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Maternal Exposure to $PM_{2.5}$ and the Risk of Congenital Heart Defects in 1.4 Million Births: A Nationwide Surveillance-Based Study

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BACKGROUND: Evidence remains limited about the association of maternal exposure to ambient fine particulate matter (airborne particles with an aerodynamic diameter ≤2.5 μm [$PM_{2.5}$]) with fetal congenital heart defects (CHDs) in highly polluted regions, and few studies have focused on preconception exposure.

METHODS: Using a nationwide surveillance-based case-control design in China, we examined the association between maternal exposure to $PM_{2.5}$ during periconception (defined as 3 months before conception until 3 months into pregnancy) and risk of CHD in offspring. The study included 1 434 998 births involving 7335 CHDs from 2014 through 2017 on the basis of the National Population-Based Birth Defects Surveillance System, covering 30 provinces, municipalities, or municipal districts in China. We assigned maternal $PM_{2.5}$ exposure during the periconception period to each participant using satellite-based $PM_{2.5}$ concentrations at 1-km spatial resolution. Multilevel logistic regression models were used to calculate the multivariable-adjusted odds ratio and 95% CI for CHDs in offspring associated with maternal $PM_{2.5}$ exposure, and the exposure–response association was investigated using restricted cubic spline analysis. Subgroup or sensitivity analyses were conducted to identify factors that may modify the association.

RESULTS: The average maternal exposure to $PM_{2.5}$ levels across all participants was 56.51 μg/m^3 (range, 10.95 to 182.13 μg/m^3). For each 10 μg/m^3 increase in maternal $PM_{2.5}$ exposure, the risk of CHDs in offspring was increased by 2% (odds ratio, 1.02 [95% CI, 1.00 to 1.05]), and septal defect was the most influenced subtype (odds ratio, 1.04 [95% CI, 1.01 to 1.08]). The effect of $PM_{2.5}$ on CHD risk was more pronounced during the preconception period. Mothers <35 years of age, those living in northern China, and those living in low-income areas were more susceptible to $PM_{2.5}$ exposure than their counterparts (all $P<0.05$). $PM_{2.5}$ exposure showed a linear association with total CHDs or specific CHD types.

CONCLUSIONS: High maternal $PM_{2.5}$ exposure, especially during the preconception period, increases risk of certain types of CHD in offspring. These findings are useful for CHD prevention and highlight the public health benefits of improving air quality in China and other highly polluted regions.

Key Words: heart defects ■ congenital ■ environment ■ pregnancy

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Clinical Perspective

What Is New?

- Maternal exposure to airborne particles with an aerodynamic diameter ≤2.5 μm ($PM_{2.5}$) during periconception, especially preconception, is associated with a risk of some types of congenital heart defect (CHD) in offspring, especially septal defect.
- Mothers <35 years of age, those living in areas with low per capita disposable income, and those living in northern China are more susceptible to high levels of $PM_{2.5}$.

What Are the Clinical Implications?

- Policies targeting air quality improvement and measures to decrease $PM_{2.5}$ exposure have potential benefits for reducing the incidence of CHD in newborns.
- Studies should be conducted to explore how preconception $PM_{2.5}$ exposure increases risk of CHD in offspring and why certain populations are more susceptible than others to such pollution.

Nonstandard Abbreviations and Acronyms

CHD	congenital heart defect
ICD-10	*International Classification of Diseases, 10th revision*
OR	odds ratio
$PM_{2.5}$	fine particulate matter
SPD	septal defect

Congenital heart defects (CHDs), with an estimated prevalence of 9 cases per 1000 births,[1] are the most common birth defect type, and are the leading cause of infant mortality attributable to congenital anomalies worldwide. More than 80% of CHDs have no known cause.[2–4] Genetic factors[5] and other noninherited factors, including maternal therapeutic drug exposure, advanced age, obesity, infection, fever, and environmental exposures,[6,7] may contribute to the development of CHD. With increasing industrialization and urbanization over the past few decades, exposure to high concentrations of fine particulate matter (airborne particles with an aerodynamic diameter ≤2.5 μm [$PM_{2.5}$]) has become a serious public health concern. According to the 2017 Global Burden of Disease Study, such exposure is associated with ≈2.94 million annual deaths.[8] This has attracted much research and policy attention to the association between $PM_{2.5}$ and health outcomes, including birth defects and other adverse pregnancy outcomes.[9,10]

The first trimester is a critical time for cardiac development of the fetus. Epidemiologic studies have investigated the association between maternal exposure to $PM_{2.5}$ during pregnancy, especially in the first trimester, and CHD in offspring, but the findings have been inconsistent.[11–13] In addition, most of these studies are from developed countries, where $PM_{2.5}$ concentration is lower than that in China and other highly polluted areas. Although several studies in China have also investigated the association, they are limited by small samples, a focus on only one province or one city, or a focus on only a few CHD types. Most of them assessed $PM_{2.5}$ exposure using data from air-quality monitoring stations.

The 3 months before conception, when the preantral follicle in the ovary gradually matures and ovulates,[14] are a critical time when maternal risk factors may be associated with adverse pregnancy outcomes.[15] Preconception exposure to $PM_{2.5}$ has been associated with damage to follicular development,[16,17] hormone homeostasis interfering with the female reproductive system,[18] intrauterine inflammation,[19] as well as development of gestational glucose intolerance and gestational diabetes.[20] All these processes can lead to abnormal placentation and adverse fetal development. However, we are aware of only 2 studies that have investigated the association between preconception exposure to $PM_{2.5}$ and CHD in offspring.[21,22] Neither came from a highly polluted region such as China.

We conducted this nationwide surveillance-based case-control study on maternal exposure to $PM_{2.5}$ before and after conception to assess the effect of such exposure on risk of CHD in offspring and whether the observed association was modified by other factors.

METHODS

Data Sharing

Data are available on reasonable request from the corresponding author and will be considered by the steering group.

Data Source and Quality Control

The data used in the case-control study were obtained from the National Population-Based Birth Defects Surveillance System, a nationwide surveillance network in China, which was established in 2006 and contained 36 counties and 28 districts in 30 provinces, municipalities, or municipal districts (Figure S1). From 2014 through 2017, the network included 330 000 births annually, accounting for 2.1% of the ≈16 million births annually in the country, according to the *China Health Statistics Yearbook*.[23]

The network is supported by a unified workflow for collecting and performing quality control on data concerning maternal and child health surveillance in China,[24] which has been described in detail previously.[25] Briefly, all fetuses and neonates (live births or stillbirths) born at ≥28 weeks of gestation to women whose registered permanent residences were in the surveillance areas or living there for ≥1 year were monitored. The period for identifying birth defects was from 28 weeks of gestation to 42 days after birth, during which major birth defects diagnosed for the first time were required to be reported. All birth defects

in the system should be diagnosed by hospitals with a prenatal diagnosis qualification or by obstetricians, pediatricians, or surgeons after delivery.

Data were collected by a multilevel surveillance network comprising community or township or village, county, city, province, and central levels, together with corresponding expert groups. Surveillance staff at the community, township, or village levels were responsible for collection, verification, and follow-up of birth information. Standardized forms were used to collect data on births and birth defects from medical records of hospitals, and all these data were reported, in turn, to the county, city, and province. Each level was responsible for verifying the data in its jurisdiction, and any uncertainties were returned and verified.[26] The data were then sent to the National Maternal and Child Health Monitoring Office (central level), where a workgroup composed of clinicians, statisticians, epidemiologists, and information technicians was responsible for checking and encoding. The data included information on maternal demographics, delivery, and birth defects. All birth defects in the database were coded by surveillance staff at the national level according to the *ICD-10* (*International Classification of Diseases, 10th revision*).[24] The data were checked for accuracy and completeness by cross-referencing with related data from other systems, such as registries of birth certificates and perinatal deaths. In addition, annual surveys were conducted to identify and correct errors and inaccuracies in the collected data. The rate of underreporting live births or birth defects and the rate of errors or missing values on report forms could not exceed 1% (Figure S2).

