

Association Between Maternal Exposure to PM₁₀ and Risk of Anorectal Atresia/Stenosis in Offspring: A Population-Based Case-Control Study in Liaoning Province, China

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Abstract

Background: The potential association between maternal exposure to PM₁₀ ranging from 3 months prior to conception to the end of the early trimester and the risk of anorectal atresia/stenosis in offspring have not been established. Thus, we determined the association in this study.

Methods: We recruited 713 patients with anorectal atresia/stenosis and 7950 randomly selected healthy offspring from the Maternal and Child Health Certificate Registry of Liaoning Province and delivered between 1 January 2010 and 31 December 2015. Monthly PM₁₀ concentrations were retrieved from the Environment Protection Bureau of each city in Liaoning Province. We established a multivariable logistic regression model to calculate the adjusted odds ratios (ORs) and 95% confidence intervals (CIs).

Results: Maternal exposure to PM₁₀ was associated with an increased risk for anorectal atresia/stenosis in offspring during the three months prior to conception (per 10 µg/m³ increment: OR = 1.15, 95% CI = 1.03–1.20; per SD [27 µg/m³] increment: OR = 1.33, 95% CI = 1.09–1.63) and the first trimester (per 10 µg/m³ increment: OR = 1.08, 95% CI = 1.00–1.17; per SD [28 µg/m³] increment: OR = 1.26, 95% CI = 1.01–1.57). Evaluation of the association with a shorter exposure window (1 month) revealed a positive association between anorectal atresia/stenosis and PM₁₀ from the 3rd month prior to pregnancy to each month of the 1st trimester.

Conclusion: Maternal exposure to PM₁₀ three months prior to conception and during the 1st trimester was associated with an increased risk of anorectal atresia/stenosis in the offspring. Future perspective studies are needed to confirm our findings.

Introduction

Anorectal atresia/stenosis refers to a congenital malformation that is characterized by absence of continuity of the anorectal canal, communication between the rectum and anus, or narrowing of the anal canal with or without a fistula to neighboring organs (Liu et al., 2019). The incidence of anorectal atresia/stenosis is high among gastrointestinal tract malformations in offspring. Previous studies have shown that the prevalence of anorectal atresia was approximately 1 per 5000 to 1 per 1500 live births (Boocock and Donnai, 1987; Cho et al., 2001). Anorectal atresia/stenosis has been associated with genetic factors; however, in most cases the etiology is complex and has not been established. Indeed, anorectal atresia/stenosis could be related to environmental factors. Recent studies have reported that several factors contribute to anorectal atresia, such as a first-degree family history of anorectal atresia, pre-pregnancy diabetes, and obesity (Correa et al., 2003; Stoll et al., 1997; Waller et al., 2007). Notably, little information is available about the association between air pollutants and anorectal atresia/stenosis.

Recently, air pollutants have become major public concerns in many countries. Increasing evidence suggests that maternal exposure to air pollutants has different adverse health effects on the fetus and newborn (Mainolfi et al., 2013; Maisonet et al., 2004). Of note, particulate matter (PM) has the highest

possibility of causing detrimental health effects (Chow et al., 2006). Several studies have indicated that prenatal exposure to PM leads to several kinds of adverse birth outcomes, including low birth weight (Coker et al., 2015), intrauterine growth retardation (Maisonet et al., 2004), and preterm birth (Chang et al., 2012). A previous study also supported the view that there is an association between maternal exposure to ambient PM during pregnancy and several types of birth deformities (Teng et al., 2016). Notably, among the constituents of the air pollution cocktail, PM with aerodynamic diameters $\leq 10 \mu\text{m}$ (PM₁₀) is considered to be a significant culprit with respect to mediating adverse health effects, including several kinds of birth defects (Girguis et al., 2016; Zhang et al., 2020; Zhang et al., 2020); however, there are no studies describing the impact of PM₁₀ on the risk of anorectal atresia/stenosis.

Air pollution is more severe in China when compared to Western countries, which has been attributed to the more pronounced and longer duration of exposure, especially in the northern China (Guan et al., 2016; Song et al., 2017). Liaoning Province is one of the most important provinces in northern China, with an area of 148,600 square kilometers and a population of nearly 42 million. Liaoning Province has witnessed a soaring development in the past decades and boosted the gross Chinese economy accordingly. In concert with the rapid economic development, severe air pollution has also become a pressing concern. In this large population-based case-control study we examined the possible relationship between maternal exposure to PM₁₀ 3 months prior to conception and during the first trimester, and the risk of filial anorectal atresia/stenosis. Six-year birth defect cases were retrieved from the Maternal and Child Health Certificate Registry of Liaoning Province and the data relevant to air pollutant monitoring was acquired from the Environment Protection Bureau of each city in Liaoning Province. Indeed, this is the first study to investigate the association between PM₁₀ and anorectal atresia/stenosis.

