Periconception Exposure to Air Pollution and Risk of Congenital Malformations

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Objective To evaluate the association between increased exposure to airborne fine particulate matter ($PM_{2.5}$) during the periconception period with risk of congenital anomalies.

Study design Using birth certificate data from the Ohio Department of Health (2006-2010) and $PM_{2.5}$ data from the US Environmental Protection Agency's 57 monitoring stations located throughout Ohio, the geographic coordinates of the mother's residence for each birth were linked to the nearest $PM_{2.5}$ monitoring station and monthly exposure averages were calculated. The association between congenital anomalies and increased $PM_{2.5}$ levels was estimated, with adjustment for coexistent risk factors.

Results After adjustment for coexisting risk factors, exposure to increased levels of $PM_{2.5}$ in the air during the periconception period was modestly associated with risk of congenital anomalies. Compared with other periconception exposure windows, increased exposure during the 1 month before conception was associated with the highest risk increase at lesser distances from monitoring stations. The strongest influences of $PM_{2.5}$ on individual malformations were found with abdominal wall defects and hypospadias, especially during the 1-month preconception.

Conclusions Increased exposure to $PM_{2.5}$ in the periconception period is associated with some modest risk increases for congenital malformations. The most susceptible time of exposure appears to be the 1 month before and after conception. Although the increased risk with $PM_{2.5}$ exposure is modest, the potential impact on a population basis is noteworthy because all pregnant women have some degree of exposure. *(J Pediatr 2017;■■:■■-■■).*

Congenital malformations are among the most serious complications of pregnancy, affecting 3% of all births in the US.[1] The spectrum of birth defects is wide, ranging from minor anomalies having no adverse health effects to severe major malformations that result in death. As a group, congenital anomalies are a leading cause of infant mortality in the US.[1]

Although some specific malformations have a clear cause–effect relationship with periconception exposure such as poor glycemic control in diabetics and the caudal regression syndrome or thalidomide and limb reduction anomalies, most congenital anomalies have no known singular teratogenic etiology.[2] Considering that embryonic maldevelopment leading to congenital anomalies is a multifactorial disease process, investigators have become increasingly interested in the contribution of modifiable risk factors such as exposure to environmental pollutants. Prior studies that have indicated the possible association of particulate matter (PM) with birth defects, have been limited by inconsistency in definitions of high exposure levels, geographic measures of exposure, and timing of high exposure assignment.[3-12] Inconsistent definitions of high exposure levels not only lead to inconsistent findings, but also introduce bias into the estimates of ORs by improperly dichotomizing $PM_{2.5}$ exposure.[13] The majority of prior studies on PM exposure examined coarse particles (aerodynamic diameter of ≤10 μg/m^3 [PM_{10}]), which can be inhaled and accumulate in the respiratory system. Fine particles, $PM_{2.5}$ (aerodynamic diameter of <2.5 μg/m^3) are believed to be a more significant health hazard because they can deposit deep into lower airways and alveoli within the lungs, and subsequently enter the systemic circulation.[14] However, findings from studies examining $PM_{2.5}$ on congenital anomaly risk have been inconsistent showing minor associations with a few individual anomalies or no effect.[3,6,7,10-12,15]

Because embryonic development occurs in the first trimester of pregnancy, the timing between an exposure and maldevelopment, assuming a true cause–effect relationship, must occur either before conception or in the early first trimester of pregnancy. Prior studies of $PM_{2.5}$ have limited the exposure period studied to a small window during the early first trimester only, and did not investigate

$PM_{2.5}$	Particular matter
QIC	Quasi-Akaike information criterion

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exposure in the months preceding conception.[3,6,7,10,11,15] In this study, we aim to describe the association between exposure to airborne fine particle pollution, $PM_{2.5}$, in a month-by-month fashion examining the time extending from 2 months before and through 2 months after conception with risk of congenital malformations. We also explore exposure–outcome associations by varying the cutoff values of geographic distance from monitoring station.

Methods

We developed a geospatial, population-based cohort study using Ohio Department of Health live birth records. The Ohio Department of Health and Human Subjects Institutional Review Board approved a protocol for this study. This study was exempt from review by the Institutional Review Board at the University of Cincinnati, Cincinnati, Ohio. A dataset generated from vital records of all live births that occurred in the state from 2006 to 2010 was provided for this analysis. We analyzed live births to women whose residential address was within a defined distance threshold of their nearest $PM_{2.5}$ monitor. A detailed description of the study population is illustrated in **Figure 1**.

Births with recorded Down syndrome or other suspected chromosomal disorder (pending or confirmed)[16,17] were not included in the primary analysis; however, they were examined as individual outcomes and also included in a separate sensitivity analysis.

Exposure values from central monitoring stations were used to estimate personal exposure levels of births during the study period. As there has been no clearly defined optimal distance cutoff to estimate exposure values related to a stationary monitor, we analyzed outcomes using multiple distances including residential address perimeters of 5, 7, and 10 km from monitoring station.[6,8,16,18,19]

$PM_{2.5}$ Exposure Assessment

$PM_{2.5}$ levels were measured daily during the study period (2005-2010) by 57 US Environmental Protection Agency stationary monitors across Ohio, and from this monthly averages were calculated.[20] The monthly averages were linked to Ohio birth records using the location of maternal residences.[21] We assigned the monthly average values of $PM_{2.5}$ to each birth for 5 different monthly time periods: 1 and 2 months before and after conception, and the month of conception, linking data from the nearest monitoring stations using ArcGIS 10.1 soft-