Study Design and Data Selection

Using the National Population-Based Birth Defects Surveillance System, maternal demographic characteristics (permanent residence, maternal ethnicity, age, and parity) and delivery characteristics (date of delivery, fetus number, fetus sex, birthweight, and diagnosis) were recorded for all births between January 1, 2014, and September 30, 2017, corresponding to a total of 1 464 074 births. The study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of Sichuan University (approval No. K2018075).

Newborns or fetuses diagnosed with CHD were treated as cases, and newborns without any birth defects were treated as controls. The following births were excluded: (1) 4070 for which data were missing on gestational age, birthweight, maternal age, ethnicity, parity, or fetus number; (2) 530 with birthweight <900 g; (3) 555 involving mothers <14 years of age or >50 years of age; (4) 20 907 without CHD but with other birth defects, stillbirths, or deaths within 42 days after birth; (5) 2967 with simple patent foramen ovale; and (6) 47 for which the residential address of the mother was unknown. Figure 1 illustrates the process of data inclusion and exclusion used in the study. After this procedure, a total of 29 076 births were removed from the subsequent analysis, yielding a final sample of 1 434 998 participants.

Exposure Assessment

Monthly mean $PM_{2.5}$ levels at 1-km spatial resolution across China from January 1, 2012, to September 30, 2017, were used to assess $PM_{2.5}$ exposure for each participant. A complete description of the establishment of $PM_{2.5}$ levels has been published previously.[27] Briefly, the Multi-Angle Implementation of Atmospheric Correction aerosol optical depth product, made available by the US National Aeronautics and Space Administration, was used to enhance the spatial resolution of $PM_{2.5}$, with estimates at 1 km.[28] A multiple imputation model was adopted to fill in the missing aerosol optical depth caused by cloud cover and to calculate accurate monthly mean aerosol optical depth values.[27] The gap-filled aerosol optical depth was then combined with meteorologic variables, land use types, road network information, elevation, and emissions, which were then used to train models separately using machine learning. To improve prediction accuracy, the predicted $PM_{2.5}$ concentrations calculated using machine learning models were averaged to represent the monthly mean $PM_{2.5}$ exposure levels in each 1-km^2 grid cell. Random 10-fold cross-validation R^2 values were 0.93 at the monthly level and 0.95 at the annual level.

To assess individual exposure to $PM_{2.5}$, we estimated the monthly average exposure to $PM_{2.5}$ for each birth by matching the geocoded maternal address, and then we calculated the average exposure levels by embryology month and period of interest, which could be preconception (3 months before conception), first trimester (3 months into pregnancy), or periconception (from 3 months before conception until 3 months into pregnancy). The 3-month average $PM_{2.5}$ was calculated on the basis of monthly average $PM_{2.5}$ in the month that covered >15 days. The dates of embryology months of interest were determined by the date of pregnancy, which was estimated by subtracting the gestational age from the date of delivery, both of which were taken from hospital medical records.

Ascertainment and Classification of CHDs

CHDs were diagnosed using transthoracic color Doppler echocardiography, catheterization, or surgery.[24] We restricted our analyses to selected major CHDs that were ascertained and coded according to the *ICD-10*. The cases in this study were classified as septal defect (SPD), conotruncal defect, left ventricular outflow tract obstruction, right ventricular outflow tract obstruction, anomalous venous return, patent ductus arteriosus, or other cardiac structure abnormalities.[29,30]

Statistical Analysis

Frequency was used to describe qualitative data, including sex of the newborn (male or female), birthweight (<2500, 2500–3999, or ≥4000 g), fetus number (1 or ≥2), maternal age (<35 or ≥35 years), maternal ethnicity (Han or minority), parity (primipara or multipara), season of conception (spring, summer, autumn, or winter), region (southern or northern), urban or rural residence, and per capita disposable income (dichotomized as low or high income). Birthweight and maternal age were also described quantitatively, using mean and SD. The 4 seasons were defined on the basis of climate characteristics of China as follows: spring, March 1 to May 31; summer, June 1 to August 31; autumn, September 1 to November 30; and winter, December 1 to February 28. Per capita disposable income was classified depending on whether it was below or above 25 185 renminbi (≈$3588 USD), corresponding to 50% of the average value across all monitored districts or counties. Differences in the frequencies of these factors between cases and controls were assessed using the Student *t* test or χ^2 test.

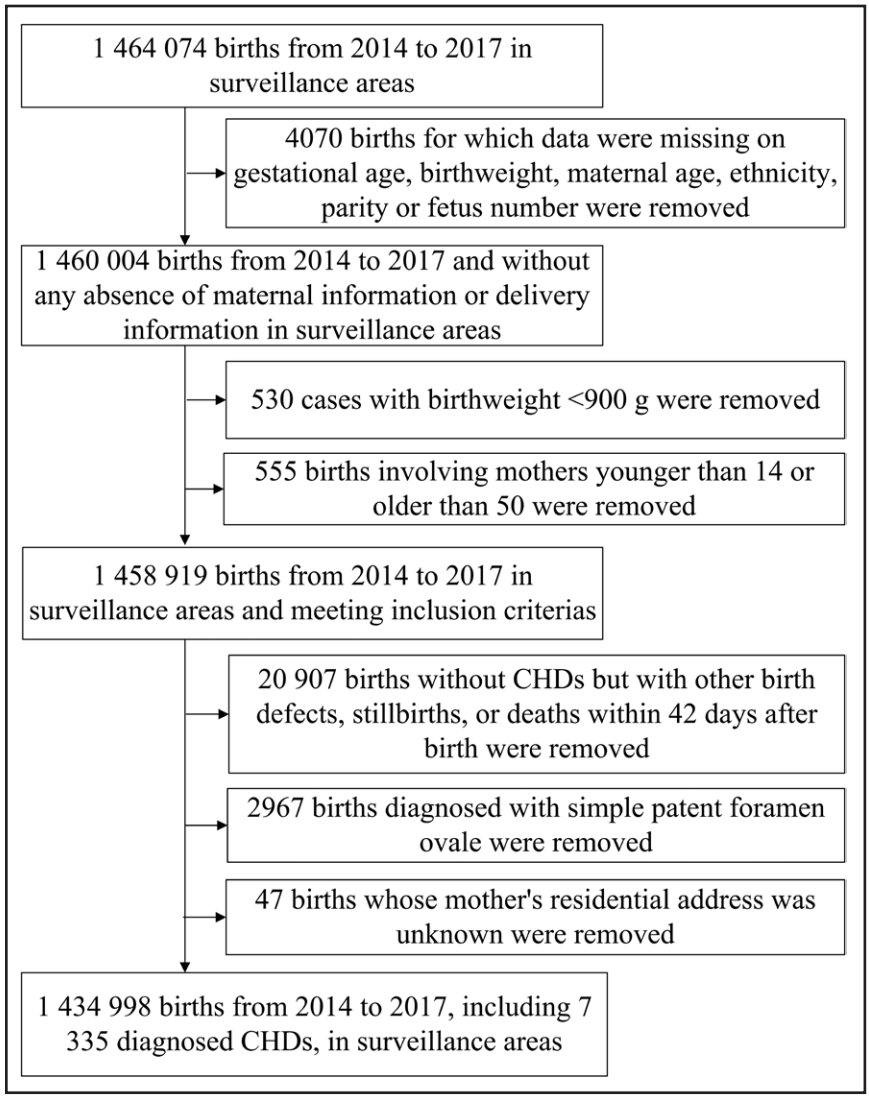

Figure 1. Flowchart of participant selection.
CHD indicates congenital heart defect.