Methods

Study population and data sources

We performed this population-based case-control study to assess the association between maternal exposure to PM₁₀ and the risk of anorectal atresia/ stenosis in offspring. The live birth, stillbirth, electively-terminated fetuses with anorectal atresia/stenosis, and healthy control data representing 1 January 2010 to 31 December 2015 were retrieved from the Maternal and Child Health Certificate Registry of Liaoning Province, which is managed by the Liaoning Women and Children's Health Hospital. Liaoning Women and Children's Health Hospital was founded in July 1986 and has established healthcare, clinical, and functional departments. Liaoning Women and Children's Health Hospital is one of the obstetrics and gynecology hospitals in Liaoning Province that provides comprehensive care and is mainly responsible for healthcare of women and children. The registry includes all 14 cities in Liaoning Province (Shenyang, Dalian, Anshan, Fushun, Benxi, Dandong, Jinzhou, Yingkou, Fuxin, Liaoyang, Panjin, Tieling, Chaoyang, and Huludao). The incidence of birth defects has fluctuated from 160.7/10,000 to 314.4/10,000 during our study period (Yu et al., 2015). Liaoning Province is one of the 31 provinces that provides data to the

national birth defects surveillance database maintained by the Chinese Birth Defects Monitoring Network. Liaoning Women and Children's Health Hospital obtains birth defect data monthly from all 14 maternal and child healthcare institutions in Liaoning Province (Huang et al., 2018). Then, specialized staff in Liaoning Women and Children's Health Hospital upload the birth defect data to the online reporting system for maternal and child health surveillance (Xu et al., 2011). The geographic divisions of Liaoning Province and the source of the control group have been previously described (Zhang et al., 2020). We chose 1.5% of the unaffected live births who were born in five cities (Shenyang, Dalian, Fuxin, Chaoyang, and Huludao) in Liaoning Province between 2010 and 2015 as healthy controls; the healthy controls were not case-related (mismatched). Offspring who did not have a permanent address or for whom key covariates were missing were excluded. The study was conducted in compliance with local and national regulations and the study protocol was approved by the Institutional Review Board of Liaoning Women and Children's Health Hospital.

Data collection and quality control

The detailed procedures of data collection have been described in a previous report (Zhang et al., 2020). Briefly, provincial and municipal monitoring network and clinical expert groups were set up for data collection. Anorectal atresia/stenosis was defined according to the 10th revision of the International Classification of Diseases (World Health Organization). The mother of the infant was interviewed by a trained obstetrics or pediatrics specialist to complete the birth defects registration form at the monitored hospital. If an anorectal atresia/stenosis case was identified and confirmed, demographic characteristics, clinical features, and obstetric factors were collected. For suspected cases of anorectal atresia/stenosis diagnosed by prenatal ultrasound scans, examinations were required for confirmation after termination or birth. Subsequently, the birth defects registration form was first submitted to the local maternal and child healthcare facility, then to the Liaoning Women and Children's Health Hospital. Data quality control was reported by Xu et al. (Xu et al., 2011). A group of state-level experts in medical genetics and pediatrics reviewed the data and confirmed the cases. The data were entered, cleaned, and analyzed in an established database. The disease diagnosis, data collection, data checking, and medical records were certified by the expert group at each level according to the program manual to ensure data quality. Additionally, to ensure data quality, the experts performed an independent retrospective survey to identify data deficiencies and inaccuracies, which were corrected before reporting.

PM₁₀ exposure assessment

The PM₁₀ exposure assessment method has been described in detail in a previous study (Zhang et al., 2020). There were 77 ambient air pollutant monitoring stations in the 14 above-mentioned cities, two of which served as controls (Figure 1). We obtained PM₁₀ concentrations monthly from the Environment Protection Bureau of each city. The exposure level was assessed using the mean concentration of PM₁₀ from all stations in the mother's city of residence. Then, the monthly means were connected to birth records through the mother's city of residence on the birth defects registration form. Finally, we evaluated the average PM₁₀ concentration value 3 months before and after conception, and in single months. The

first day of the last menstrual period was assumed as the day of conception, in agreement with a previous study, and we calculated the date of conception based on the date of birth and gestational age on the form. If the date of conception occurred in the first half of the month, then the month was considered to be the first month after pregnancy; otherwise, the month was considered as the first month before conception.

Statistical analysis

The categorical data are summarized as counts and percentages. The distribution of ambient PM₁₀ concentrations between cases and controls in each exposure window are depicted by the mean (standard deviation [SD]), median (interquartile range), and minimum and maximum to provide an overall view of the ambient air pollution features of the study areas. The differences in characteristics between cases and controls were calculated by a Chi-square test. A multivariable logistic regression model was used to calculate the odds ratios (ORs) and 95% confidence intervals (CIs) for the association between maternal PM₁₀ exposure and anorectal atresia/ stenosis risk in offspring. The ambient PM₁₀ level was calculated using tertile results according to the controls, and the lowest tertile was used as the reference. We also calculated the OR for each 10 µg/m³ increment or an increase equal to 1 SD of the distribution among the controls. The covariates included in the multivariable logistic regression model were as follows: maternal age (<20, 20–34, and ≥35 years); gravidity (<2 and ≥2); parity (0, 1, and ≥2); infant gender; season of conception [spring (March–May), summer (June–August), autumn (September–November), and winter (December–February)]; maternal education (elementary school or less, middle school, high school, and college or above); and sulfur dioxide and nitrogen dioxide exposure levels (continuous). We conducted a sensitivity analysis to reduce the heterogeneity between the studied individuals and calculated the actual effect of PM₁₀ on anorectal atresia/stenosis by propensity score matching [PSM] (Austin, 2011).

Matching was performed based on maternal age, maternal education, parity, infant gender, and season of conception. One-to-one nearest-neighbor matching without replacement was performed for estimated propensity scores using a caliper width set at 20% of the SD of the propensity scores. A standardized difference < 10% between cases and controls was considered negligible, and balance was assumed to be met.

All analyses were carried out using SAS (version 9.4; SAS Institute, Inc., Cary, NC, USA). Statistical significance was set at a $p < 0.05$ and based on a two-sided test.