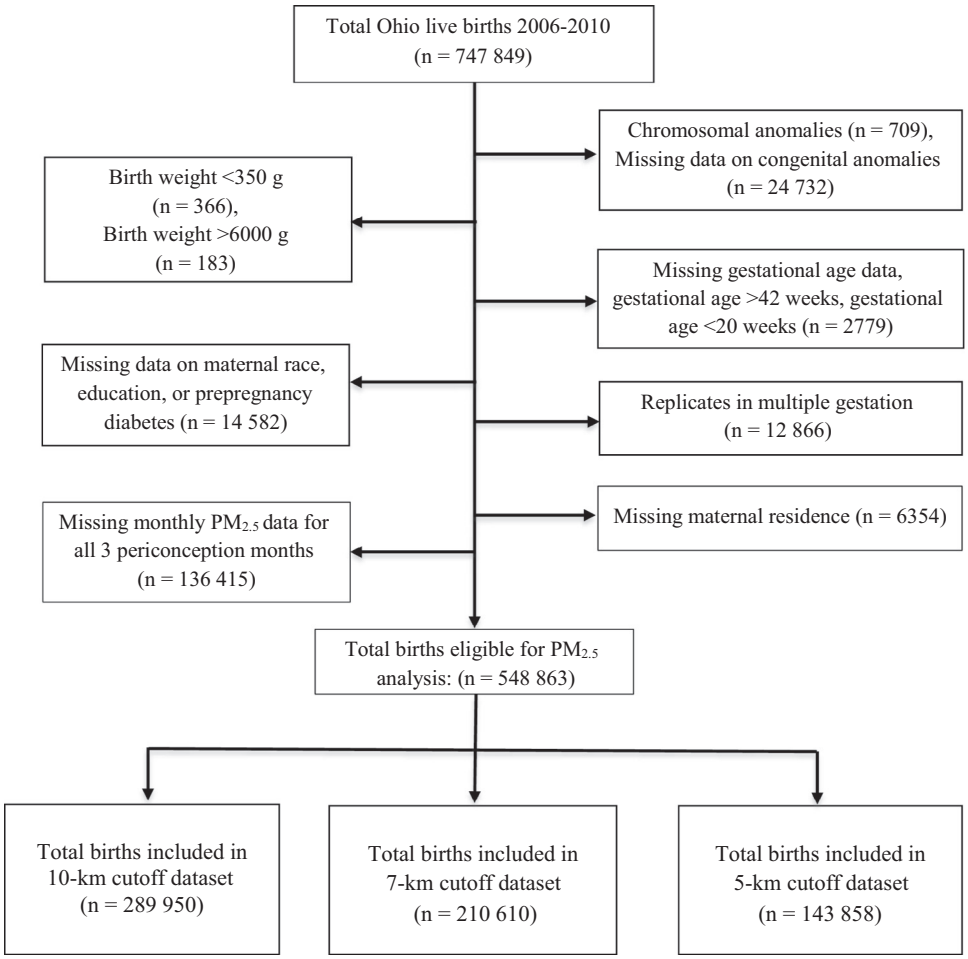

Figure 1. Flow diagram of the study population.

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ware (ESRI, Redlands, Calif). These periconception time periods were calculated based on the gestational age at birth recorded in the birth certificate. There is no standard for the definition of "high exposure" in studies using stationary monitor exposure data for birth outcome.[16] Dichotomizing exposure values may be problematic and may introduce bias into the estimates of ORs.[13] Therefore, in our study, we treated $PM_{2.5}$ exposure as a continuous variable, and reported ORs in both per IQR and per 10 $\mu g/m^3$ increase.

The primary outcome was major congenital anomaly at birth, as recorded on the 2003 version of the US birth certificate. Congenital anomaly of a newborn is recorded in the US standard certificate of live birth in a standardized manner. Strict criteria for the definition of each congenital anomaly are outlined in the Guide to Completing The Facility Worksheets for the Certificate of Live Birth and Report of Fetal Death (2003 revision), from the National Center for Health Statistics.[22] The presence of a major congenital anomaly in this study was defined as the presence of 1 or more of those reported anomalies. The frequency of the primary outcome of any congenital anomaly and the secondary outcomes of individual congenital anomalies were calculated.

Statistical Analyses

The frequency of individual congenital anomalies recorded on the live birth certificate within the defined areas of study, stratified by distance cutoff from monitor (5, 7, and 10 km) were calculated. Baseline maternal and delivery characteristics were compared between the outcome group with congenital anomalies and the referent group of births with no anomaly, with *P* value reported for χ^2 test comparisons for the 10- km cutoff dataset (n = 289 950). Rates of congenital anomalies among each baseline characteristic are reported as number of anomaly cases per 1000 live births. Summary statistics of $PM_{2.5}$ levels were then calculated for births with congenital anomalies and those with no anomalies, stratified by month of exposure. No adjustment for multiple comparisons is preferable in this type of observational study because it leads to fewer errors of interpretation and allows for detection of natural observations of association.[23]

We used binomial regression with logistic link to analyze the association between congenital anomalies and $PM_{2.5}$ exposures. Considering the spatial correlation of subjects sharing the same monitoring station, the use of a marginal model for this study is suitable. We used generalized estimating equations with an exchangeable correlation structure to account for spatial correlation of subjects sharing the same $PM_{2.5}$ monitor.[24] Estimates of association were adjusted for the confounding effects of maternal and newborn factors. After model selection criteria described elsewhere in this article, some of those individual covariates were removed from the final adjusted model.

To assess the influence of time of $PM_{2.5}$ exposure on the primary outcome of any congenital anomaly, we stratified the exposure–outcome adjusted analyses by multiple time periods during the periconception period: 1 and 2 months before and after conception, the month of conception, and the average of 3 periconception months. To provide a more comprehensive description of the influence of $PM_{2.5}$ exposure on specific organ systems, analyses were repeated for the secondary outcomes of individual anomalies grouped by organ systems. Results are reported as aOR with 95% CI. Displaying the association as ORs with CI provides more information with regard to the direction of effect and effect size compared with just presenting association with *P* values, and also avoids the need of complicated multiple testing adjustment methods for the *P* values, because they are highly correlated.[25]

The following rules were considered in model selection. (1) Biological plausibility: Based on previously published data[8,11,26] as well as known factors associated with congenital anomalies, we included some covariates in our adjusted models based on their biological plausibility, rather than selection by small *P* value or "best" fit under a model selection rule. Such variables included maternal age, race, smoking status, season of conception, and prepregnancy diabetes. (2) Quasi-Akaike information criterion (QIC): The QIC is a model fitting criteria for generalized linear models using generalized estimating equations.[27] Models with lower QIC values were favored as they represent better model fit. (3) Covariate set selection for consistent adjustment in multiple analyses. Owing to the varying quantity of missing data or observations in the multiple stratified analysis using different distance cutoffs and time periods of exposure, a single consistent set of covariates was chosen for all adjusted analyses rather than model-specific covariate sets selected for each individual analysis.

Final models were constructed incorporating a group of covariates selected based on biological plausibility and low QIC. The final models included the following covariates: maternal age (coded as categorical variables with 3 levels: less than 18, 19-34, and greater than 34 years of age),[14] race/ethnicity (Hispanic, non-Hispanic white, non-Hispanic black, and non-Hispanic others), prepregnancy diabetes, smoking status, marital status, educational level (coded as categorical variables with 3 levels: less than high school, high school graduate, and post-secondary education), season of conception, and infant sex.

We performed sensitivity analyses modeling smoking in pregnancy as average number of cigarette smoked during the immediate preconception period as a categorical variable composed of 4 groups: non-smokers, 1-9 cigarettes per day, 10-19 cigarettes per day, and more than 20 cigarettes smoked per day. In addition, we performed sensitivity analyses measuring the association between the $PM_{2.5}$ and congenital anomalies by including and excluding genetic abnormalities in the outcome analyses.

Results

The locations of congenital anomaly cases, $PM_{2.5}$ monitors, and the buffer regions representing 5- and 10-km circumferences around monitoring stations in Ohio are demonstrated in **Figure 2**. The relationship of monitoring stations, congenital anomaly cases, and density by county in Ohio are further represented in **Figure 3** (available at www.jpeds.com). Some of