After descriptive analysis, we performed multilevel logistic regression to evaluate the association between $PM_{2.5}$ levels and the occurrence of CHD. We estimated the odds ratio (OR) with 95% CI per 10 μg/m^3 increase in $PM_{2.5}$. In the analyses, we adjusted for the following individual-level covariates: newborn sex, birthweight, fetus number, parity, maternal ethnicity, maternal age, month of conception, temperature, and relative humidity. Maternal age, month of conception, temperature, and relative humidity were splined. We also adjusted county-level per capita disposable income, which was collected by routine monitoring. To account for the nonindependence of participants within the same county or district and for differences in the completeness or accuracy of CHD diagnosis across regions, county or district was specified as a random intercept in the model. Because $PM_{2.5}$ concentrations and CHD prevalence varied across months of conception (Figure S3), month of conception was also specified as a random intercept. Using the counterfactual estimation method for burden of disease attributable to risk factors,[31] we estimated the attributable risk proportion of $PM_{2.5}$ >35 μg/m^3 (defined as the China class II standard of the annual mean of $PM_{2.5}$).

To evaluate the shape of the association between $PM_{2.5}$ and the prevalence of CHD, we performed restricted cubic spline analyses for $PM_{2.5}$, with the aforementioned 35 μg/m^3 as the reference. Restricted cubic spline was added in the model on the basis of $PM_{2.5}$ level in the preconception period, the first trimester, and the periconception period. We ran the models using various numbers of knots recommended by Harrell[32] and selected the knots with the lowest values for the minimum Akaike information criterion or Bayesian information criterion. The following restricted cubic spline knots were selected for the 3 periods (Table S1): preconception period and the first trimester, knots p10, p50, and p90; and periconception period, knots p5, p27.5, p50, p72.5, and p95.

We performed subgroup analyses on the basis of infant sex (male or female), fetus number (singleton or multiple), maternal parity (primipara or multipara), maternal ethnicity (Han or minority), maternal age (<35 or ≥35 years), region (southern or northern), residence (urban or rural), and per capita disposable income (high or low). We used the 2-sample Z test to assess whether effect estimates differed significantly between subgroups.[33]

We performed sensitivity analysis to explore the association between $PM_{2.5}$ exposure and risk of CHD, with or without other birth defects, separately. We also conducted a sensitivity analysis to assess whether effect estimates changed significantly

when we calculated maternal $PM_{2.5}$ exposure during the study period by using the monthly average of $PM_{2.5}$ from all the months covered or the monthly average of $PM_{2.5}$ after being weighted by the proportion of days covered in each month. Analyses were carried out using STATA 15.0 (StataCorp) and R 3.6.1 (R Foundation for Statistical Computing; http://www.r-project.org). Two-tailed $P<0.05$ was considered significant.

RESULTS

Descriptive Results

Table 1 presents the characteristics of 1 434 998 births from 2014 to 2017, including 7335 births with CHD and 1 427 663 live births without CHD. Newborns diagnosed with CHD were more likely to have a birthweight <2500 g and to be born to mothers with a multiple pregnancy ($P<0.001$). The proportions of primiparae and mothers ≥35 years of age were higher in the CHD group than in the non-CHD group ($P<0.05$), and mothers in the CHD group were more likely to be pregnant in summer and autumn ($P<0.001$). Most CHD cases were distributed in the southern region, urban areas, and areas with higher per capita disposable income ($P<0.001$). The average $PM_{2.5}$ exposure during the periconception period across all study participants was 56.51 μg/m³, ranging from 10.95 to 182.13 μg/m³. During the periconception period, the average temperature was 16.63°C (range, −14.03 to 29.30°C), and relative humidity was 67.43% (range, 22.61 to 89.94%; Table 2).

Associations of Maternal $PM_{2.5}$ Exposure and CHD in Offspring

In general, the risk of delivering a neonate with CHD increased by 2% (OR, 1.02 [95% CI, 1.00 to 1.05]) for each increase of 10 μg/m³ in maternal exposure to $PM_{2.5}$ during the periconception period (Figure 2), and the exposure–response curve (Figure 3) showed a linear association between maternal exposure to $PM_{2.5}$ and CHD in offspring ($P_{linear}<0.001$). The effect of $PM_{2.5}$ exposure was more pronounced during the preconception period (OR, 1.03 [95% CI, 1.01 to 1.05]) than during the first trimester (OR, 1.02 [95% CI, 1.00 to 1.04]; Figure 2). The exposure–response association was more evident during preconception than during the first trimester (Figure 3).

The risks of developing different types of CHD in association with $PM_{2.5}$ exposure varied greatly, and only the association between $PM_{2.5}$ exposure and SPD was statistically significant (Figure 2), regardless of whether the exposure window was periconception (OR, 1.04 [95% CI, 1.01 to 1.08]), preconception (OR, 1.04 [95% CI, 1.01 to 1.07]), or the first trimester (OR, 1.03 [95% CI, 1.01 to 1.06]). The exposure–response association was also evident in curves plotted for SPD (Figures S4 through S6). Moreover, we estimated the attributable risk proportion for SPD with $PM_{2.5}$ concentrations >35 μg/m³ during each exposure period, and the attributable risk proportion was 8.44%, 8.45%, and

Table 1. Characteristics of Participants With and Without CHD (2014–2017)

Characteristics	Total (n=1 434 998)	No CHD (n=1 427 663)	CHD (n=7335)	*P* value
Male	754 854	751 038 (52.61)	3816 (52.02)	0.326
Birthweight, g	3274±457	3275±454	3005±739	<0.001
<2500	54 004	52 419 (3.67)	1585 (21.61)	<0.001
2500–3999	1 296 381	1 291 123 (90.44)	5258 (71.68)	
≥4000	84 613	84 121 (5.89)	492 (6.71)	
Singleton	1 401 344	1 394 323 (97.66)	7021 (95.72)	<0.001
Maternal age, y	28.37±4.82	28.37±4.82	28.86±4.82	<0.001
Maternal age <35 y	1 273 038	1 266 725 (88.73)	6313 (86.07)	<0.001
Maternal Han ethnicity	1 328 917	1 322 160 (92.61)	6757 (92.11)	0.115
Primipara	802 038	797 813 (55.88)	4225 (57.60)	0.003
Pregnancy season				
Spring	351 981	350 317 (24.54)	1664 (22.69)	<0.001
Summer	365 064	363 109 (25.43)	1955 (26.65)	
Autumn	375 239	373 189 (26.14)	2050 (27.95)	
Winter	342 714	341 048 (23.89)	1666 (22.71)	
Southern China	834 028	829 221 (58.08)	4807 (65.54)	<0.001
Urban residence	1 073 207	1 066 918 (74.73)	6289 (85.74)	<0.001
Low per capita disposable income*	713 244	710 736 (49.78)	2508 (34.19)	<0.001

Values are n (%) or mean±SD. CHD indicates congenital heart defect.

*Low income was defined as being <50% of the average per capita disposable income across all the monitored districts or counties (25 185 renminbi [≈$3588 USD]).