Results

The population of our study consisted of 713 patients with anorectal atresia/stenosis (cases) and 7950 healthy controls in Liaoning Province from 2010–2015. Table 1 presents the characteristics of the selected cases and controls. Compared with the controls, the number of males with anorectal atresia/stenosis was significantly greater than the number of affected females. Furthermore, the birth weights and gestational ages of the patients with anorectal atresia/stenosis were significantly less than the healthy controls, and the mothers of affected patients were less well-educated and greater parity than

the mothers of healthy controls; however, the maternal age and gravidity between affected cases and healthy controls were not significantly different.

During the study period, Figure 2 presents the continuous fluctuation of the monthly PM₁₀ levels in Liaoning Province. The average level of PM₁₀ during the study period was 86 µg/m³, and the highest concentration of PM₁₀ was 150 µg/m³ in February 2015. The highest seasonal level occurred in the winter, while the lowest level was in the summer (Figure 3). Particulate air pollution in Shenyang City, the capital of Liaoning Province, was more serious than in the other 13 cities in Liaoning Province (Supplemental Figure 1). Furthermore, Table 2 shows the distribution of maternal PM₁₀ exposure concentrations in the affected cases, controls, and all subjects during different pregnancy periods.

We summarized the results of logistic regression analysis with and without adjusting for several confounders, mainly including maternal age, gravidity, parity, infant gender, season of conception, maternal education, and SO₂ and NO₂ exposure levels during the same period. There was an association between maternal exposure to the PM₁₀ concentration and anorectal atresia/stenosis in offspring risk 2 months prior to conception and during 2 months of pregnancy without adjusting any variables. Additionally, based on the multiple logistic regression model, a high level of maternal PM₁₀ exposure 3 months prior to conception was associated with an increased risk of anorectal atresia/stenosis in the analysis of high versus low tertiles (OR = 3.73; 95% CI = 2.52–5.53), and a continuous increase in exposure (per 10 µg/m³ increment: OR = 1.15, 95% CI = 1.03–1.20; per SD [27 µg/m³] increment: OR = 1.33, 95% CI = 1.09–1.63) was also evident. Furthermore, we analyzed the single months from the 3rd month before pregnancy to the 1st month before pregnancy; the results showed that maternal PM₁₀ exposure was positively associated with anorectal atresia/stenosis risk.

Positive associations with the aforementioned topic were also observed during the first trimester (OR T3 vs. T1 = 4.90; 95% CI = 3.23–7.42; per 10 µg/m³ increment: OR = 1.08, 95% CI = 1.00–1.17; per SD [28 µg/m³] increment: OR = 1.26, 95% CI = 1.01–1.57). Upon evaluation by shorter exposure windows (1 month), positive associations between anorectal atresia/stenosis and PM₁₀ were observed in each month of the first trimester. In addition, the effect estimate was highest in the second tertile (OR = 3.57, 95% CI = 2.62–4.86), whereas the effect estimate was attenuated in the third tertile at higher exposure levels in the second month of pregnancy (OR = 2.87, 95% CI = 1.99–4.15). Crude estimates were mostly similar to adjusted estimates for risk of anorectal atresia/stenosis.

Based on sensitivity analysis, we presented the 1:1 PSM to generate a more balanced sub-sample of 575 anorectal atresia/stenosis cases and 575 matched controls. As shown in Supplemental Table 1, the PSM process was repeated until the balance of the covariate distribution was reached. Among the PSM sub-sample, maternal exposure to PM₁₀ was still strongly related to the increased risk of anorectal atresia/stenosis prior to conception and during early pregnancy, whether exposure was treated as a categorical or continuous variable (Supplemental Table 2).

Discussion

We performed this large population-based case-control study to determine the association between maternal PM₁₀ exposure and anorectal atresia/stenosis in offspring in Liaoning Province. This is the first study to investigate aforementioned topic. The high anorectal deformity rate where the PM₁₀ concentration was rather high as well, enabled us to conclude that maternal exposure to PM₁₀ 3 months prior to conception and in the 1st trimester was associated with an increased risk of anorectal atresia/stenosis in offspring.

Recently, several studies have suggested that maternal air pollution exposure is associated with birth defects in offspring (Hu et al., 2020; Salavati et al., 2018). Notably, as a main component of air pollutants, additional studies showed that PM₁₀ plays a critical role with respect to birth defects. For example, Vinceti et al. (Vinceti et al., 2016) suggested that higher exposure to PM₁₀ increases the overall risk of birth defects. Anomaly categories suggested that the strongest dose-response associations with exposure to PM₁₀ were musculoskeletal and chromosomal abnormalities, such as Down syndrome (Vinceti et al., 2016). Additionally, Hu et al. (Hu et al., 2020) reported that maternal exposure to PM₁₀ increased the risk of selected subtypes of congenital heart defects in offspring. In addition, Zhang et al. (Zhang et al., 2020) reported that maternal exposure to PM₁₀ prior to conception and during the 1st trimester were related to increased risks of polydactyly and syndactyly in the offspring, suggesting that PM₁₀ has a teratogenic effect. Moreover, there are other studies that have shown that maternal exposure to PM₁₀ is related to birth defects, such as cleft lip with or without cleft palate (Zhang et al., 2020) and neural tube defects (Zhang et al., 2020). Compared with previous studies, our study suggested a teratogenic effect of PM₁₀ in offspring with anorectal atresia/stenosis. Therefore, evidence from these studies showed that pregnant women should avoid exposure to high levels of PM₁₀ because of the increased risk of several types of birth defects in offspring.