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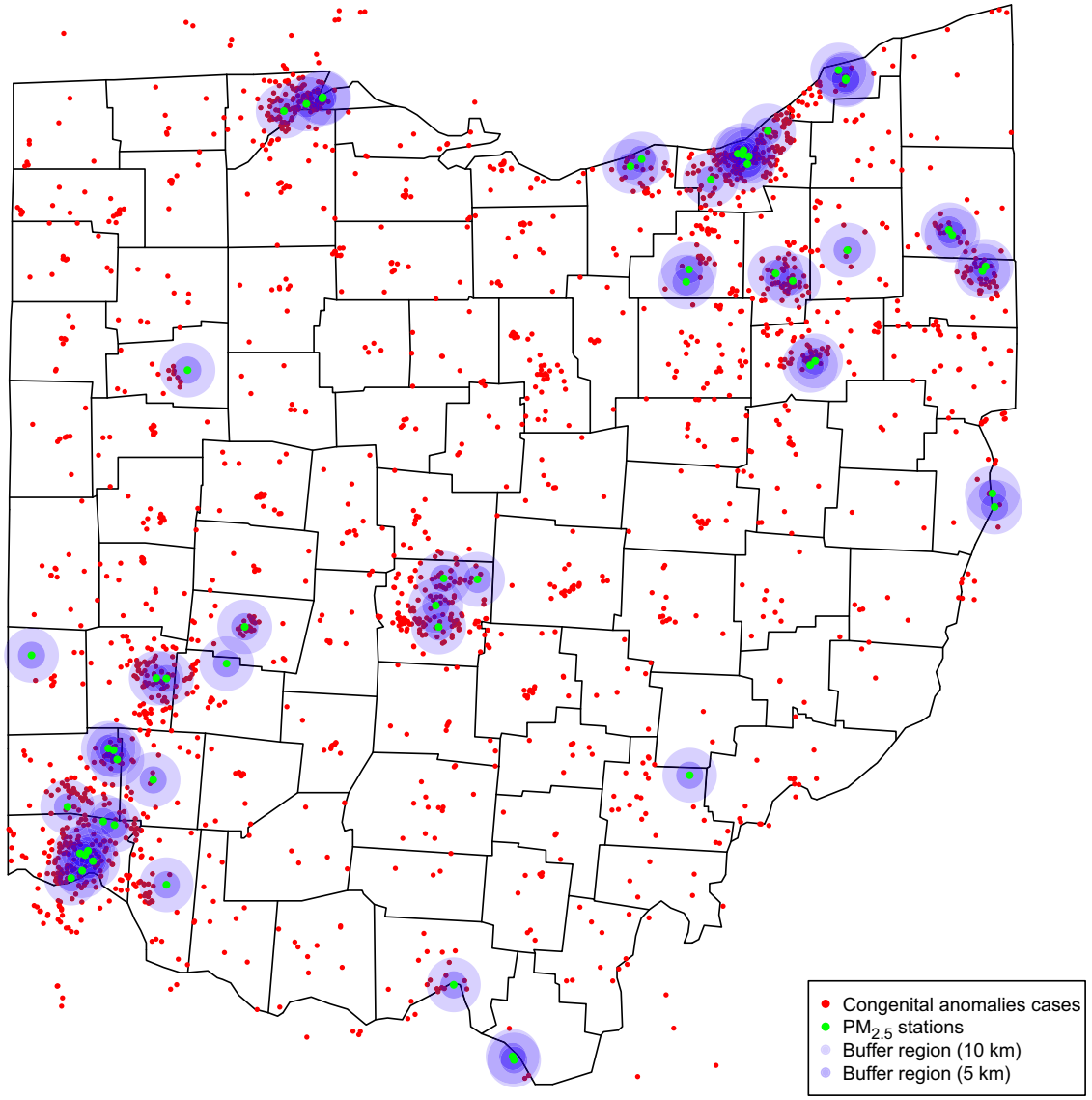

Figure 2. Maternal residence of congenital anomalies cases, locations of monitor stations, and their buffer regions. *Red dots* denote congenital anomalies cases, *green dots* denote the locations of monitor stations, 5- and 10-km buffer regions were indicated by *darker and lighter purple circles*.

the most densely populated counties have the highest number of congenital anomalies cases (**Figure 3**, A); however, they have a relatively low frequency of congenital anomalies based on high birth density within the county (**Figure 3**, B). Likewise, some counties with low birth density have higher rates of congenital anomalies.

The frequency of congenital anomalies that occurred within the 3 specified distance cutoffs are presented in **Table I** (available at www.jpeds.com). The most common anomaly was cleft lip/palate, followed by abdominal wall defects. Differences in maternal demographic and pregnancy characteristics between the outcome group with congenital anomalies and the referent group of births with no anomaly are presented in **Table II** (available at www.jpeds.com). Births complicated by congenital anomalies occurred more commonly in young mothers 18 years of age or younger, non-Hispanic white mothers, those with low educational attainment, and those of low socioeconomic status (as measured by use of Medicaid insurance). Cigarette smoking and prepregnancy diabetes were also significantly associated with presence of congenital anomalies. The rate of congenital anomalies was highest among pregnancies complicated by pregestational diabetes, at 7.1 cases per 1000 live births. Anomalies occurred slightly more frequently in the earlier years of study (2006 and 2007), and in births during the summer and fall seasons.

The mean $PM_{2.5}$ level during the periconception period for the study population was 13.79 $\mu g/m^3$ among the 10-km cohort, which was slightly lower than Environmental Protection Agency standard during the study period of 15 $\mu g/m^3$, but higher than the current standard of 12 $\mu g/m^3$.[28] Births with any congeni-

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Table III. Summary statistics of $PM_{2.5}$ levels in Ohio, 2006-2010, stratified by different distance cohorts and periconception exposure periods*

Datasets by exposure periods ($PM_{2.5}$ level)	Congenital Anomalies		Normal		*P* value‡
	Mean (SD)	IQR (Q1, Q3)	Mean (SD)	IQR (Q1, Q3)	
10 km					
2 months before	13.93 (3.97)	4.54 (11.28, 15.82)	13.86 (3.84)	4.95 (11.08, 16.03)	.59
1 month before	13.97 (4.00)	5.02 (11.10, 16.13)	13.77 (3.79)	4.83 (11.04, 15.87)	.16
Month of conception	13.85 (3.94)	5.27 (10.99, 16.26)	13.75 (3.83)	4.88 (10.99, 15.87)	.44
Average of 3 months†	13.92 (2.90)	3.73 (11.85, 15.57)	13.79 (2.77)	3.50 (11.86, 15.36)	.23
1 month after conception	13.99 (3.82)	5.40 (11.00, 16.40)	13.65 (3.80)	4.90 (10.90, 15.80)	**.02**
2 months after conception	13.58 (3.87)	5.30(10.60, 15.90)	13.43 (3.70)	4.90 (10.70, 15.60)	.27
7 km					
2 months before	13.92 (3.95)	4.70 (11.12, 15.82)	13.91 (3.85)	4.95 (11.13, 16.08)	.94
1 month before	14.13 (4.01)	5.14 (11.37, 16.51)	13.81 (3.79)	4.84 (11.10, 15.94)	**.04**
Month of conception	13.92 (4.00)	5.24 (11.13, 16.37)	13.79 (3.83)	4.92 (11.02, 15.94)	.40
Average of 3 months†	13.99 (2.90)	3.75 (11.92, 15.67)	13.84 (2.77)	3.52 (11.89, 15.41)	.21
1 month after conception	13.98 (3.79)	5.40 (11.10, 16.40)	13.65 (3.80)	4.90 (10.90, 15.80)	**.04**
2 months after conception	13.64 (4.01)	5.40 (10.60, 15.90)	13.43 (3.70)	4.90 (10.70, 15.60)	.19
5 km					
2 months before	14.07 (3.94)	4.94 (11.34, 16.28)	13.92 (3.84)	4.97 (11.14, 16.11)	.44
1 month before	14.23 (3.89)	5.13 (11.52, 16.65)	13.81 (3.77)	4.87 (11.12, 15.99)	.03
Month of conception	13.89 (3.97)	5.12 (11.21, 16.32)	13.81 (3.82)	4.96 (11.04, 16.00)	.67
Average of 3 months†	14.07 (2.86)	3.84 (11.88, 15.72)	13.85 (2.76)	3.54 (11.90, 15.44)	.12
1 month after conception	13.77 (3.81)	5.50 (10.90, 16.40)	13.65 (3.80)	4.90 (10.90, 15.80)	.55
2 months after conception	13.64 (3.99)	5.00 (10.70, 15.70)	13.43 (3.70)	4.90 (10.70, 15.60)	.30

