovascular anomalies.[12] Further, exposure to PM$_{2.5}$ before and early in pregnancy is reported to increase the risk for congenital hypospadias.[13]

Some Korean studies have examined the relationship between PM exposure concentration during pregnancy and low birth weight. However, very few have examined the relationship between PM exposure and congenital anomalies. Moreover, there is a complete lack of studies studying the relationship between PM exposure and congenital anomalies in the field of pediatric surgery.[14,15] South Korea began measuring PM$_{2.5}$ concentrations in five metropolitan areas in 2013, with nationwide measurement and reporting of PM$_{2.5}$ concentration forecasts beginning in 2015.[1] As of October 2020, PM$_{2.5}$ was being measured at 558 monitoring stations nationwide, with a growing number of stations.[16] Before 2015, PM$_{2.5}$ was measured at only a few stations in Korea, representing a wide area. Therefore, computing maternal exposure to PM$_{2.5}$ based on these measurements would inevitably introduce substantial errors.

Thus, it is prudent to shed light on the relationship between PM$_{2.5}$ exposure and congenital anomalies based on PM$_{2.5}$ concentration data from 2015 onwards. Therefore, this study aimed to investigate the correlation between the PM$_{2.5}$ exposure concentration during pregnancy and the incidence of congenital anomalies from 2015 onwards.

METHODS

Subjects

All the deliveries at Keimyung University Dongsan Medical Center between July 2016 and June 2019 (36 months) were considered. Mothers and infants with registered addresses in Daegu Metropolitan City were selected, assuming that a mother and her infant shared the same address. Cases of stillbirths, multifetal births, mothers transferred from a different region hospital, and infants born elsewhere and transferred to our hospital were excluded. In total, 1,624 mother-infant dyads born at ≥ 35 weeks of gestation were enrolled in the study.

Collection of clinical data

The electronic medical records (EMRs) of mothers and infants were retrospectively analyzed. Information about maternal age, delivery date, gestation period, diabetes mellitus (DM), hypertension, parity, mother's address, infant's sex, birth weight, 1-and 5-minute Apgar scores, the presence of congenital anomaly, and diagnosis, was collected. Patients'

diagnosis codes and diagnoses recorded in the admission and discharge records were reviewed. Information about congenital anomalies was obtained by reviewing radiologic records. Congenital anomalies were classified into nervous, cardiovascular, gastrointestinal, urogenital, musculoskeletal, facial, and other anomalies. Addresses were anonymized by conversion to the mean monthly PM$_{2.5}$ exposure concentration. Gestation was calculated based on the delivery day. Mean PM$_{2.5}$ concentrations were calculated for the pregnancy period and by month. The day of delivery was not used in the analysis. Only non-personally identifiable variables were used in the analysis.

Computation of the pregnancy period

The pregnancy period was divided into months and trimesters based on the delivery date and clinically estimated gestation period. The month of the first day of pregnancy was set as the reference month (month one of pregnancy). The month of delivery was set as the final month of pregnancy.