The exact physiopathology of anorectal atresia/stenosis remains unclear. Genetic factors are important contributing factors in the pathogenesis of anorectal atresia/stenosis. The development of the hindgut is governed by multiple genes in the relevant signaling pathways, and each gene may regulate organogenesis of the anorectal region at different stages of hindgut development. Specifically, cloacal septation depends on epithelial-to-mesenchymal signaling mediated by Shh signaling from endoderm in the early stage (Wang et al., 2015). The Bmp signaling pathway plays a critical role in mesoderm induction and patterning (Wang et al., 2015). Hox genes and Fgf signaling are also involved in the specification of each body part along the anteroposterior body axis during embryogenesis (Wang et al., 2015). In addition, Notch-1 and Jagged-2 have been shown to be involved in the maintenance and function of neuronal cells in the enteric nervous system (Wang et al., 2015). In addition these important genes, evidence suggests that environmental factors are also involved in the development of anorectal atresia/stenosis. How environmental factors influence the development of anorectal atresia/stenosis

remains largely unknown. Further studies are warranted to better understand the effect of environmental factors on the development of anorectal atresia/stenosis, including air pollutants.

The mechanisms underlying the developmental effects from PM exposure, especially PM₁₀, have yet to be fully understood; however, a few studies have suggested that the teratogenic effect of PM might be related to oxidative stress. Specifically, Massarsky et al. (Massarsky et al., 2015) examined the effects of total PM (TPM) on the early development of zebrafish, and showed that TPM increases mortality, delay hatching, and the incidence of deformities, and also affects biomarkers of xenobiotic metabolism and oxidative stress. Similarly, exposure to cigarette smoke in mice prior to conception induces oxidative stress and compromises embryonic development (Huang et al., 2009). At the molecular level, reactive oxygen species (ROS) overproduction induces oxidative stress, a state in which increased ROS generation overwhelms antioxidant protection and subsequently leads to oxidative damage of cellular macromolecules, including proteins, lipids, and nucleic acids (Jezek and Hlavata, 2005). Therefore, intervention strategies, such as antioxidant nutritional therapies, may contribute to embryonic and fetal development and neonatal growth, but further studies are warranted. In addition, angiogenesis and the embryonic movement (EM) pathway are also involved in the process of embryonic development. A study based on a chicken embryo model showed that TPM plays a vital role in endothelial cell proliferation, migration, tube formation, and sprouting, which are crucial factors in angiogenesis (Ejaz et al., 2009). Video recordings and kinematic analyses of TPM-exposed chicken embryos revealed a striking decrease in EM (Ejaz et al., 2009). These limited findings partly explain the mechanisms regarding PM and its teratogenic effect; however, more studies are needed to explore the exact molecular mechanisms between PM, especially PM₁₀ and birth defects, providing preventive strategies of birth defects for pregnant women.

Our study had several strengths. Notably, this is the first study to evaluate the potential association between maternal PM₁₀ exposure and anorectal atresia/stenosis in offspring. Additionally, our study used the Maternal and Child Health Certificate Registry of Liaoning Province, a large database accommodating data on birth defects for six consecutive years. The large number of birth records reduces random errors and increases statistical power in identifying any meaningful relationship. In addition, because teratogen exposure prior to pregnancy may also result in a higher risk of birth defects, we evaluated the potential effect between PM₁₀ and the risk of congenital atresia of the rectum and anus during the 3 months before pregnancy, and investigated the risk each month. Furthermore, because using birth defect controls may create selection bias if the exposure also causes other birth defects, we used unaffected live births as controls in our analysis.

Our study had limitations that necessitate cautious interpretation of the results. First, the air pollution exposure was measured using the average concentration of all monitoring stations in the city where each mother resided, which might not include the small regional variability of some air pollutants, which then compromised our exposure. A more accurate exposure assessment method is needed in future studies on the relationship between newborn defects and the effect of air pollution. For example, the land-use regression model, which takes transportation, population information, meteorologic factors, and

industrial emission into account (Schembari et al., 2014). We had no access to indoor or workplace air pollution levels, which limited the accuracy of exposure assessment. In addition, we estimated maternal air pollution exposures during the 3 months prior to conception and the 1st trimester based on the residential address at the time of delivery, whereas gravidas may have incurred a wider range of movement for work and recreation. A previous study suggested that the median distance of migration was < 10 kilometers (Bell and Belanger, 2012) and another study conducted in China reported that only 3.1% of pregnant women relocated during pregnancy (Jin et al., 2015). Consequently, movement is unlikely to affect the exposure estimation. Second, our data were abstracted from the birth registrations. Even though the patients with birth defects were recorded by active surveillance and rigorous quality control, potential defects, including underreported and misclassified congenital atresia of the rectum and anus are difficult to avoid, particularly in regions with limited medical resources (Zhang et al., 2017). Moreover, congenital atresia of the rectum and anus diagnoses were made at different levels of hospitals in Liaoning Province, where consistency and uniformity was difficult to guarantee in the case cohort. Third, certain information, such as maternal diet, income, occupation, and maternal smoking during pregnancy, were absent due to the specific characteristics of the registry data, which may compromise the reported relationship between maternal PM₁₀ exposure and congenital atresia of the rectum and anus. A previous study, however, suggested that when occupation, income, and maternal smoking were adjusted, the estimated effect changed by < 5% (Ritz et al., 2007). Finally, we failed to eliminate the influence of some different baseline characteristics completely using multivariate analysis with adjusted covariates. We used the PSM method to establish a balanced case-control subgroup. A significant positive association was also found in the PSM subjects; nevertheless, the result should be interpreted with caution because of the biases of control selection.