P values <.05 are indicated in bold.
$PM_{2.5}$ levels are expressed in micrograms per cubic meter ($\mu g/m^3$); Q1/Q3, lower/upper quartile.
*Local $PM_{2.5}$ level for each subject is assigned by the nearest monitoring station during that time period. This table shows the summary statistics of population average of local $PM_{2.5}$ using this assignment (estimation) method.
†Average of 3 months = 2 months before conception, 1 month before conception, and the month of conception.
‡*P* values were calculated using the 2-sample *t* test.

tal anomaly had a higher mean $PM_{2.5}$ exposure level compared with nonanomalous births across all periconception months and within each distance cohort. Table III demonstrates the mean $PM_{2.5}$ levels in pregnancies complicated by congenital anomalies compared with births with no anomaly, stratified by periconception month of exposure and distance from the monitoring station.

The association between $PM_{2.5}$ exposure and congenital anomalies during each periconception period is displayed in Table IV as adjusted ORs with 95% CI for each distance cutoff

Table IV. aOR and corresponding 95% CI for the association of any congenital anomaly and $PM_{2.5}$ levels, stratified by different distance cohorts and periconception exposure periods*

Datasets by exposure periods	No. of cases	No. of total subjects	Continuous (per IQR increment)	Continuous (per 10 $\mu m/m^3$ increment)
10 km				
2 months before	782	287 862	1.00 (0.89-1.13)	1.01 (0.80-1.27)
1 month before	779	287 283	1.06 (0.96-1.18)	1.14 (0.92-1.41)
Month of conception	773	286 566	1.02 (0.92-1.13)	1.05 (0.85-1.29)
Average of 3 months†	779	287 412	1.04 (0.92-1.18)	1.13 (0.80-1.59)
1 month after	759	285 842	**1.09 (1.01-1.18)**	**1.19 (1.02-1.40)**
2 months after	759	285 421	1.02 (0.95-1.10)	1.05 (0.91-1.22)
7 km				
2 months before	583	209 007	0.99 (0.88-1.11)	1.00 (0.81-1.25)
1 month before	580	208 609	1.11 (0.98-1.25)	1.24 (0.97-1.58)
Month of conception	577	208 100	1.03 (0.93-1.15)	1.07 (0.86-1.32)
Average of 3 months†	580	208 703	1.06 (0.93-1.20)	1.18 (0.82-1.68)
1 months after	565	206 868	**1.09 (1.00-1.20)**	**1.20 (1.00-1.44)**
2 months after	566	206 565	1.06 (0.97-1.17)	1.13 (0.94-1.37)
5 km				
2 months before	397	142 626	1.04 (0.93-1.17)	1.09 (0.87-1.36)
1 month before	393	142 349	**1.17 (1.03-1.34)**	**1.39 (1.05-1.83)**
Month of conception	392	141 981	1.03 (0.90-1.17)	1.05 (0.82-1.36)
Average of 3 months†	393	142 424	1.12 (0.99-1.27)	1.38 (0.97-1.97)
1 months after	393	141 540	1.02 (0.90-1.15)	1.04 (0.81-1.34)
2 months after	393	141 381	1.05 (0.91-1.20)	1.09 (0.83-1.45)

Statistically significant results with lower bound of 95% confidence interval >1.0 are indicated in bold.
*Births with a chromosome disorder were not included in these analyses.
†Average of 3 months = 2 months before conception, 1 month before conception, and the month of conception.

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(10, 7, and 5 km). We reported the adjusted odds for congenital anomalies associated with $PM_{2.5}$ exposure in 2 ways: continuous exposure level (per IQR increment) and (continuous exposure level [per 10 μg/m^3 increase]) for each period. Comparison of results between the 3 distance cutoff models shown in **Table IV** allows for examination of consistency or inconsistency of findings based on distance from the monitoring station exposure assessment. Of all the time periods and distance cutoffs under investigation, nearly all point estimates of effect demonstrate an OR of greater than 1. However, only several of the associations reached statistical significance with lower limit of the 95% CI of greater than 1. These modeling results are also consistent with the unadjusted comparisons shown in **Table III**.

We found that increasing $PM_{2.5}$ exposure levels occurring 1 month before conception consistently demonstrated the highest aOR point estimates and corresponding 95% CI lower bounds among all 3 preconception time windows from the 10-km model to the 5-km model. In addition, this finding shown in **Table IV** is consistent with unadjusted descriptive results in **Table III**, which implies that this association cannot be explained by factors adjusted in the models. Therefore, these results suggest that compared with other preconception periods, increasing $PM_{2.5}$ exposure during the 1 month before conception is more likely to be associated with increasing risk of congenital anomalies.

We also assessed the inconsistency of results between the 3 distance cutoff models shown in **Table IV**. First, increasing $PM_{2.5}$ exposure 1 month after conception exposure was significantly associated with congenital anomalies in the 10-km and 7-km models, but not in the smaller 5-km model. Second, the association between $PM_{2.5}$ exposure 1 month before conception is only significant at 5% significance level for the 5-km model; however, this association became stronger with smaller distance cutoffs from the 10-km cohort to the 5-km cohort (**Tables III** and **IV**). Our findings demonstrate some evidence of spatial variability of $PM_{2.5}$ exposure within the 10-km cutoff, considering some inconsistency of results compared with more narrow distance cutoff cohorts.

Secondary Outcomes: Individual Congenital Anomalies

Tables V, VI, and **VII** (available at www.jpeds.com) demonstrate the association of $PM_{2.5}$ exposure with individual anomalies, grouped by organ system.[16] Considering the small number of cases for each individual anomaly, the CIs shown in these tables are comparatively wider than those in **Table IV** among each distance cutoff. The small sample size in these individual comparisons limits the ability to draw significant conclusions from these analyses. However, stratifying the analyses by individual anomalies in an exploratory manner does highlight several specific organ systems associated with $PM_{2.5}$, such as urogenital and gastrointestinal organ systems, which may be useful for hypothesis generation and validation in larger analyses. The interpretation of modeling results for anomalies with a small number of cases may also be limited owing to model overfitting, if considering a general practice of having at least 10 cases per 1 covariate variable. Overfitting with a high ratio of covariates to cases may lead to less reliable risk estimates and exaggerated CIs. For anomalies with a larger number of cases, such as abdominal defects, neural tube defects, and cleft lip or cleft palate, the results should be more reliable.

The primary adjusted models presented in this study used the covariate cigarette smoking as a dichotomous yes/no (1, 0) variable. In sensitivity analyses, we modeled average number of cigarettes smoked per day as a categorical covariate rather than dichotomous, which resulted in findings consistent with our initial results (**Table IV**). We also performed sensitivity analyses considering the influence of genetic disorders.