Table 2. $PM_{2.5}$ Levels and Meteorologic Factors Across Different Exposure Periods

Levels and factors	Minimum	Mean	Maximum	IQR
$PM_{2.5}$, μg/m³				
Periconception period	10.95	56.51	182.13	30.18
Preconception period	9.37	56.42	220.87	32.50
First trimester	10.20	56.61	233.47	32.60
Temperature, °C				
Periconception period	−14.03	16.63	29.30	10.51
Preconception period	−19.94	16.73	32.44	13.77
First trimester	−19.34	16.52	32.91	14.29
Relative humidity, %				
Periconception period	22.61	67.43	89.94	17.76
Preconception period	17.25	67.29	92.12	18.05
First trimester	20.10	67.58	93.42	17.35

IQR indicates interquartile range; and $PM_{2.5}$, airborne particles with an aerodynamic diameter ≤2.5 μm.

6.36% during periconception, preconception, and the first trimester period, respectively (Table S2). Sensitivity analysis showed that the association between $PM_{2.5}$ exposure and CHD without other birth defects was significant, but because of the limited number of CHD cases with other birth defects, the association was not significant (Table S3). The effects of $PM_{2.5}$ exposure were robust to the method we used to estimate exposure (Table S4).

Effect Modification of Individual Characteristics

Per increase of 10 μg/m³ in maternal exposure to $PM_{2.5}$, the risk of CHD in offspring increased by 4% for births in northern China and by 9% for births in areas with low per capita disposable income, which were more susceptible than their counterparts (Table 3).We also found that the effect of $PM_{2.5}$ could be modified by maternal age (P=0.039) such that births to mothers <35 years of age were more susceptible to $PM_{2.5}$ exposure (OR, 1.03 [95% CI, 1.00 to 1.05]; Table 3). These results were supported by the observed exposure–response associations of $PM_{2.5}$ with CHD (Figure S7).

DISCUSSION

In this large national surveillance-based study, we identified significantly increased risk of some types of CHD in association with maternal exposure to $PM_{2.5}$ in the periconception period. We measured a linear exposure–response association across a wide exposure range, from 10.95 to 182.13 μg/m³. This association may be modified by maternal age, residence area, and per capita disposable income.

To our knowledge, this is the first nationwide study focusing on associations of maternal exposure to $PM_{2.5}$ and risk of CHD in China. Although many epidemiologic studies have reported associations between maternal exposure to $PM_{2.5}$ and CHD in offspring, the results and the affected subtypes of CHD have been inconsistent.[34–38] In our study, risk of SPD increased with $PM_{2.5}$ exposure during periconception on the basis of data from 30 provinces, municipalities, or municipal districts in China. Thus, our work may provide more reliable estimates than the small-scale studies on the adverse effects of maternal $PM_{2.5}$ exposure. In addition, previous studies were conducted mainly in developed countries, where the $PM_{2.5}$ exposure is <26.1 μg/m³,[11,13] whereas most studies in China focused on certain cities or provinces. Thus, the current study has expanded the understanding of the exposure–response association between maternal $PM_{2.5}$ exposure and CHD across the widest range of $PM_{2.5}$ exposure. Similar to findings of other studies,[7]

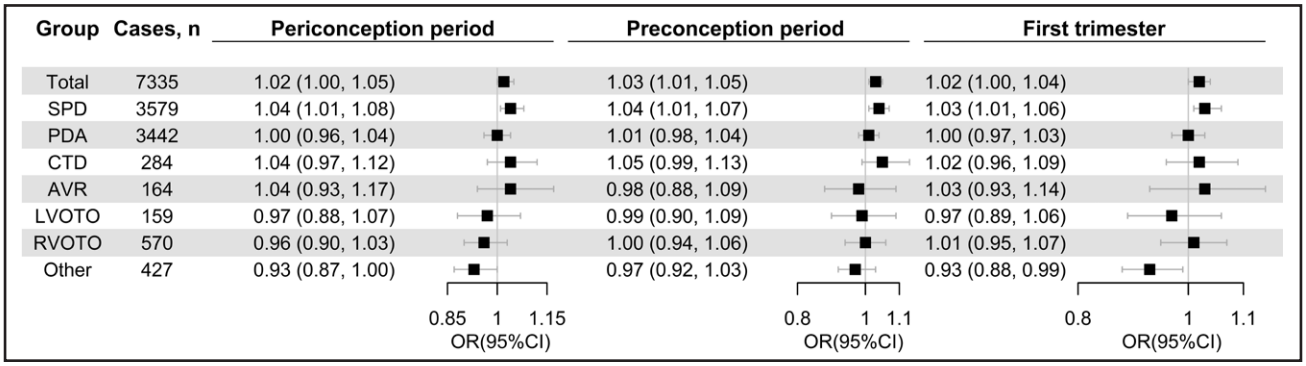

Figure 2. Risk of congenital heart defect in offspring per increase of 10 μg/m³ in PM2.5 level according to exposure period. Odds ratios (ORs) and 95% CIs were calculated using multilevel logistic regression. The periconception period was defined as the interval from 3 months before conception to 3 months into pregnancy. The preconception period was defined as the 3 months before conception. The first trimester was defined as the first 3 months of pregnancy. AVR indicates anomalous venous return; CTD, conotruncus defect; LVOTO, left ventricular outflow tract obstruction; Other, cardiac structure abnormalities not classified into the other types; Overall, all types of CHD combined; PDA, patent ductus arteriosus; $PM_{2.5}$, airborne particles with an aerodynamic diameter ≤2.5 μm; RVOTO, right ventricular outflow tract obstruction; and SPD, septal defect.

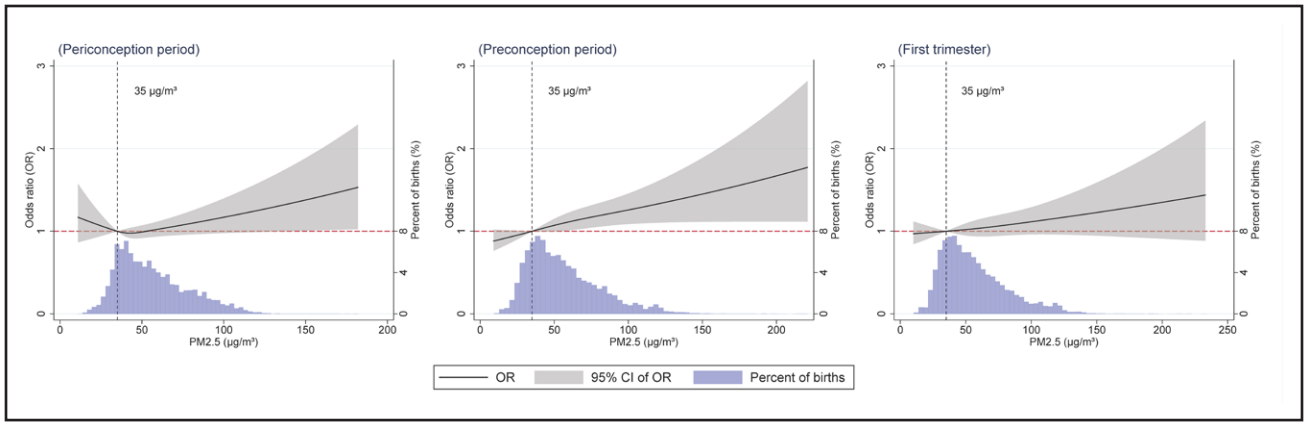

Figure 3. Association between maternal exposure to PM2.5 and risk of congenital heart defect in offspring according to exposure period.