Analysis of PM$_{2.5}$ concentration at the mother's address

The mean monthly PM$_{2.5}$ concentration during pregnancy was calculated based on each mother's address. AirKorea of the Korea Environment Corporation (http://www.airkorea.or.kr) provides six real-time atmospheric contamination indices, including PM$_{2.5}$. Currently, PM$_{2.5}$ is measured at 558 monitoring stations in 164 cities and districts nationwide. In this study, we used the monthly atmospheric and environmental reports provided by AirKorea to obtain data measured at stations within Daegu Metropolitan City during the analysis period (July 2015–June 2019). There were eight monitoring stations in Daegu Metropolitan City when we began our analysis. However, the number of stations increased to 16 by the end of the analysis period (June 2019). Therefore, data were obtained from 8 to 16 stations depending on the time point. **Fig. 1** shows the locations of the 16 PM$_{2.5}$ stations in Daegu Metropolitan City and the residences of the 1,624 mothers enrolled in this study.
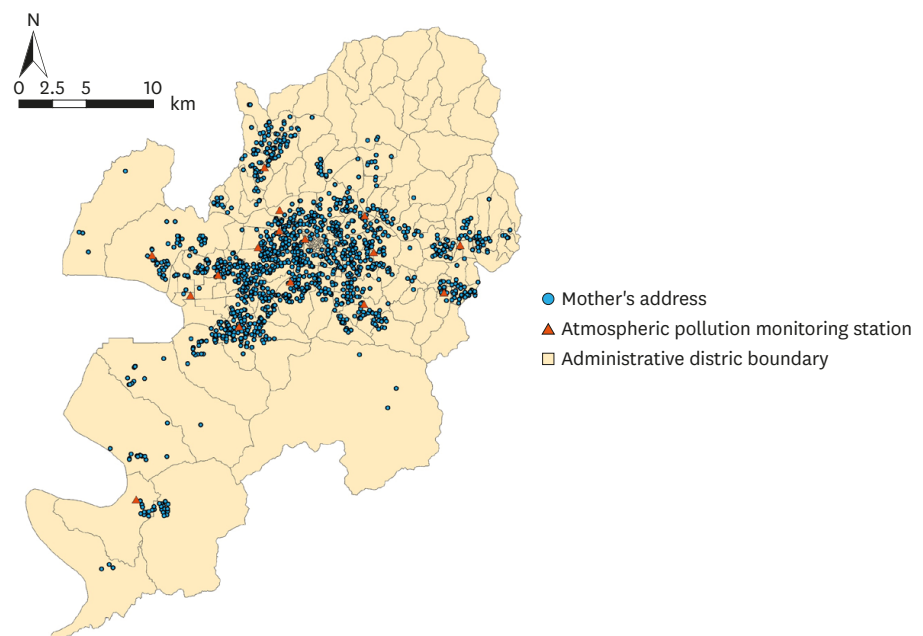

Fig. 1. Mothers' addresses and atmospheric pollution monitoring stations used in this study.

In this study, the inverse distance weighting (IDW) technique was used, and the equation is shown below.[17] IDW is widely used in computing PM_{10} or $PM_{2.5}$ concentrations.[17,18]

$$Z_p = \frac{\sum_{i=1}^{n}[\frac{Z_i}{D_i^p}]}{\sum_{i=1}^{n}[\frac{1}{D_i^p}]}$$

Z_p: Interpolated value
Z_i: Value measured from n observed values near Z
p: Power to explain weighted function
D_i^p: distance between i and p

We developed a $PM_{2.5}$ map for Daegu Metropolitan City for a 48-month period beginning one year before the delivery date (from July 2015 to June 2019) using the IDW technique. **Fig. 2** is an example of a $PM_{2.5}$ map of the Daegu Metropolitan City for June 2019. Mothers' (n = 1,624) monthly exposures to $PM_{2.5}$ during pregnancy (month one of pregnancy to delivery) were then computed based on the monthly $PM_{2.5}$ map. Spatial interpolation using the IDW technique was performed using ArcGIS 10.6 (ESRI, Redlands, CA, USA).

Statistical analysis

Statistical analysis was performed using IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM. Normality was tested with the Kolmogorov-Smirnov test. The means of quantitative variables were compared using independent t-tests. Qualitative variables were compared using the χ^2 test. The predictors of congenital anomalies were analyzed using binomial logistic regression. Statistical significance was set at P value < 0.05.
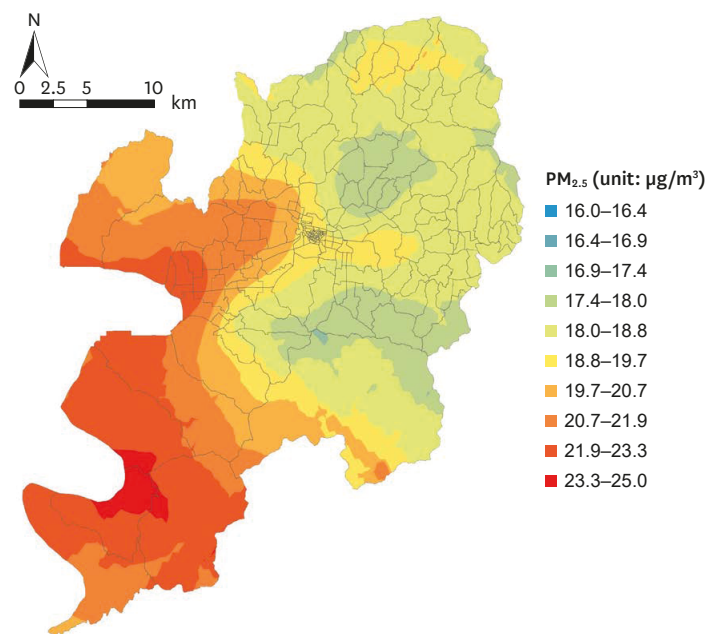

Fig. 2. Spatially interpolated $PM_{2.5}$ concentration using the inverse distance weighting technique (as of June 2019). $PM_{2.5}$ = particulate matter ≤ 2.5 μm.