Most prior published studies examining the association of $PM_{2.5}$ with congenital anomalies excluded cases of chromosome disorders. Considering the possibility that chromosome disorders could be on the causal pathway of $PM_{2.5}$ exposure and congenital anomalies, we performed sensitivity analysis including and excluding live births with chromosome disorders as recorded on the US birth certificate for the study population. The primary results excluding chromosome disorders are displayed in **Table IV**, as described previously. For sensitivity analyses, first we examined the association of births complicated by chromosome disorders (Down syndrome or other, karyotype confirmed or pending) with $PM_{2.5}$ exposure. This initial sensitivity analysis included only cases with chromosome disorders, in the absence of other congenital anomalies. As shown in **Tables V-VII**, we found no risk increase of chromosome disorders with $PM_{2.5}$ exposure. Then, we analyzed the association between $PM_{2.5}$ and congenital anomalies including cases with chromosome disorders. We found that, after including the chromosome disorder subjects in the analysis, no risk increases were observed at any periconception periods (data not shown). However, the trends persisted, with higher point estimate and 95% CI lower bounds at 1 month before conception than other periconception time periods. Given the lack of a significant association between $PM_{2.5}$ and chromosome disorders demonstrated in these analyses, we prefer to model the analyses excluding births complicated by chromosome disorders (results as demonstrated in **Table IV**).

Discussion

We found that exposure to increasing levels of $PM_{2.5}$ in the air during some critical periods during the periconception period may be associated with a modest increased risk of a major congenital anomaly, even after adjustment for confounding influences of other factors associated with malformation risk. The association with $PM_{2.5}$ exposure during the other time periods, either earlier or later, was nonsignificant, suggesting the times nearest to conception may be the most susceptible time of exposure for this risk. Our analysis adds depth and clarity to the current body of evidence investigating the possible association between air pollutants and the risk of birth defects. We provide novel data by exploring a detailed month-by-month exposure risk assessment, including the months before conception, to assess if there is a particularly

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susceptible time in the periconception period when exposure to airborne PM may pose a hazard to development of fetal anomalies. The time of embryonic development, weeks 3-10 of gestational age or weeks 1-8 of embryonic age, are thought to be the critical times of exposure for most teratogenic agents to risk of birth defects. This window would indeed be the most critical time if the exposure were known to have a deleterious embryonic effect with only acute high-level exposure. However, the association between air pollutants and adverse health outcomes may not be a clear immediate temporal exposure–outcome relationship. Buildup or accumulation of high concentrations of some pollutants or their metabolites over a longer period of time may pose a more notable risk for congenital anomalies if the high-level exposure occurs during the preconception period.[29] Long-term high $PM_{2.5}$ exposure specifically has been shown to cause oxidative stress, inflammation, and mitochondrial alteration,[30] and to have a higher risk of deleterious health effects.[31] Therefore, exposure to increased amounts of air pollutants may also affect birth defect risk in the time period preceding pregnancy, rather than only during the first trimester (weeks 1-12 of gestation). Prior studies examining the association between $PM_{2.5}$ and birth defects have only measured this relationship during a brief period of exposure in the first trimester only, and did not measure $PM_{2.5}$ exposure in the months preceding conception.[3,6,7,10-12,15] In the present study, we aimed to assess the specific time of exposure in the periconception period when increased pollutant exposure may be the most deleterious, by examining exposure timing of exposure in a month-by-month fashion extending from 2 months before to 2 months after conception.

In this study, we report the association of $PM_{2.5}$ exposure with any anomaly, as recorded in the US birth certificate, and also with individual malformations and malformations grouped by organ systems involved. We found a modest but positive association with increasing levels of $PM_{2.5}$ exposure 1 month before and 1 month after conception with risk of any congenital anomaly, when assessed as a composite variable. Additionally, we found some risk increases among individual anomalies limited to cases of hypospadias and abdominal defects, which had not been reported previously as individual outcomes associated with $PM_{2.5}$ exposure.[3,6,7,10-12,15] A review of ambient air pollution and risk of congenital anomalies highlighted the narrow focus of the number of birth defects included in prior studies. The authors suggested future studies should focus on anomalies other than just cardiac and facial clefts, have clear definitions of case classification, and use of classifications and exclusions in sensitivity analyses.[16] Few studies included the spectrum of all reported anomalies,[11,17,18] and most looked only at cardiac anomalies.[5,6,10,19]

Some studies have also suggested that air pollutant exposure may be associated with increased risk of common fetal chromosome abnormalities, such as trisomy 21 and Down syndrome.[32] Inclusion and exclusion of chromosomal, syndromic, and multiple anomalies have differed between studies,[16] contributing to significant study heterogeneity and limiting the generalizability of the findings. To assess whether chromosome abnormalities may be in the causal pathway of $PM_{2.5}$ exposure to birth defect risk, we measured the association with anomalies both including and excluding cases of chromosome disorders. We further analyzed the association between $PM_{2.5}$ and chromosome disorders, with congenital anomaly cases excluded. We found no association between $PM_{2.5}$ exposure and risk of fetal chromosome abnormalities, regardless of the periconception timing of exposure. Additionally, the risk of anomalies was not detectable with the inclusion of cases with concomitant chromosome disorders. Based on these findings, we feel that the preferable approach to assess PM–birth defect risk is to limit the analysis to congenital anomalies without concurrent chromosome disorders.

Although the use of stationary monitors to assign individual-level exposures within a specified radius surrounding the monitor has obvious limitations, it has been widely used for measurement in prior air particulate–birth outcome assessment studies. Using this approach, measurement error owing to spatial variability may lead to erroneous negative results, often biasing the risk estimates toward the null.[33] Studies including a large perimeter around a PM monitor for exposure quantification and also reporting a null association with birth defects have been a common theme in previously published studies on this topic. However, limiting analyses to narrow distance cutoffs decreases sample size. Given the low frequency of congenital anomalies in the population (3%-8%),[1] investigators must balance the tradeoff between sample size and accuracy of exposure assessment when choosing the best cutoff for their studies. Of the prior published studies on PM and birth defects, reported distances from maternal residence to stationary monitors have varied greatly, with some not reporting the distance,[4,9,34] to others reporting distances of 10 km,[18] 16 km,[8] 40 km,[6] or even a maximum distance as far as 50-80 km from a monitor.[10,19] The large population-based cohort included in our study allowed us to model several relatively narrow distance cutoffs and compare their findings among air exposure–outcome assessment for birth defects. We found that the use of various distance cutoffs, including the commonly used 10-km distance, compared with more narrow areas with 7- and 5-km cutoffs provided some advantages and disadvantages. The consistency and inconsistency of results identified in the 3 exposure measurement distance cutoffs presented here are likely related to spatial heterogeneity within the larger distances and more precise exposure quantification but smaller sample size and power when using a smaller distance as a cutoff. An additional contributor to variation and inconsistency of results is that the location of exposure identified by maternal residential address does not account for women who moved during the pregnancy. Likewise, it also does not account for exposure at nonresidential addresses, such as work or school, which may be outside of the 10-km radius of the recorded home address.