Conclusion

In conclusion, our study suggested that maternal exposure to PM₁₀ from 3 months prior to conception through the early trimester of pregnancy is associated with an increased risk of anorectal atresia/stenosis in offspring. Future studies should concentrate on more accurate calculation of maternal exposure to air pollutants and on the risk of anorectal atresia/stenosis in offspring. Corollary studies are warranted to explore the molecular mechanisms between PM, especially PM₁₀, and birth defects. Our study has critical public health implications; specifically, pregnant women should avoid air pollutants before conception and during the 1st trimester as much as possible.

Declarations

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Author Contribution

Tie-Ning Zhang: Writing-Original draft preparation. Qi-Jun Wu: Writing-Reviewing and Editing. Yan-Hong Huang: Conceptualization, Methodology. Jing Li: Data curation. Zong-Jiao Chen: Validation. Li-Li Li: Software. Yan-Ling Chen: Investigation. Shu Liu: Visualization. Cheng-Zhi Jiang: Software. Yu-Hong Zhao: Supervision.

Competing interests

The authors declare that they have no competing interests

Ethics approval

This study has been approved by the Institutional Review Board of Liaoning Women and Children's Health Hospital.

Consent to participate

Informed written consent was taken voluntarily from each eligible participant.

Consent to publication

Not applicable

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Tables

Table 1. Characteristics of controls and congenital atresia of rectum and anus cases in Liaoning Province, China, 2010-2015 [no. (%)].

Characteristic	Congenital atresia of rectum and anus (n = 713)	Controls (n = 7950)	P value
Maternal age, years			<i>P</i> = 0.06
<20	10 (1.4)	53 (0.7)	
20-34	627 (87.9)	6948 (87.4)	
≥35	76 (10.7)	949 (11.9)	
Gravidity			<i>P</i> = 0.40
<2	462 (64.8)	5026 (63.2)	
≥2	251 (35.2)	2924 (36.8)	
Parity			<i>P</i> < 0.01
0	11 (1.6)	5931 (74.6)	
1	570 (79.9)	1764 (22.2)	
≥2	132 (18.5)	255 (3.2)	
Sex of infant			<i>P</i> < 0.01
Male	480 (76.3)	4023 (50.6)	
Female	233 (32.7)	3927 (49.4)	
Gestational age, weeks			<i>P</i> < 0.01
<37	91 (12.8)	257 (3.2)	
≥37	622 (87.2)	7693 (96.8)	
Birth weight, grams			<i>P</i> < 0.01
<2500	81 (11.4)	174 (2.2)	
2500-<4000	593 (83.2)	6840 (86.0)	
≥4000	39 (5.4)	936 (11.8)	
Season of conception			<i>P</i> < 0.01
Spring	178 (25.0)	2106 (26.5)	
Summer	206 (28.9)	2829 (35.6)	
Autumn	208 (29.1)	1705 (21.4)	
Winter	121 (17.0)	1310 (16.5)	
Maternal education			<i>P</i> < 0.01

Elementary school or less	34 (4.8)	265 (3.3)
Middle school	291 (40.8)	2912 (36.6)
High school	223 (31.3)	1723 (21.7)
College or above	165 (23.1)	3050 (38.4)

Table 2. Distribution of ambient PM₁₀ concentrations (µg/m³) in congenital atresia of rectum and anus cases and controls during different gestation periods

Gestation periods	Mean	SD	Minimum	Median	IQR	Maximum
<i>The first month before pregnancy</i>						
All subjects	92	33	40	85	36	246
Controls	92	33	48	85	35	246
Congenital atresia of rectum and anus cases	97	33	40	88	44	246
<i>The second month before pregnancy</i>						
All subjects	93	32	36	85	36	246
Controls	93	32	46	85	36	246
Congenital atresia of rectum and anus cases	96	32	36	89	41	246
<i>The third month before pregnancy</i>						
All subjects	93	31	34	87	37	246
Controls	93	31	46	86	37	246
Congenital atresia of rectum and anus cases	94	31	34	89	35	246
<i>The three months before pregnancy</i>						
All subjects	93	27	40	89	30	178
Controls	93	27	49	89	30	177
Congenital atresia of rectum and anus cases	95	26	40	91	31	178

Table 2 continued

Gestation periods	Mean	SD	Minimum	Median	IQR	Maximum
<i>The first month of pregnancy</i>						
All subjects	91	33	44	83	37	246
Controls	90	33	48	82	38	246
Congenital atresia of rectum and anus cases	96	34	44	87	38	246
<i>The second month of pregnancy</i>						
All subjects	91	34	36	82	37	246
Controls	91	34	48	82	36	246
Congenital atresia of rectum and anus cases	96	33	36	87	38	246
<i>The third month of pregnancy</i>						
All subjects	93	33	40	83	37	246
Controls	93	34	40	83	38	246
Congenital atresia of rectum and anus cases	94	31	40	87	35	246
<i>The first trimester</i>						
All subjects	92	28	40	87	38	177
Controls	91	28	52	87	38	177
Congenital atresia of rectum and anus cases	95	27	40	90	30	177

Abbreviations: PM₁₀, particulate matter with an aerodynamic diameter ≤ 10 µm; SD, standard deviation; IQR, interquartile range.