The periconception period was defined as the interval from 3 months before conception to 3 months into pregnancy. The preconception period was defined as the 3 months before conception. The first trimester was defined as the first 3 months of pregnancy. Restricted cubic spline analysis was used to evaluate the shape of the association between airborne particles with an aerodynamic diameter ≤2.5 μm ($PM_{2.5}$) and the prevalence of congenital heart defects. ORs were estimated by comparing with a reference value of 35 μg/m³, which is the China class II standard of the annual mean of $PM_{2.5}$. Percentages of births were calculated over all births during the period from 2014 to 2017 per unit of $PM_{2.5}$. The solid line represents point estimates, and the gray area represents 95% CI.

our results suggested a slightly elevated risk of CHD associated with $PM_{2.5}$ exposure. Nevertheless, at the current concentration of $PM_{2.5}$ in China, the attributable risk proportion for SPD was 8.44%, which may have public health significance. Apart from SPD, the other types of CHD that we examined showed no significant association with $PM_{2.5}$ exposure. This may reflect the relatively smaller number of births with these types of CHD. We also observed that the risk of unclassified CHD ("other" category) showed an inverse association with $PM_{2.5}$ exposure. Consistent with previous studies,[39,40] a higher proportion of unclassified CHD was observed in stillbirths than in live births after 28 weeks of gestation in our database, which implied that fetuses with unclassified CHD may be more likely to experience spontaneous abortion or termination of pregnancy within 28 weeks of gestation, especially with exposure to high $PM_{2.5}$ levels.[41,42] Therefore, the interpretation of these findings should be cautious, and confirmation and explanation in studies having information on CHD before 28 weeks of gestation are needed.

Although evidence on the association of maternal exposure to $PM_{2.5}$ and CHD in offspring has been growing, most studies focused on exposure during pregnancy rather than exposure during preconception.[21,35,37,43] Our study appears to be the first to report that higher $PM_{2.5}$ levels in the 3 months before conception may increase the risk of some types of CHD in China. Cardiac development occurs at 3 to 8 weeks of gestation, which is therefore the critical exposure window for most teratogenic agents and CHD.[44] This window is indeed likely to be the most critical if acute high-level exposure is sufficient to harm the embryo. However, the association between air pollution and CHD may depend not on acute exposure but on the buildup or accumulation of high concentrations of pollutants or their metabolites over a longer period, in which case risk of CHD may increase strongly when high-level exposure occurs during the preconception period.[45] Three months before conception is the critical time for the preantral follicle in the ovary to mature gradually and ovulate,[14] and preconception care in China is recommended from 3 months before conception.[46] Preconception exposure to $PM_{2.5}$ has been proposed to lead to adverse pregnancy outcomes through processes involving oxidative stress, inflammation, mitochondrial alteration, and compromised placental growth and function.[47] Maternal exposure to $PM_{2.5}$ can affect oocyte quality, reduce embryo viability and development, or alter placental function, leading to impaired fetal growth.[48] In addition, paternal preconception exposure to air pollution may also affect embryonic development through mutagenesis or epigenetic changes in spermatozoa.[49,50]

Some population characteristics may modify the health effects of particulate pollutants by differentiating the exposure to other risk factors as well as access to prevention measures.[51,52] Similar to results reported by the World Health Organization that socioeconomically deprived groups are more susceptible to air pollution,[53] we found that mothers living in areas with a per capita disposable income ≤50% of the average income across all monitored districts or counties (25 185 renminbi [≈$3588 USD]) were more susceptible to $PM_{2.5}$ exposure. Mothers living in the areas with low per capita disposable income may have less access to medical services, less ability to protect themselves from high levels of $PM_{2.5}$ exposure, and low capacity for managing risks and health outcomes.[53] The differences in $PM_{2.5}$ components between northern and southern China potentially affect the results as well.[54] In addition, mothers <35 years of age were more susceptible to $PM_{2.5}$ exposure, the reason

Table 3. Association of Maternal $PM_{2.5}$ Exposure With CHD Stratified by Maternal or Infant Characteristics (per Increase of 10 μg/m³ in $PM_{2.5}$)

Groups	Control, n (%)	Case, n (%)	Periconception period		Preconception period		First trimester	
			OR (95% CI)	*P**	OR (95% CI)	*P**	OR (95% CI)	*P**
Infant sex								
Male	751 038 (52.61)	3816 (52.02)	1.02 (0.99, 1.05)	1.000	1.03 (1.00, 1.06)	1.000	1.02 (0.99, 1.05)	0.644
Female	676 625 (47.39)	3519 (47.98)	1.02 (0.99, 1.05)		1.03 (1.00, 1.06)		1.01 (0.98, 1.04)	
Fetus status								
Singleton	1 394 323 (97.66)	7021 (95.72)	1.02 (1.00, 1.05)	0.411	1.03 (1.01, 1.05)	0.162	1.01 (0.99, 1.03)	0.610
Multiple	33 340 (2.34)	314 (4.28)	0.98 (0.89, 1.07)		0.97 (0.90, 1.06)		1.03 (0.96, 1.11)	
Maternal parity								
Primipara	797 813 (55.88)	4225 (57.60)	1.01 (0.98, 1.04)	0.432	1.03 (1.00, 1.05)	1.000	1.01 (0.98, 1.03)	0.362
Multipara	629 850 (44.12)	3110 (42.40)	1.03 (0.99, 1.07)		1.03 (1.00, 1.06)		1.03 (0.99, 1.06)	
Maternal ethnicity								
Han	1 322 160 (92.61)	6757 (92.11)	1.01 (0.99, 1.04)	0.093	1.03 (1.00, 1.05)	0.285	1.01 (0.99, 1.03)	0.098
Minority	105 503 (7.39)	578 (7.88)	1.08 (1.00, 1.16)		1.07 (1.00, 1.14)		1.07 (1.00, 1.14)	
Maternal age, y								
<35	1 266 725 (88.73)	6313 (86.07)	1.03 (1.00, 1.05)	0.039	1.03 (1.01, 1.05)	0.055	1.02 (1.00, 1.04)	0.115
≥35	160 938 (11.27)	1022 (13.93)	0.97 (0.92, 1.02)		0.99 (0.95, 1.04)		0.98 (0.94, 1.03)	
Region								
Southern	829 221 (58.08)	4807 (65.54)	0.98 (0.94, 1.02)	0.028	0.98 (0.95, 1.02)	0.003	0.96 (0.93, 0.99)	<0.001
Northern	598 442 (41.92)	2528 (34.46)	1.04 (1.00, 1.07)		1.05 (1.02, 1.08)		1.05 (1.02, 1.08)	
Urban or rural residence								
Urban	1 066 918 (74.73)	6289 (85.74)	1.01 (0.98, 1.03)	0.805	1.01 (0.99, 1.04)	0.569	1.00 (0.98, 1.03)	1.000
Rural	360 745 (25.27)	1046 (14.26)	1.00 (0.93, 1.08)		1.03 (0.97, 1.10)		1.00 (0.94, 1.07)	
Per capita disposable income†								
Low	710 736 (49.78)	2508 (34.19)	1.09 (1.05, 1.14)	0.004	1.10 (1.06, 1.14)	<0.001	1.08 (1.04, 1.12)	<0.001
High	716 927 (50.22)	4827 (65.81)	0.98 (0.95, 1.01)		0.99 (0.97, 1.02)		0.98 (0.95, 1.00)	

CHD indicates congenital heart defect; OR, odds ratio; and $PM_{2.5}$, airborne particles with an aerodynamic diameter ≤2.5 μm.

**P* values from a *Z* test assess whether the effect estimates between subgroups were statistically different.

†High income and low income were defined as being higher or lower than 50% of the average per capita disposable income across all the monitored districts or counties (25 185 renminbi [≈$3588 USD]).

for which needs to be further explored. Although some effects were not significant in certain subgroup analyses, they may be diluted by the association between $PM_{2.5}$ and other types of CHD rather than SPD, which needs further investigation with accumulating cases.