An additional challenge in the interpretation of results from prior studies is the variability in the methods used to define high levels of PM exposure. A variety of exposure quantification strategies have been used modeling PM levels in the air as a continuous variable, or defining high PM exposure in a dichotomous approach considering the upper quantile or

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greater than mean plus IQR as "high." Still others quantified high exposure as per unit increases or per quantile increases associated with risk of congenital anomalies. These variations in measurement of exposure, analytic strategy, and reporting of results make it quite challenging to interpret the results into a way that has practical generalizability.[16] Dichotomizing exposure values may be problematic and may introduce bias into the estimates of ORs.[13] Therefore, in this study, we provide data from an analytic approach using a continuous model of exposure assessment in an attempt to provide the most informative and nonbiased results.

There are a number of inherent limitations to this type of study aimed to measure the association between airborne PM exposure and birth defect risk. However, by using multiple methodologic approaches, we feel we provide an important breadth of data on the optimal exposure ascertainment, measurement, and design characteristics that contribute to the reliability of the associations we have identified regarding $PM_{2.5}$ exposure and risk of congenital malformations. The overall rate of anomalies reported in this study is lower than the known population prevalence. Birth certificate records have a lower sensitivity for identifying birth defects compared with review of medical records, as not all birth defects are readily identifiable within the first few days of birth when the birth certificate is generated. Therefore, some congenital anomalies that are not yet identified may be coded as no anomaly in the birth certificate, biasing the results of our study and those of many similar in design toward the null. Alternatively, some birth defects recorded on the birth certificate may not be documented accurately, which could lead to some misclassification of case or referent group status. Additionally, some defects are recorded within a category by organ system and do not provide data on the specific malformation, which limits the ability to assess individual malformation exposure risks, such as in the category of congenital heart defects.

The mechanism of teratogenicity for airborne pollutant exposures are generally speculative.[16] Some hypothesized mechanisms include oxidative stress, coagulation aberrations, and placental inflammation.[35] These mechanisms could affect embryogenesis by influencing the migration and differentiation of neural crest cells. Additionally, some pollutants have demonstrated embryotoxicity in animal models.[16]

Future investigations should build on the knowledge gained from this study and use approaches aimed to optimize scientific rigor, minimize bias, and report the most accurate assessment of risk for air pollutants and development of congenital anomalies. Specific areas of focus should include individual level exposure methods and improved knowledge on the mechanism of action of air pollutants with regards to teratogenic effects on the developing embryo and fetus. Public health efforts should continue to highlight the importance of minimizing population-level exposure to harmful PM in the air. Although the increased risk of birth defects observed in our study with $PM_{2.5}$ exposure in the month before conception is modest, the potential impact on a population basis is noteworthy as all reproductive age women have some degree of exposure. ■

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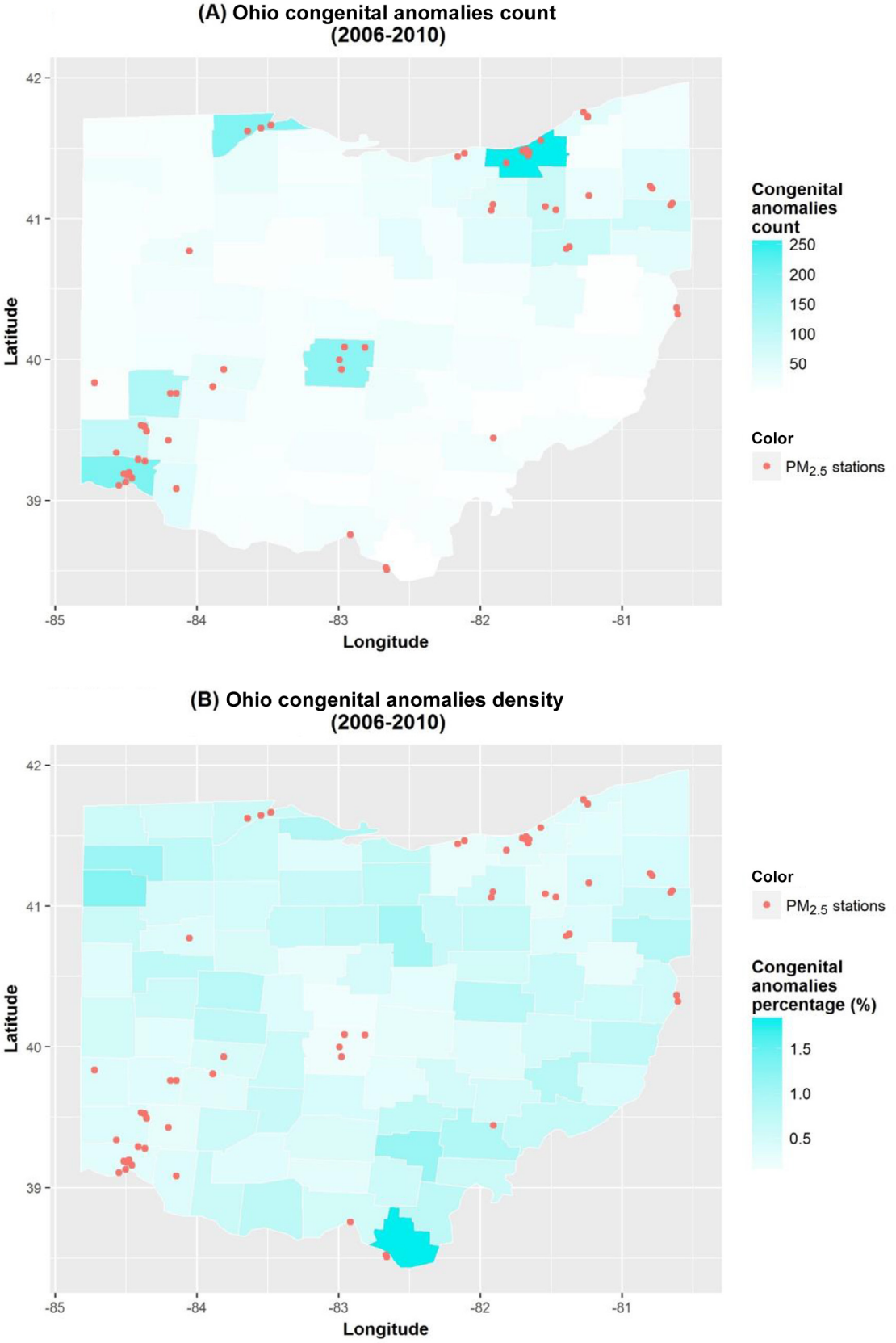

Figure 3. Congenital anomalies count and density by counties across Ohio from 2006 to 2010; **A,** congenital anomalies count map by counties; and **B,** congenital anomalies density map by counties.