Ethic statement

This study was approved by the institutional review board of Keimyung University Dongsan Medical Center (IRB No. 2020-09-045) and the requirement for informed consent was waived.

RESULTS

There were 216 (13.3%) neonates born with congenital anomaly with respect to pediatric surgery in this study.

Demographic characteristics and classification of congenital anomalies

Table 1 shows the demographic characteristics of the mothers and their infants. Congenital anomalies were classified according to type in **Table 2**.

Differences in demographic characteristics between the congenital and non-congenital anomaly groups

Table 3 shows the differences in maternal ages, gestational ages, prevalence of maternal DM and hypertension, parity, birth weights, gender, and Apgar scores between the congenital and non-congenital anomaly groups.

Correlation between the incidence of congenital anomalies and PM₂.₅

There was a significant association between the incidence of congenital anomalies in the second trimester ($P = 0.023$) with mean $PM_{2.5}$ exposure of 24.01 μg/m³ and 24.82 μg/m³ in the non-congenital and congenital anomaly groups (**Table 4**). On the other hand, there was no significant difference in the incidence of congenital anomalies according to $PM_{2.5}$ exposure in the first or third trimesters. The mean $PM_{2.5}$ exposure in months three to eight was higher in the congenital anomaly group. Further, the incidence of congenital anomalies significantly differed statistically according to $PM_{2.5}$ exposure in months five and six (**Fig. 3A**).

For specific types of congenital anomalies, there was no significant difference in the presence of nervous system anomalies associated with $PM_{2.5}$ exposure by trimester (**Table 4**). The mean monthly $PM_{2.5}$ exposure in months one to six was higher in the nervous system anomaly group

Table 1. Demographic characteristics of subjects

Subjects	Characteristics	Values
Pregnant (n = 1,624)	Mean age, yr	33.8 ± 4.5 (16–46)
	Diabetes mellitus	172 (10.6)
	Hypertension	150 (9.2)
	Parity	
	0	799 (49.2)
	1	663 (40.8)
	2	127 (7.8)
	3	30 (1.8)
	4	5 (0.3)
Newborn (n = 1,624)	Gestational age, wk	37.6 ± 1.4 (35–42)
	Gender, M:F, No. (ratio)	861:763 (1.13:1)
	Birth weight, g	3,015 ± 477 (1,300–4,650)
	Apgar score	
	1 min	7.7 ± 0.6
	5 min	8.9 ± 0.4
	Associated anomalies	216 (13.3)

Values are presented as patient number (%) or mean ± standard deviation.

Table 2. Classification of associated anomalies in newborns

Anomaly	No. of newborn	Case of anomaly, No.	
Nervous system	22 (1.4)	Macrocephaly, microcephaly	5
		Hydrocephalus	8
		Filum terminale, spinal cord lipoma, myelomeningocele	4
		Spinal deformity, sacrococcygeal deformity	2
		Cranial deformity	5
		Intracranial vascular malformation	1
Cardiovascular	86 (5.3)	Patent ductus arteriosus	17
		Atrial septal defect	76
		Ventricular septal defect	19
		Transposition of great arteries, situs inversus	5
		Valvular disease	4
		Tetralogy of Fallot	3
		Aortic coarctation, right side aortic arch	2
Gastrointestinal	30 (1.8)	Small bowel atresia	9
		Anorectal malformation	9
		Gastroschisis	2
		Meconium peritonitis	1
		Choledochal cyst	1
		Meckel's diverticulum	1
		Mesenteric lymphangioma	1
		Umbilical cord anomaly	7
Genitourinary	61 (3.8)	Renal	39
		Genital	25
Musculoskeletal	45 (2.8)	Upper limb anomaly	6
		Lower limb anomaly	35
		Others	6
Others	20 (1.2)	Cleft lip & palate	16
		Ear deformity	4

Values are presented as patient number (%).