Table 3 The associations between maternal exposure to ambient PM₁₀ during different study periods and congenital atresia of rectum and anus in offspring

Tertile of PM ₁₀ level ^a	Number of cases /controls	OR (95%CI) ^b	OR (95%CI) ^c	Tertile of PM ₁₀ level ^a	Number of cases /controls	OR (95%CI) ^b	OR (95%CI) ^c
Pre-pregnancy				Prophase of pregnancy			
The first month before pregnancy				The first month of pregnancy			
<75	194/2471	1.00	1.00	<72	160/2562	1.00	1.00
75 to <98	230/2808	1.04 (0.86-1.27)	1.90 (1.41-2.55)	72 to <95	263/2692	1.56 (1.28-1.92)	2.81 (2.07-3.83)
≥98	289/2671	1.38 (1.14-1.67)	3.13 (2.15-4.55)	≥95	290/2696	1.72 (1.41-2.11)	2.90 (2.01-4.19)
Per 10 µg/m ³ increase		1.04 (1.01-1.06)	1.09 (1.03-1.15)	Per 10 µg/m ³ increase		1.04 (1.02-1.07)	1.08 (1.02-1.14)
Per 1-SD increase		1.13 (1.05-1.21)	1.33 (1.11-1.58)	Per 1-SD increase		1.15 (1.07-1.23)	1.27 (1.07-1.52)
The second month before pregnancy				The second month of pregnancy			
<77	221/2590	1.00	1.00	<72	159/2583	1.00	1.00
77 to <100	228/2637	1.01 (0.84-1.23)	1.58 (1.18-2.11)	72 to <95	257/2692	1.55 (1.26-1.90)	3.57 (2.62-4.86)
≥100	264/2723	1.14 (0.94-1.37)	3.04 (2.10-4.40)	≥95	297/2675	1.80 (1.48-2.20)	2.87 (1.99-4.15)
Per 10 µg/m ³ increase		1.03 (1.00-1.05)	1.12 (1.06-1.18)	Per 10 µg/m ³ increase		1.04 (1.02-1.06)	1.08 (1.02-1.14)
Per 1-SD increase		1.08 (1.01-1.17)	1.42 (1.19-1.70)	Per 1-SD increase		1.13 (1.06-1.22)	1.29 (1.07-1.54)

Table 3 continued

Tertile of PM ₁₀ level ^a	Number of cases /controls	OR (95%CI) ^b	OR (95%CI) ^c	Tertile of PM ₁₀ level ^a	Number of cases /controls	OR (95%CI) ^b	OR (95%CI) ^c
Pre-pregnancy				Prophase of pregnancy			
The third month before pregnancy				The third month of pregnancy			
<79	261/2636	1.00	1.00	<74	198/2574	1.00	1.00
79 to <100	193/2578	0.76 (0.62-0.92)	1.04 (0.78-1.38)	74 to <99	282/2716	1.35 (1.12-1.63)	2.18 (1.63-2.93)
≥100	259/2736	0.96 (0.80-1.15)	1.90 (1.32-2.75)	≥99	233/2660	1.14 (0.94-1.39)	2.53 (1.71-3.72)
Per 10 µg/m ³ increase		1.01 (0.99-1.04)	1.08 (1.02-1.15)	Per 10 µg/m ³ increase		1.01 (0.98-1.03)	1.09 (1.04-1.15)
Per 1-SD increase		1.04 (0.97-1.12)	1.28 (1.07-1.53)	Per 1-SD increase		1.02 (0.94-1.10)	1.35 (1.13-1.62)
The three months before pregnancy				The first trimester			
<80	216/2738	1.00	1.00	<76	162/2648	1.00	1.00
80 to <100	216/2497	1.10 (0.90-1.33)	1.95 (1.44-2.63)	76 to <97	275/2636	1.71 (1.39-2.09)	3.47 (2.54-4.73)
≥100	281/2715	1.31 (1.09-1.58)	3.73 (2.52-5.53)	≥97	276/2666	1.69 (1.38-2.07)	4.90 (3.23-7.42)
Per 10 µg/m ³ increase		1.04 (1.01-1.07)	1.15 (1.03-1.20)	Per 10 µg/m ³ increase		1.04 (1.01-1.07)	1.08 (1.00-1.17)
Per 1-SD increase		1.10 (1.03-1.19)	1.33 (1.09-1.63)	Per 1-SD increase		1.12 (1.04-1.21)	1.26 (1.01-1.57)

Abbreviations: CI: confidence intervals, OR: odds ratio, PM₁₀: particulate matter with an aerodynamic diameter ≤ 10 µm; SD: standard deviation.

^a PM₁₀ levels (µg/m³) are based on 24 h average measurements, which are then averaged over different periods of pregnancy and analyzed in tertiles (determined from controls).

^b The OR (95%CI) was used to test the odds ratio of the cases exposure to PM₁₀ in different prophase of pregnancy in the simple logistic regression model..

^c The OR (95%CI) was used to test the odds ratio of the cases exposure to PM₁₀ in different prophase of pregnancy in the binary logistic regression model adjusted for confounding factors of maternal age, gravidity, parity, sex of infant, season of conception, maternal education, and sulfur dioxide and nitrogen dioxide exposure levels during the same period.