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Table I. Number of congenital anomalies in each birth cohort, stratified by distance from residential address to $PM_{2.5}$ monitor station*

Congenital anomalies	No. of cases and rate (‰) per 1000 live births					
	10 km		7 km		5 km	
Total number of births in the study population†	290 173		210 777		143 968	
Chromosome disorders						
Suspected chromosomal disorder‡	227 (0.8)	93 (0.3)	167 (0.8)	69 (0.3)	110 (0.8)	45 (0.3)
Down syndrome‡		140 (0.5)		103 (0.5)		66 (0.5)
Hypospadias	116 (0.4)	116 (0.4)	82 (0.4)	82 (0.4)	54 (0.4)	54 (0.4)
Cleft lip/palate						
Cleft palate	230 (0.8)	124 (0.4)	178 (0.8)	95 (0.5)	124 (0.9)	64 (0.4)
Cleft lip with or without cleft palate		166 (0.6)		132 (0.6)		95 (0.7)
Limb reduction defect	61 (0.2)	61 (0.2)	39 (0.2)	39 (0.2)	26 (0.2)	26 (0.2)
Abdominal defect						
Gastroschisis	184 (0.6)	114 (0.4)	135 (0.6)	88 (0.4)	93 (0.6)	64 (0.4)
Omphalocele		28 (0.1)		21 (0.1)		11 (0.1)
Congenital diaphragmatic hernia		44 (0.2)		27 (0.1)		19 (0.1)
Cyanotic congenital heart disease	108 (0.4)	108 (0.4)	86 (0.4)	86 (0.4)	47 (0.3)	47 (0.3)
Neural tube defect						
Meningomyelocele/spina bifida	126 (0.4)	63 (0.2)	99 (0.5)	51 (0.2)	77 (0.5)	42 (0.3)
Anencephaly		66 (0.2)		51 (0.2)		38 (0.3)

*Subjects are counted multiple times if they have multiple congenital anomalies.
†Chromosome disorders subjects are included in this table, but they are excluded in main statistical analysis.
‡Both confirmed and pending subjects are included.

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Table II. Characteristics of study population (Ohio Birth Cohort 2006-2010)

Pregnancy and birth characteristics, 10-km cutoff cohorts	Any congenital anomaly, n (%)* (n = 784)	No Anomaly, n (%) (n = 289 950)	*P* value†	Congenital anomaly rate per 1000
Demographic factors				
Maternal age (y)				
≤18	81 (10.3)	21 080 (7.3)	<.01	3.8
19-34	620 (79.1)	234 400 (81.1)		2.6
≥35	83 (10.6)	33 686 (11.7)		2. 5
Race and ethnicity				
Non-Hispanic white	548 (69.9)	182 378 (63.1)	<.01	3.0
Non-Hispanic black	181 (23.1)	83 077 (28.7)		2.2
Non-Hispanic other	18 (2.3)	8321 (2.9)		2.2
Hispanic	37 (4.7)	15 390 (5.3)		2.4
Social behaviors and socioeconomic factors				
Education				
Less than high school	191 (24.4)	57 650 (19.9)	<.01	3.3
High school graduate	396 (50.5)	137 913 (47.7)		2.9
College education	197 (25.1)	93 603 (32.4)		2.1
Tobacco use				
Yes	189 (24.1)	54 215 (18.8)	<.01	3.5
No	595(75.9)	234 951 (81.3)		2.5
Marital status				
Yes	337 (43.0)	144 282 (49.9)	<.01	2.3
No	447 (57.0)	144 884 (50.1)		3.1
Low social economic status				
Yes	378 (50.2)	120 593 (43.6)	<.01	3.1
No	375 (49.8)	155 842 (56.4)		2.4
Prepregnancy diabetes				
Yes	16 (2.0)	2247 (0.8)	<.01	7.1
No	768 (98.0)	286 919 (99.2)		2.7
Year of birth				
2006	187 (23.9)	63 076 (21.8)	<.01	3.0
2007	176 (22.5)	62 581 (21.6)		2.8
2008	144 (18.4)	58 714 (20.3)		2.4
2009	121 (15.4)	55 897 (19.3)		2.2
2010	156 (19.9)	48 898 (16.9)		3.2
Season of conception				
Winter	157 (20.0)	70 745 (24.5)	.04	2.2
Spring	201 (25.6)	71 321 (24.7)		2.8
Summer	210 (26.8)	73 278 (25.3)		2.9
Fall	216 (27.6)	73 822 (25.5)		2.9
Infant sex				
Male	482 (61.5)	147 268 (50.9)	<.01	3.3
Female	302 (38.5)	141 898 (49.1)		2.1

*Cases of chromosome disorders were excluded in this table in order to be consistent with main statistical analysis, whose results are shown in **Tables II**, **III**, and **IV** and **Figure 1**.
†*P* values were calculated using the χ^2 test for each factor (contingency table). For comparisons where the χ^2 test was not appropriate, the Fisher exact test was used.

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Table V. aOR and corresponding 95% CI for the association of individual congenital anomalies and $PM_{2.5}$ levels for the 10-km cohort, stratified by periconception exposure periods*

10-km cutoff datasets by exposure periods	No. of cases	No. of total subjects used	Continuous (per IQR increment)	Continuous (per 10 μm/m³ increment)
Chromosome disorders				
2 months before	226	287 303	1.07 (0.87-1.30)	1.14 (0.76-1.70)
1 month before	226	286 727	1.00 (0.85-1.18)	1.00 (0.71-1.41)
Month of conception	225	286 015	0.92 (0.77-1.10)	0.84 (0.59-1.21)
Average of 3 months	226	286 856	0.99 (0.84-1.18)	0.98 (0.61-1.60)
Hypospadias†,§				
2 months before	111	146 326	1.00 (0.77-1.31)	1.01 (0.59-1.72)
1 month before	111	146 056	1.16 (0.96-1.40)	1.36 (0.92-2.00)
Month of conception	111	145 695	**1.39 (1.07-1.81)**	**1.97 (1.14-3.38)**
Average of 3 months	111	146 114	1.27 (0.99-1.61)	1.97 (0.98-3.96)
Cleft lip/palate				
2 months before	218	287 295	1.05 (0.92-1.21)	1.11 (0.85-1.46)
1 month before	216	286 717	1.05 **(**0.88-1.27**)**	1.12 (0.76-1.63)
Month of conception	214	286 004	0.97 (0.83-1.14)	0.95 (0.69-1.31)
Average of 3 months	216	286 846	1.04 (0.89-1.22)	1.12 (0.71-1.78)
Cyanotic congenital heart disease				
2 months before	101	287 178	0.80 (0.60-1.06)	0.63 (0.36-1.13)
1 month before	100	286 601	1.17 (0.90-1.53)	1.39 (0.81-2.40)
Month of conception	100	285 890	0.84 (0.58-1.22)	0.70 (0.33-1.49)
Average of 3 months	100	286 730	0.90 (0.62-1.30)	0.74 (0.26-2.13)
Abdominal defects‡				
2 months before	181	287 258	1.03 (0.84-1.26)	1.06 (0.71-1.60)
1 month before	180	286 681	1.06 **(**0.89-1.27**)**	1.13 (0.79-1.63)
Month of conception	176	285 966	0.98 (0.79-1.23)	0.96 (0.61-1.52)
Average of 3 months	180	286 810	1.04 **(**0.85-1.27**)**	1.12 (0.64-1.96)
Neural tube defects§				
2 months before	125	287 202	1.04 (0.82-1.32)	1.09 (0.68-1.76)
1 month before	124	286 625	0.97 (0.69-1.36)	0.94 (0.47-1.90)
Month of conception	125	285 915	0.99 (0.81-1.20)	0.97 (0.65-1.45)
Average of 3 months	124	286 754	1.00 (0.73-1.38)	1.01 (0.40-2.52)

Statistically significant results with lower bound of 95% confidence interval >1.0 are indicated in bold.
*For cases of individual congenital anomalies, births with a chromosome disorder in addition to the congenital anomaly were not included in this analysis.
†Hypospadias analysis was limited to male infants, and the infant sex covariate was excluded from the adjusted model.
‡Abdominal defect models did not include prepregnancy diabetes owing to a lack of observations of that covariate in the outcome group.
§Neural tube defects and hypospadias models did not include maternal race owing to a lack of observations in one race category within the outcome group.