Table 3. Clinical differences according to the association with anomaly in newborns

Variables	No congenital anomaly (n = 1,408)	Congenital anomaly (n = 216)	P value
Gender, M:F	733:675 (1.09:1)	128:88 (1.45:1)	0.048*
Gestational age, wk	36.6 ± 1.4	37.7 ± 1.3	0.588
Birth weight, g	3,013.6 ± 469.5	3,024.5 ± 526.9	0.756
Apgar score			
1 min	7.7 ± 0.6	7.5 ± 0.8	0.002**
5 min	8.9 ± 0.4	8.6 ± 0.6	0.003**
Maternal age, yr	33.8 ± 4.5	33.4 ± 4.5	0.145
Maternal diabetes	143 (10.2)	29 (13.4)	0.146
Maternal hypertension	135 (9.6)	15 (6.9)	0.210
Maternal parity			0.204
0	682 (48.4)	117 (54.2)	
1	585 (41.5)	78 (36.1)	
2	112 (8.0)	15 (6.9)	
3	26 (1.8)	4 (1.9)	
4	3 (0.2)	2 (0.9)	

Values are presented as patient number (%) or mean ± standard deviation.
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

though not statistically significantly (**Fig. 3B**). There was no significant difference in the presence of cardiovascular anomalies associated with PM₂.₅ exposure by trimester (**Table 4**). The monthly mean PM₂.₅ exposure in months three to seven was higher in the cardiovascular anomaly group, with a significant difference in PM₂.₅ exposure in month three between the two groups (**Fig. 3C**). There was no significant difference in the presence of gastrointestinal anomalies associated with PM₂.₅ exposure by trimester (**Table 4**). There were no statistically significant differences in
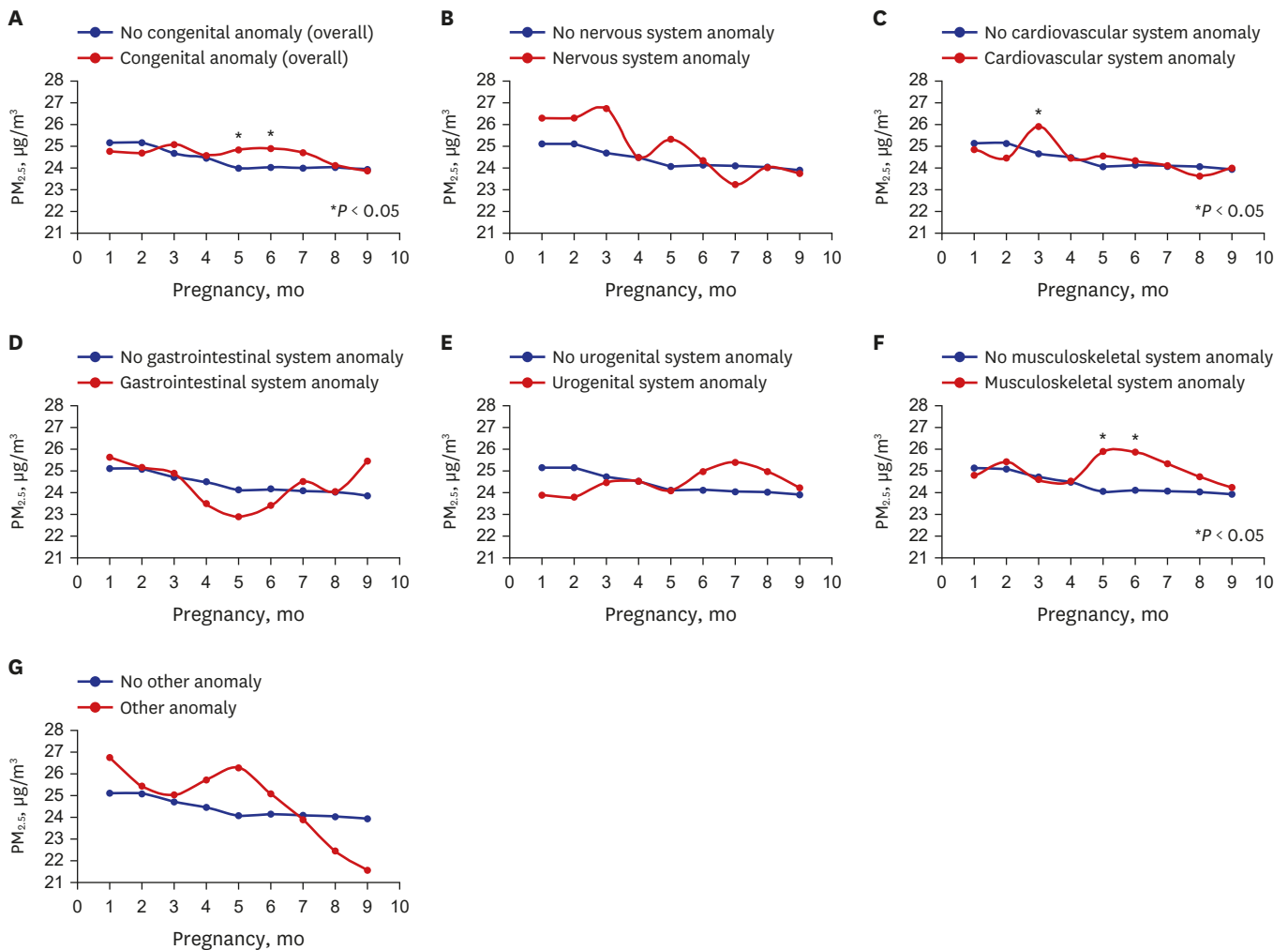
Fig. 3. Correlation between congenital anomalies and PM$_{2.5}$ concentration (congenital anomaly by type). Correlation between (**A**) congenital anomaly and prenatal monthly PM$_{2.5}$ exposure. (**B**) nervous system anomaly and prenatal monthly PM$_{2.5}$ exposure. (**C**) cardiovascular anomaly and prenatal monthly PM$_{2.5}$ exposure. (**D**) gastrointestinal anomaly and prenatal monthly PM$_{2.5}$ exposure. (**E**) urogenital anomaly and prenatal monthly PM$_{2.5}$ exposure. (**F**) musculoskeletal anomaly and prenatal monthly PM$_{2.5}$ exposure. (**G**) other anomalies and prenatal monthly PM$_{2.5}$ exposure.
PM$_{2.5}$ = particulate matter ≤ 2.5 μm.