Figures

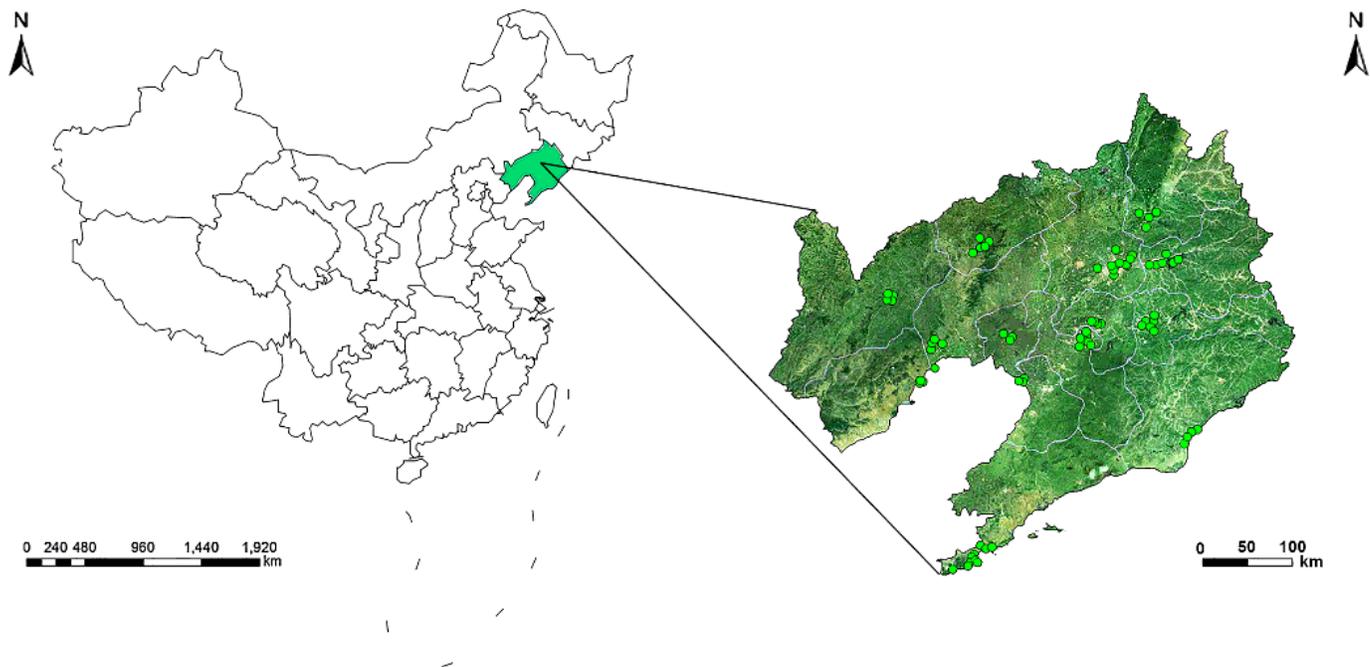


Figure 1

Geographic locations of air monitoring stations in 14 cities in Liaoning Province, China. Note: The designations employed and the presentation of the material on this map do not imply the expression of any opinion whatsoever on the part of Research Square concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. This map has been provided by the authors.