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Table VI. aOR and corresponding 95% CI for the association of individual congenital anomalies and $PM_{2.5}$ levels for the 7-km cohort, stratified by periconception exposure periods*

7-km cutoff datasets by exposure periods	No. of cases	No. of total subjects used	Continuous (per IQR increment)	Continuous (per 10 μm/m³ increment)
Chromosome disorders				
2 months before	169	208 591	1.00 (0.80-1.26)	1.00 (0.63-1.60)
1 month before	169	208 196	0.88 (0.72-1.09)	0.77 (0.50-1.18)
Month of conception	170	207 691	0.92 (0.77-1.10)	0.84 (0.59-1.21)
Average of 3 months	169	208 290	0.90 (0.73-1.10)	0.74 (0.42-1.31)
Hypospadias†,§				
2 months before	78	106 052	1.02 (0.79-1.31)	1.03 (0.62-1.73)
1 month before	78	105 877	**1.39 (1.15-1.69)**	**2.00 (1.34-2.95)**
Month of conception	78	105 615	**1.47 (1.06-2.02)**	**2.18 (1.13-4.20)**
Average of 3 months	78	105 920	**1.44 (1.07-1.94)**	**2.82 (1.21-6.58)**
Cleft lip/palate				
2 months before	168	208 590	1.08 (0.93-1.25)	1.17 (0.86-1.57)
1 month before	166	208 193	0.99 (0.83-1.19)	0.99 (0.68-1.43)
Month of conception	164	207 685	0.94 (0.78-1.13)	0.88 (0.60-1.29)
Average of 3 months	166	208 287	1.01 (0.86-1.19)	1.02 (0.64-1.63)
Cyanotic congenital heart disease				
2 months before	80	208 502	0.73 (0.55-0.97)	0.52 (0.29-0.93)
1 month before	79	208 106	1.21 (0.91-1.59)	1.47 (0.83-2.62)
Month of conception	79	207 600	0.91 (0.62-1.33)	0.82 (0.38-1.78)
Average of 3 months	79	208 200	0.91 (0.62-1.33)	0.76 (0.26-2.23)
Abdominal defects‡				
2 months before	132	208 554	1.08 (0.86-1.35)	1.16 (0.73-1.84)
1 month before	131	208 158	**1.25 (1.00-1.54)**	**1.57 (1.01-2.46)**
Month of conception	130	207 651	1.03 (0.81-1.31)	1.06 (0.65-1.74)
Average of 3 months	131	208 252	1.17 (0.95-1.45)	1.56 (0.85-2.87)
Neural tube defects§				
2 months before	98	208 520	0.99 (0.72-1.38)	0.99 (0.51-1.91)
1 month before	97	208 124	0.96 (0.63-1.48)	0.93 (0.39-2.23)
Month of conception	98	207 619	1.01 (0.82-1.25)	1.03 (0.67-1.58)
Average of 3 months	97	208 218	0.99 (0.65-1.49)	0.96 (0.30-3.11)

Statistically significant results with lower bound of 95% confidence interval >1.0 are indicated in bold.
*For cases of individual congenital anomalies, births with a chromosome disorder in addition to the congenital anomaly were not included in this analysis.
†Hypospadias analysis was limited to male infants, and the infant sex covariate was excluded from the adjusted model.
‡Abdominal defect models did not include prepregnancy diabetes owing to a lack of observations of that covariate in the outcome group.
§Neural tube defects and hypospadias models did not include maternal race owing to a lack of observations in 1 race category within the outcome group.

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Table VII. aOR and corresponding 95% CI for the association of individual congenital anomalies and $PM_{2.5}$ levels for the 5-km cohort, stratified by periconception exposure periods*

5-km cutoff datasets by exposure periods	Number of cases	Number of total subjects used	Continuous (per IQR increment)	Continuous (per 10 μm/m³ increment)
Chromosome disorders				
2 months before	112	142 339	1.04 (0.72-1.50)	1.08 (0.52-2.25)
1 month before	112	142 066	0.90 (0.70-1.16)	0.80 (0.48-1.35)
Month of conception	113	141 700	0.95 (0.77-1.18)	0.91 (0.59-1.38)
Average of 3 months	112	142 141	0.94 (0.69-1.29)	0.85 (0.35-2.04)
Hypospadias†,§				
2 months before	50	72 296	1.22 (0.93-1.59)	1.48 (0.87-2.54)
1 month before	50	72 194	**1.41 (1.08-1.85)**	**2.05 (1.17-3.59)**
Month of conception	50	71 985	1.39 (0.96-2.02)	1.96 (0.92-4.17)
Average of 3 months	50	72 225	**1.53 (1.10-2.14)**	**3.35 (1.31-8.61)**
Cleft lip/palate				
2 months before	117	142 344	1.10 (0.92-1.31)	1.20 (0.84-1.73)
1 month before	115	142 069	0.97 (0.81-1.17)	0.94 (0.64-1.38)
Month of conception	115	141 702	1.02 (0.78-1.32)	1.04 (0.61-1.76)
Average of 3 months	115	142 144	1.05 (0.88-1.26)	1.15 (0.69-1.91)
Cyanotic congenital heart disease				
2 months before	43	142 270	0.79 (0.60-1.04)	0.62 (0.35-1.09)
1 month before	42	141 996	1.28 (0.90-1.83)	1.66 (0.80-3.45)
Month of conception	42	141 629	0.76 (0.45-1.30)	0.58 (0.20-1.71)
Average of 3 months	42	142 071	0.90 (0.57-1.42)	0.75 (0.21-2.70)
Abdominal defects‡				
2 months before	91	142 318	1.11 (0.82-1.49)	1.23 (0.68-2.23)
1 month before	89	142 043	**1.51 (1.17-1.96)**	**2.33 (1.37-3.97)**
Month of conception	88	141 675	0.98 (0.72-1.34)	0.97 (0.52-1.79)
Average of 3 months	89	142 118	1.28 (0.99-1.65)	2.00 (0.97-4.14)
Neural tube defects§				
2 months before	76	142 303	0.99 (0.70-1.41)	0.98 (0.48-1.98)
1 month before	75	142 029	1.01 (0.63-1.61)	1.02 (0.39-2.66)
Month of conception	76	141 663	0.95 (0.73-1.24)	0.90 (0.53-1.54)
Average of 3 months	75	142 104	0.97 (0.64-1.48)	0.92 (0.28-3.04)

Statistically significant results with lower bound of 95% confidence interval >1.0 are indicated in bold.
*For cases of individual congenital anomalies, births with a chromosome disorder in addition to the congenital anomaly were not included in this analysis.
†Hypospadias analysis was limited to male infants, and the infant sex covariate was excluded from the adjusted model.
‡Abdominal defect models did not include prepregnancy diabetes owing to a lack of observations of that covariate in the outcome group.
§Neural tube defects and hypospadias models did not include maternal race owing to a lack of observations in one race category within the outcome group.

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