the monthly PM$_{2.5}$ exposure in all months between the two groups. However, the mean PM$_{2.5}$ exposure in months one–three was higher in the gastrointestinal anomaly group (**Fig. 3D**). No significant difference was observed in the presence of urogenital anomalies associated with PM$_{2.5}$ exposure by trimester (**Table 4**). In terms of monthly PM$_{2.5}$ exposure, there were no statistically significant differences in PM$_{2.5}$ exposure in all months between the two groups. However, the mean PM$_{2.5}$ exposure was higher in months six–nine in the urogenital anomaly group (**Fig. 3E**). We analyzed the difference in the presence of musculoskeletal anomalies associated with PM$_{2.5}$ exposure by trimester. We found that the presence of musculoskeletal anomalies significantly differed according to the second trimester PM$_{2.5}$ exposure ($P = 0.014$) (**Table 4**). The PM$_{2.5}$ exposures in the second trimester were 24.07 μg/m^3 and 25.69 μg/m^3 in the non-musculoskeletal and musculoskeletal anomaly groups, respectively, with a higher exposure in the musculoskeletal anomaly group. The monthly mean PM$_{2.5}$ exposure level was generally higher in the musculoskeletal anomaly group in months two–nine. The difference in PM$_{2.5}$ exposure in months five and six was statistically significant between the two groups (**Fig. 3F**). The association of PM$_{2.5}$ exposure by trimester with the presence of other anomalies was not

Table 4. Comparison of mean PM$_{2.5}$ concentration (µg/m³) by trimester according to the association with congenital anomaly