Our analysis adds depth and clarity to the current body of evidence investigating the possible association between $PM_{2.5}$ and the risk of CHD using a large sample from the National Population-Based Birth Defects Surveillance System, covering a wide geographic scope in China, which allowed analyses of individual types of CHD. Our work may be the first assessment of the effect of $PM_{2.5}$ in the periconception period on CHD on the basis of a nationwide surveillance-based study.

Our research has some limitations that should be addressed through additional study. First, ambient monitors do not consider personal activity patterns, such as time spent indoors or outdoors and time spent at work or home. This exposure misclassification is assumed to be random, with no systematic differences between pregnant women with fetuses having CHD or not, so it seems likely to have no net effect on our findings. Second, our data came from routine monitoring, and some potential risk factors of CHD could not be controlled in our study, including maternal education, folate supplementation, smoking, and alcohol consumption.[55] Nevertheless, we adjusted for several potential covariates that might influence our findings, including per capita disposable income, temperature, and relative humidity. $PM_{2.5}$ level in the study showed a wide exposure range, with a skewed distribution, and because of the limited sample size of high concentrations, the effect of high $PM_{2.5}$ level needs further verification. Fourth, neonates diagnosed with CHD beyond 42 days after birth would have been assigned to the control group in our study, such that the observed associations of exposure and CHD risk may underestimate the true associations. We did not examine fetuses delivered before 28 weeks of

gestation, which may have biased our sample against severe CHD, as fetuses with severe CHD may not survive to 28 weeks. The net effect would again underestimate $PM_{2.5}$ effects. Therefore, studies involving a dedicated cohort with a diverse range of CHD types and severities, and involving comprehensive analysis of covariates, are needed to verify and extend our findings on the association of maternal exposure to $PM_{2.5}$ and CHD in offspring.

CONCLUSIONS

Maternal exposure to $PM_{2.5}$, especially during the preconception period, may be positively associated with risk of certain types of CHD in offspring, especially SPD. This association may be modified by maternal age, per capita disposable income, and area of residence. These results may help guide efforts to prevent CHD and highlight the public health benefits of improving air quality in China and other highly polluted regions. Future studies should examine potential associations of air pollution with congenital malformations other than CHD.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S4
Figures S1–S7
Appendix S1

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SUPPLEMENTAL MATERIAL

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Table S1. Akaike Information Criteria (AIC) and Bayesian Information Criteria (BIC) of restricted cubic spline modeling with various knots.

Knots	Periconception period		Preconception period		The first trimester	
	AIC	BIC	AIC	BIC	AIC	BIC
p10, p50, p90	85120.93	85352.29	85122.80	85122.8	85133.95	85365.31
p5, p35, p65, p95	85123.07	85390.96	85127.97	85127.97	85131.64	85399.53
p5, p27.5, p50, p72.5, p95	85116.02	85240.43	85129.48	85129.48	85134.40	85438.81
p5, p23, p41, p59, p77, p95	85120.13	85461.21	85131.81	85472.75	85135.03	85475.98

Table S2. Attributable risk proportion (ARP) for the risk of septal defect (SPD) with $PM_{2.5}$ levels over 35 μg/m^3.

Exposure windows	Mean of $PM_{2.5}$ (μg/m^3)	ARP of $PM_{2.5}$ in SPD (%) *
Periconception period	56.51	8.44
Preconception period	56.42	8.45
The first trimester	56.61	6.36

$PM_{2.5}$: fine particulate matter.

Table S3. Sensitivity analyses in relation to congenital heart defects (CHDs) with or without other birth defects.

Groups	Case, n	Exposure windows		
		Periconception period	Preconception period	First trimester
Overall CHDs	7,335	1.02 (1.00, 1.05)	1.03 (1.01, 1.05)	1.02 (1.00, 1.04)
CHDs without other birth defects	6,592	1.03 (1.00, 1.06)	1.04 (1.01, 1.06)	1.02 (1.00, 1.04)
CHDs with other birth defects	743	1.00 (0.95, 1.06)	1.00 (0.95, 1.05)	1.02 (0.97, 1.07)

Table S4. Sensitivity analyses in relation to different methods of calculating 3-month average $PM_{2.5}$.

Exposure window	Method 1*		Method 2†		Method 3‡	
	Mean ± SD	OR(95%CI)	Mean ± SD	OR(95%CI)	Mean ± SD	OR(95%CI)
Periconception period	56.51±21.78	1.02 (1.00, 1.05)	56.41±22.63	1.04 (1.02, 1.07)	56.52±22.57	1.03 (1.00, 1.05)
Preconception period	56.42±24.76	1.03 (1.01, 1.05)	56.31±27.54	1.03 (1.01, 1.05)	56.39±25.45	1.04 (1.01, 1.06)
First trimester	56.61±25.22	1.02 (1.00, 1.04)	56.57±25.17	1.02 (0.99, 1.04)	56.60±24.85	1.02 (0.99, 1.04)

*: When the "90" days were spread over 4 months, the 3-month average $PM_{2.5}$ was calculated based on monthly average $PM_{2.5}$ in the month in which data covered more than 15 days.

†: When the "90" days were spread over 4 months, the 3-month average $PM_{2.5}$ was calculated based on monthly average $PM_{2.5}$ during 4 months.

‡ : When the "90" days were spread over 4 months, the 3-month average $PM_{2.5}$ was calculated based on monthly average $PM_{2.5}$ values during 4 months, each weighted by the proportion of days covered in the month.