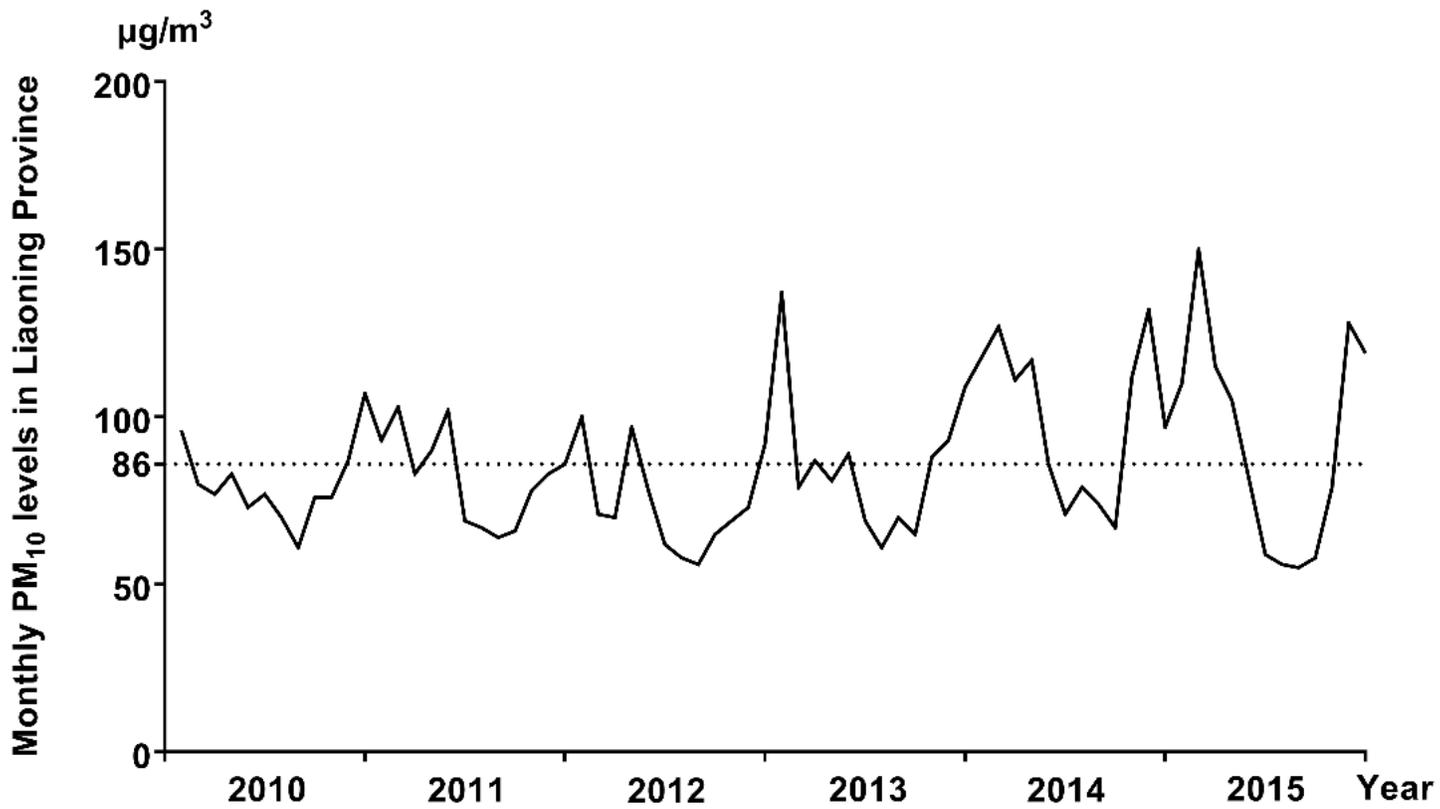


Figure 2

Monthly mean PM10 levels in Liaoning Province, China, during 2010-2015.

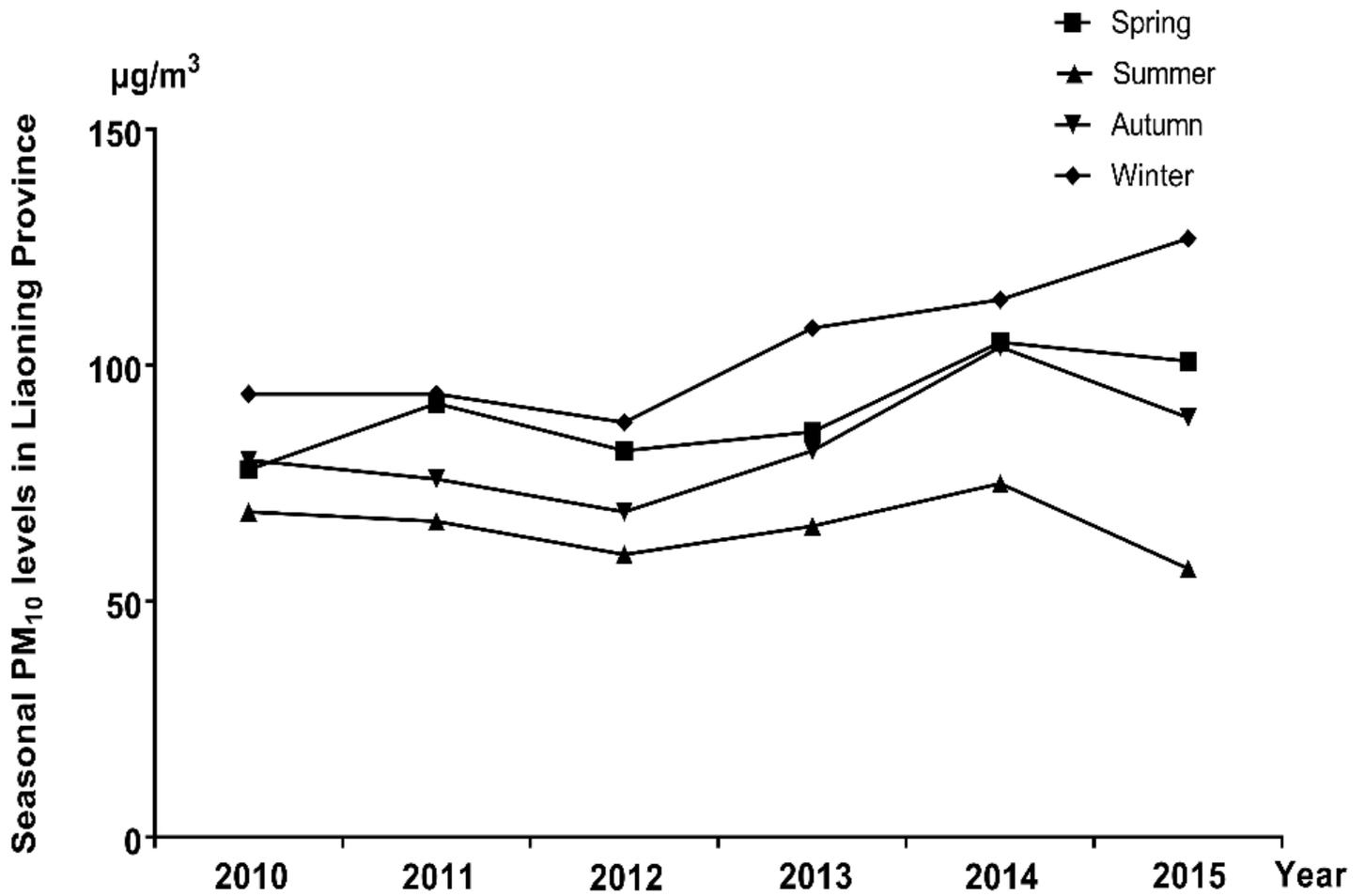


Figure 3

Seasonal mean PM10 levels in Liaoning Province, China, during 2010-2015.

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