Anomaly	1st trimester	P value	2nd trimester	P value	3rd trimester	P value
Overall		0.818		0.023*		0.564
No	25.86 ± 4.29		24.01 ± 4.85		24.06 ± 5.17	
Yes	24.79 ± 4.54		24.82 ± 4.78		23.84 ± 5.30	
Nervous system		0.229		0.857		0.748
No	24.84 ± 4.32		24.12 ± 4.85		24.04 ± 5.19	
Yes	25.96 ± 4.67		24.30 ± 5.04		23.68 ± 4.78	
Cardiovascular		0.872		0.673		0.516
No	24.85 ± 4.32		24.11 ± 4.82		24.05 ± 5.19	
Yes	24.93 ± 4.41		24.33 ± 5.30		23.68 ± 5.03	
Gastrointestinal		0.948		0.572		0.634
No	24.86 ± 4.33		24.13 ± 4.86		24.02 ± 5.18	
Yes	24.80 ± 3.91		23.62 ± 4.19		24.48 ± 5.39	
Genitourinary		0.205		0.256		0.523
No	24.88 ± 4.33		24.09 ± 4.84		24.02 ± 5.17	
Yes	24.16 ± 4.31		24.81 ± 5.05		24.45 ± 5.44	
Musculoskeletal		0.976		0.014*		0.783
No	24.86 ± 4.30		24.07 ± 4.86		24.03 ± 5.17	
Yes	24.83 ± 5.18		25.69 ± 4.16		24.24 ± 5.57	
Others		0.355		0.370		0.125
No	24.84 ± 4.32		24.11 ± 4.85		24.05 ± 5.18	
Yes	25.75 ± 4.84		25.09 ± 4.82		22.27 ± 5.32	

Values are presented as patient number (%) or mean ± standard deviation.
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

significantly different statistically (**Table 4**). The monthly mean PM$_{2.5}$ exposure was higher in months one to six in the "other anomalies" group, though not statistically significant (**Fig. 3G**).

Effects of PM$_{2.5}$ exposure by trimester on the incidence of congenital anomalies

We analyzed the effects of PM$_{2.5}$ exposure on the incidence of congenital anomalies. Multivariable binomial logistic regression was performed to examine the effects of PM$_{2.5}$ exposure by trimester after adjusting for maternal factors (age, DM, hypertension, parity) (**Table 5**).

The effects of second trimester PM$_{2.5}$ exposure on the development of congenital anomalies were significant ($P = 0.020$). Overall congenital anomaly development increased by 26.0% (95% CI of 4.3% and 49.2%) per 7.23 µg/m3 increase of PM$_{2.5}$ interquartile range (IQR) in the second trimester. The effects of second trimester PM$_{2.5}$ exposure on the development of musculoskeletal anomalies were significant ($P = 0.029$). Musculoskeletal anomaly development increased by 54.2% (95% CI of 5.7% and 106.2%) per 7.23 µg/m³ increase of PM$_{2.5}$ IQR in the second trimester.

Table 5. Effects of PM$_{2.5}$ by trimester on congenital anomalies by percentage per IQR increases of PM$_{2.5}$ after adjusting from maternal factors (age, diabetes mellitus, hypertension, parity)

Anomaly	1st Trimester		2nd Trimester		3rd Trimester	
	(IQR = 7.21 µg/m³)	P value	(IQR = 7.23 µg/m³)	P value	(IQR = 8.05 µg/m³)	P value
Overall	−16.5 (−25.9, 21.6)	0.837	26.0 (4.3, 49.2)	0.020*	−5.6 (−28.1, 16.1)	0.595
Nervous system	12.2 (−178.0, 268.9)	0.914	4.3 (−57.1, 70.8)	0.902	−7.2 (−69.2, 60.3)	0.828
Cardiovascular	4.3 (−31.0, 42.5)	0.803	8.6 (−23.8, 41.9)	0.611	−12.0 (−45.0, 21.7)	0.477
Gastrointestinal	−2.1 (−20.9, 60.5)	0.942	−15.9 (−66.5, 38.3)	0.557	14.4 (−40.2, 74.0)	0.607
Genitourinary	−27.3 (−67.0, 14.4)	0.191	22.4 (−16.6, 63.6)	0.272	13.6 (−25.7, 54.7)	0.507
Musculoskeletal	−1.4 (−49.0, 49.0)	0.948	54.2 (5.7, 106.2)	0.029*	82.1 (−35.4, 57.1)	0.690
Others	36.7 (−38.9, 120.4)	0.355	32.5 (−34.7, 106.2)	0.358	−49.9 (−112.7, 18.5)	0.146