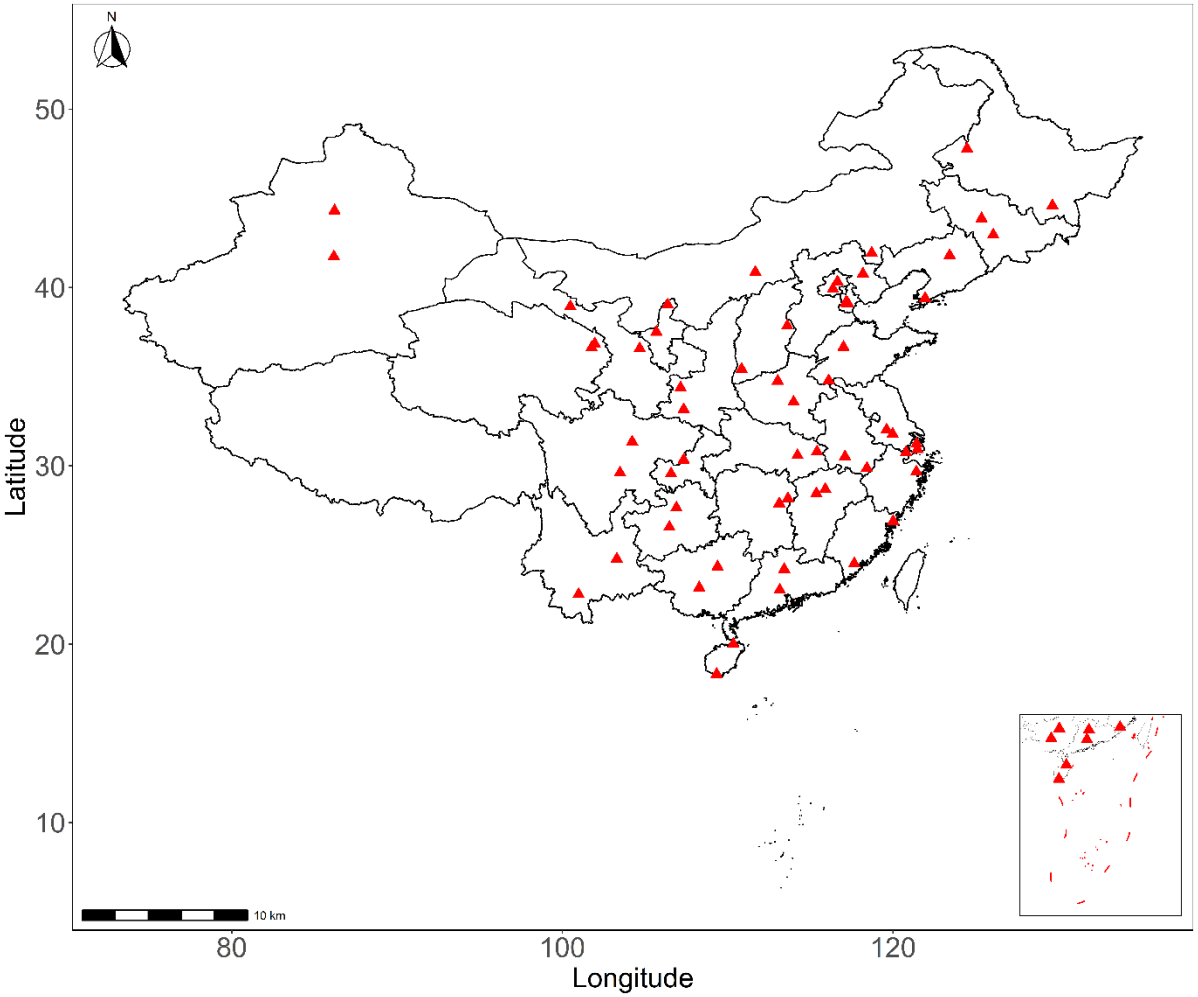

Figure S1. Spatial distributions of monitored districts or counties for population-based birth defects in China.

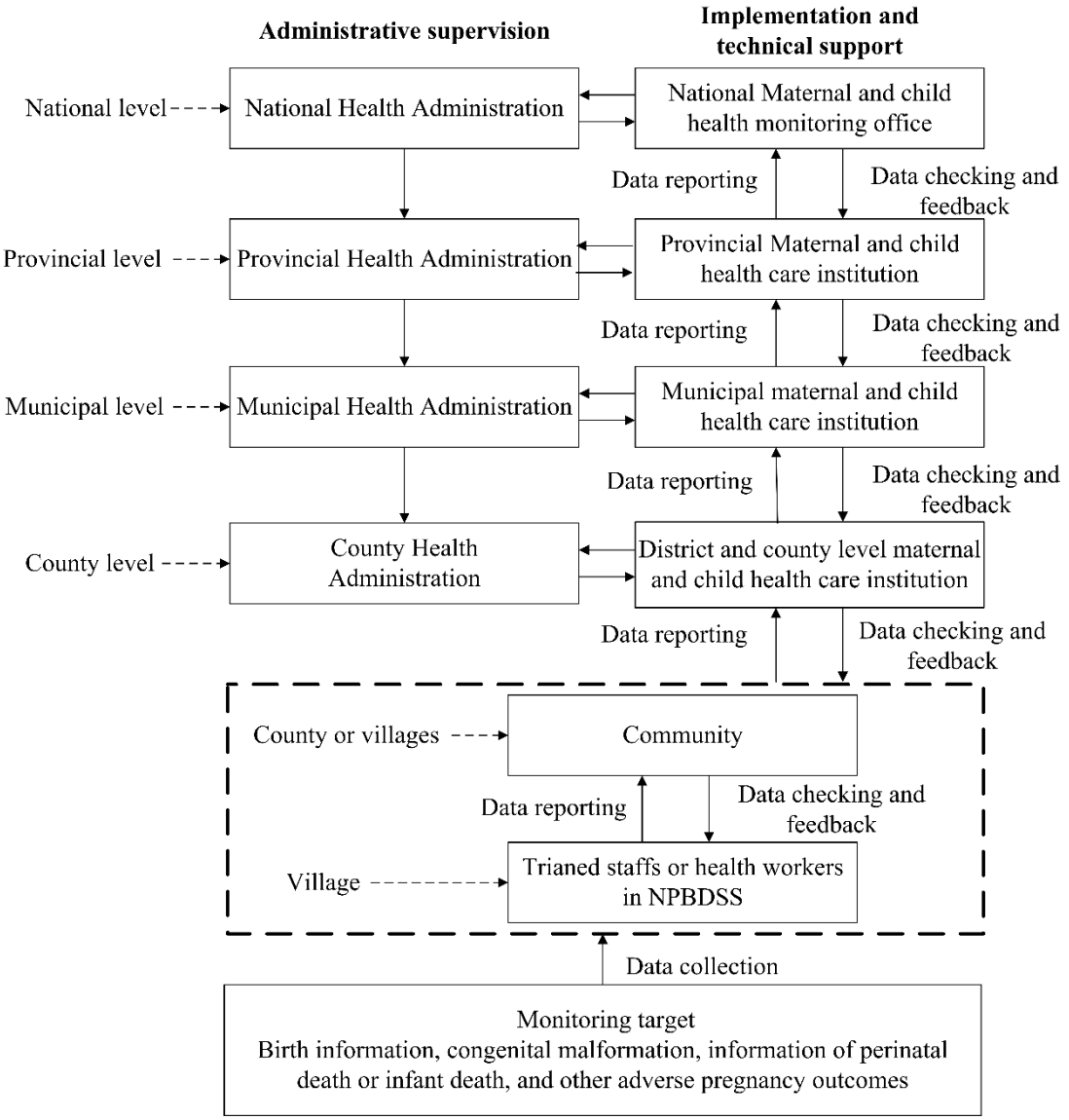

Figure S2. Flow chart of data reporting and quality control for NPBDSS. NPBDSS, national population-based birth defects surveillance system.