IQR = interquartile range, PM$_{2.5}$ = particulate matter ≤ 2.5 µm.
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

DISCUSSION

According to our results, overall congenital anomalies were significantly associated with second trimester PM$_{2.5}$ exposure concentration. Most body organs develop between weeks three-eight after conception,[19] this being a sensitive and high risk period concerning exposure to various teratogens, such as drugs, alcohol, and cigarettes, without being aware of their pregnancy. However, our results show that second trimester PM$_{2.5}$ exposure can also increase the odds for congenital anomalies. These findings suggest that external factors may also induce anomalies even after the period of major organ development. A recent Korean study reported that PM$_{2.5}$ exposure in the second trimester, in addition to the first trimester, also contributes to the development of cardiovascular, musculoskeletal, and urogenital anomalies.[15]

Compared with previous studies, our study had a relatively smaller sample size limited to a single region. Therefore, the absence of statistically different first trimester PM$_{2.5}$ concentrations between the congenital and non-congenital anomaly groups should be carefully interpreted. It should not be interpreted simply as the absence of an effect of PM$_{2.5}$ exposure in the first trimester on the onset of congenital anomalies. Although statistically insignificant, the nervous, cardiovascular, gastrointestinal, musculoskeletal, and other congenital anomaly groups tended to have higher PM$_{2.5}$ exposure levels in the first trimester. Further research is required on this finding. Moreover, although statistically insignificant, the congenital anomaly group tended to show higher monthly PM$_{2.5}$ exposure throughout the pregnancy (from 3rd to 8th month of pregnancy). This suggests that continuous exposure to high PM$_{2.5}$ concentrations during pregnancy predicts congenital anomaly development.

Four weeks after conception, upper limb buds sprout followed by lower limb buds. The limbs develop in the distal direction from the trunk. Exposure to a teratogen during this period can result in amelia.[20] Musculoskeletal anomalies can be induced not only by factors present in this sensitive period but also by the intrauterine environment or external factors post-conception. Club foot often occurs with syndactylia and can also be induced when the legs are placed in an abnormal position in the uterus. Our results showed that the second trimester PM$_{2.5}$ exposure concentration was associated with musculoskeletal malformations. This suggests that malformations can be induced by the intrauterine environment or external factors after organ development.

In this study, we assumed that the PM$_{2.5}$ concentration at the mother's registered address is the PM$_{2.5}$ concentration to which the mother was exposed. The mothers' addresses were obtained from their medical records, and we could not verify whether the mothers had moved during their pregnancy. If they had moved during pregnancy, the PM$_{2.5}$ concentration of their residence would also differ. Further, it is possible that mothers did not stay within their residence throughout the day. Thus, the places in which they spent much of their time should also be taken into consideration. If more time would be spent at the workplace, it would be necessary to consider the PM$_{2.5}$ concentration near that workplace instead of that at the residence.

Previous study used the PM$_{2.5}$ concentration measured from an atmospheric pollution monitoring station closest to the woman's address.[8] However, this measurement included a considerably broad area; thus, it cannot be viewed as accurate PM$_{2.5}$ or PM concentrations at the woman's address. In the present study, we computed PM$_{2.5}$ concentrations at the mothers' addresses through spatial interpolation by dividing the entire Daegu region into 30 m × 30 m districts, thus substantially increasing the value accuracy. Moreover, previous studies

often used disease classification codes when collecting data about congenital anomalies.[21,22] However, the present study included data on specific types of congenital anomalies for 1,624 infants by having clinicians cross review EMRs and radiologic findings, in addition to disease classification codes. This also enhanced the accuracy of the data. Furthermore, by computing monthly PM$_{2.5}$ exposure, we were also able to perform a more thorough study compared to past studies that used mean PM$_{2.5}$ concentrations by trimester or for the entire pregnancy.[10]

Previous studies have reported that exposure to atmospheric pollutants (PM$_1$, PM$_{2.5}$, PM$_{10}$) for the first three years of life increased the incidence of autism spectrum disorders.[23] Further, exposure to PM$_{2.5}$ in the third trimester has been shown to increase the odds ratios (OR) for autism spectrum disorders.[24] While only a handful of studies have shed light on the correlation between nervous system malformations and PM$_{2.5}$, several studies have reported significant effects of PM$_{2.5}$ concentration on the cognitive-behavioral disorder, Alzheimer's disease, and autism. We hope for more active studies on the relationship between nervous and neurological functions and PM$_{2.5}$ concentrations.

In this study, the association between congenital cardiovascular anomalies and PM$_{2.5}$ concentration was not significant. A previous animal study using rat models observed that prenatal PM$_{2.5}$ exposure alters cardiac cells, thus affecting heart development.[25] Besides, exposure to ultrafine particles smaller than 0.1 μm in women at weeks two–eight of gestation increased the OR for ventricular septal defect.[12] Exposure to a higher PM$_{2.5}$ concentration early in pregnancy further increased the OR for cardiovascular anomalies, such as atrial septal defect, endocardial defect, and pulmonary valve stenosis.[12,26] Our findings that the PM$_{2.5}$ concentration in month three of pregnancy was higher in the cardiovascular anomaly group, corroborate these results. Thus, further in-depth studies on the relationship between the onset of cardiovascular anomalies and PM$_{2.5}$ concentrations, as well as other atmospheric pollutants, are crucial.

Although statistically insignificant, the gastrointestinal anomaly group had a higher PM$_{2.5}$ concentration early in pregnancy. The urogenital anomaly group had a high PM$_{2.5}$ concentration from month six of pregnancy. Gastrointestinal anomalies encompass anomalies of various organs. Moreover, the sensitive period or substances that induce anomalies are presumed to differ with regard to the development of each organ. A typical cause of gastrointestinal anomalies is maternal smoking during pregnancy. Cigarette smoke is known to induce vasoconstriction and result in small intestine obstruction and gastroschisis.[27,28] Although we did not include maternal smoking as an anomaly-inducing factor in this study, subsequent studies should examine the relationship between smoking and congenital anomalies. Moreover, considering the high PM$_{2.5}$ exposure early in pregnancy, the relationship between PM$_{2.5}$ concentration and specific types of gastrointestinal anomalies should also be examined. The urogenital system is derived from the intermediate mesoderm. The morphologic features of the urological and reproductive systems appear at approximately four and seven weeks, respectively, post-conception. Early prenatal exposure to atmospheric pollutants is known to increase the incidence of congenital hypospadias.[13,29] Testicular descent is triggered by the gubernaculum with the effect of the testicular hormone, insulin-like 3, between weeks 8 and 15 of pregnancy. The testicles continue to move to the scrotum past the inguinal canal between weeks 25 and 35 of pregnancy.[30] This prolonged developmental process of the urogenital system may be significantly at risk according to our results.

Even after adjusting for maternal factors, such as age, DM, and hypertension, that may affect the onset of congenital anomalies, there were significant effects of PM$_{2.5}$ concentration on

the incidence of congenital anomalies. The onset of congenital anomalies is multifactorial, and a substantial part can be attributed to the so-called divinity (an unknown area). However, some factors have been identified in previous studies. PM$_{2.5}$ is a recently highlighted environmental problem, and this study investigated the effects of this environmental issue on the onset of congenital anomalies. However, we only enrolled mother-infant dyads from tertiary hospitals, where high-risk pregnant women are mostly referred. Therefore, our study is vulnerable to selection bias; thus, it does not represent the entire maternal and infant population. Subsequent studies should expand the scope of their samples, as this would ensure findings representative of the entire maternal or infant population of a region or country. Furthermore, we did not investigate factors such as maternal smoking history, drinking history, comorbidities, marital status, and education level. Subsequent studies should complement the findings of our study by considering the effects of these factors on congenital anomalies.

In conclusion, this study suggests that exposure to high PM$_{2.5}$ concentration during pregnancy may be associated with the development of congenital anomalies in surgical respects. Moreover, each type of congenital anomaly generally had a high PM$_{2.5}$ exposure concentration in the first trimester. Overall congenital anomalies and musculoskeletal anomalies were associated with increased PM$_{2.5}$ concentration in the second trimester of pregnancy. This study discovered some significant clues regarding the effects of PM$_{2.5}$ on the development of congenital anomalies. The findings of this study can serve as evidence for developing recommendations about PM$_{2.5}$ exposure for pregnant women. Moreover, the findings will be useful for subsequent studies on the correlation of each type of anomaly or a specific anomaly with PM$_{2.5}$.

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