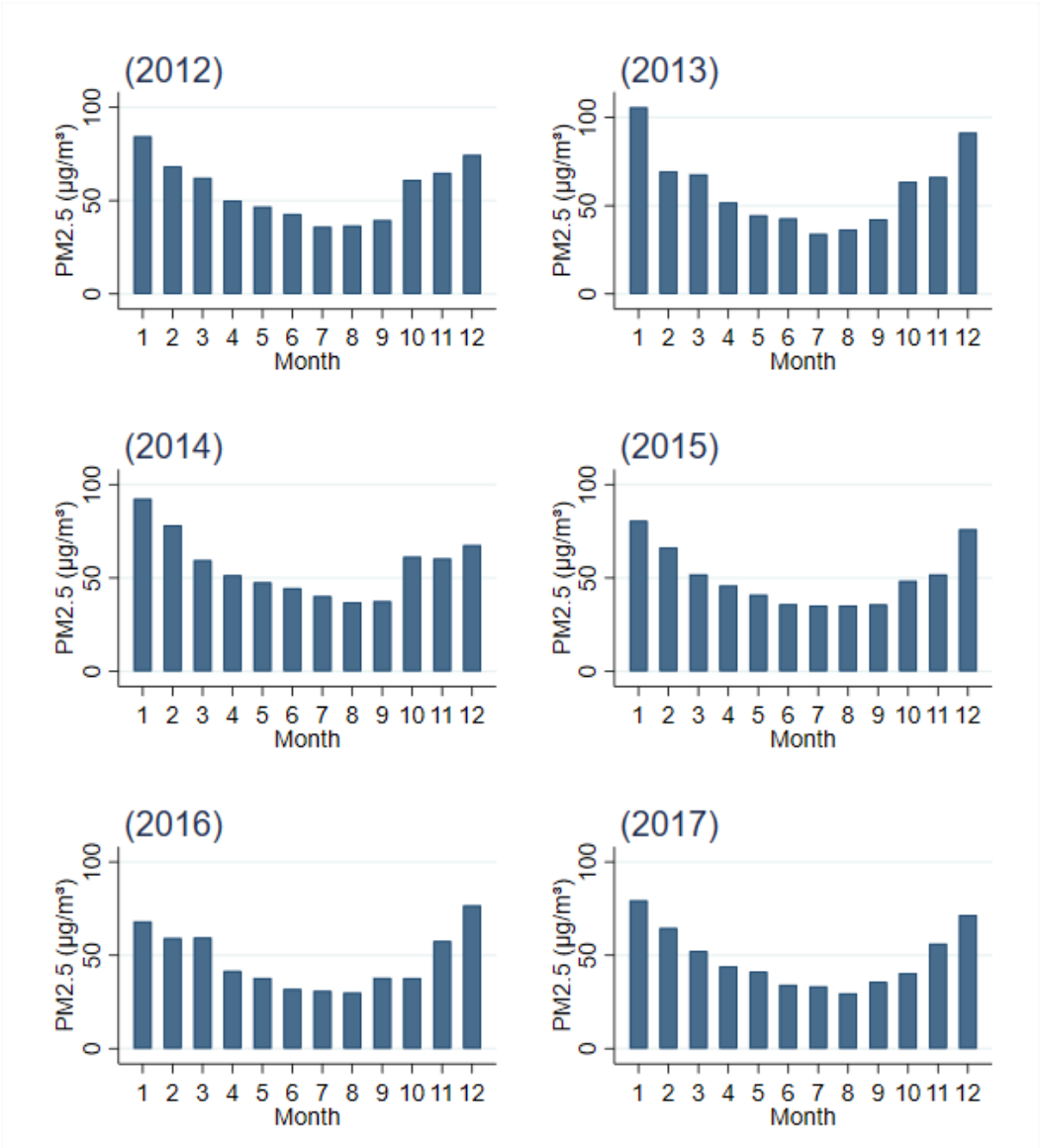

Figure S3. $PM_{2.5}$ concentrations for all study participants during study period.

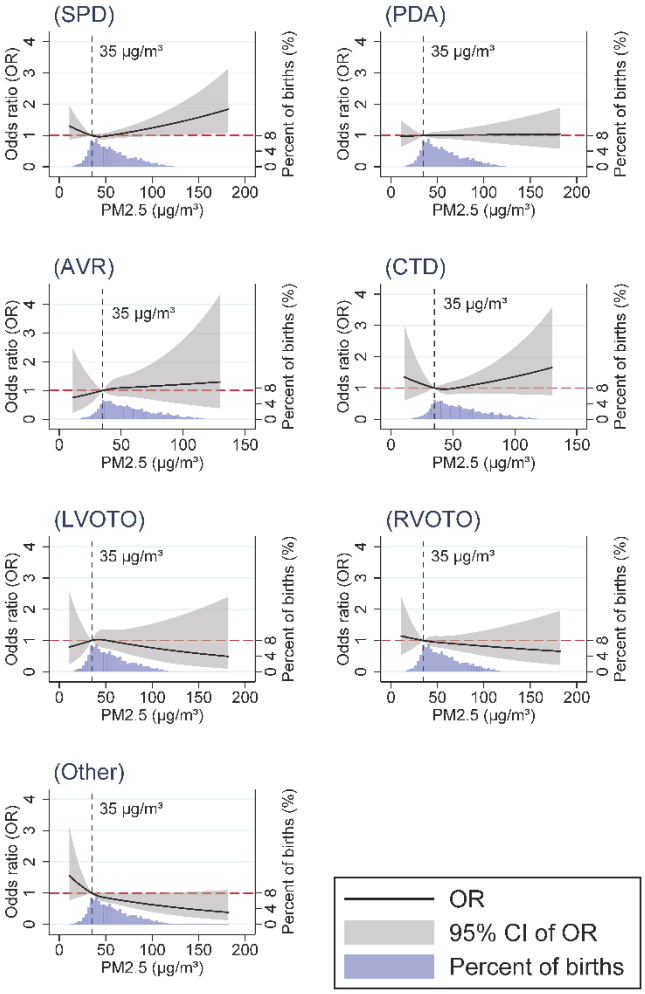

Figure S4. Exposure-response association of maternal exposure to $PM_{2.5}$ in the periconception period and CHDs in offspring. Restricted cubic spline analysis was used to evaluate the shape of the association between $PM_{2.5}$ and the prevalence of CHDs. Odds ratios were estimated by comparing to a reference value of 35 μg/m³, which is the China Class II standard of the annual mean of $PM_{2.5}$. Percentages of births were calculated over all births during the period from 2014 to 2017 per unit of $PM_{2.5}$. Solid line represents point estimates and gray area represents 95% confidence intervals. AVR, anomalous venous return; CTD, conotruncus defect; LVOTO, left ventricular outflow tract obstruction; PDA, patent ductus arteriosus; Other, cardiac structure abnormalities not classified into the other types; RVOTO, right ventricular outflow tract obstruction; SPD, septal defect.

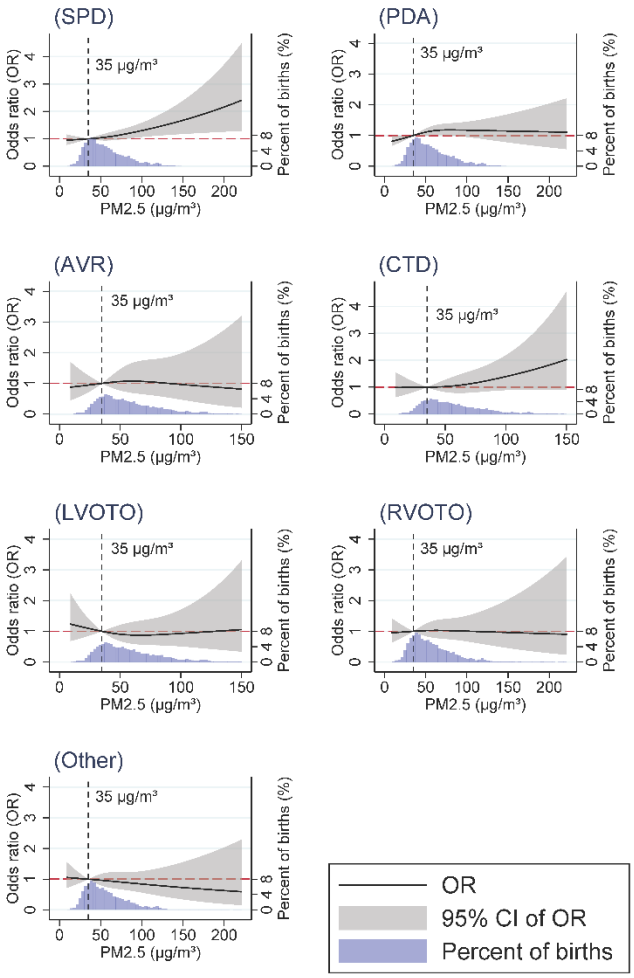

Figure S5. Exposure-response association of maternal exposure to $PM_{2.5}$ in the preconception period and CHDs in offspring. Restricted cubic spline analysis was used to evaluate the shape of the association between $PM_{2.5}$ and the prevalence of CHDs. Odds ratios were estimated by comparing to a reference value of 35 μg/m³, which is the China Class II standard of the annual mean of $PM_{2.5}$. Percentages of births were calculated over all births during the period from 2014 to 2017 per unit of $PM_{2.5}$. Solid line represents point estimates and gray area represents 95% confidence intervals. AVR, anomalous venous return; CTD, conotruncus defect; LVOTO, left ventricular outflow tract obstruction; PDA, patent ductus arteriosus; Other, cardiac structure abnormalities not classified into the other types; RVOTO, right ventricular outflow tract obstruction; SPD, septal defect.

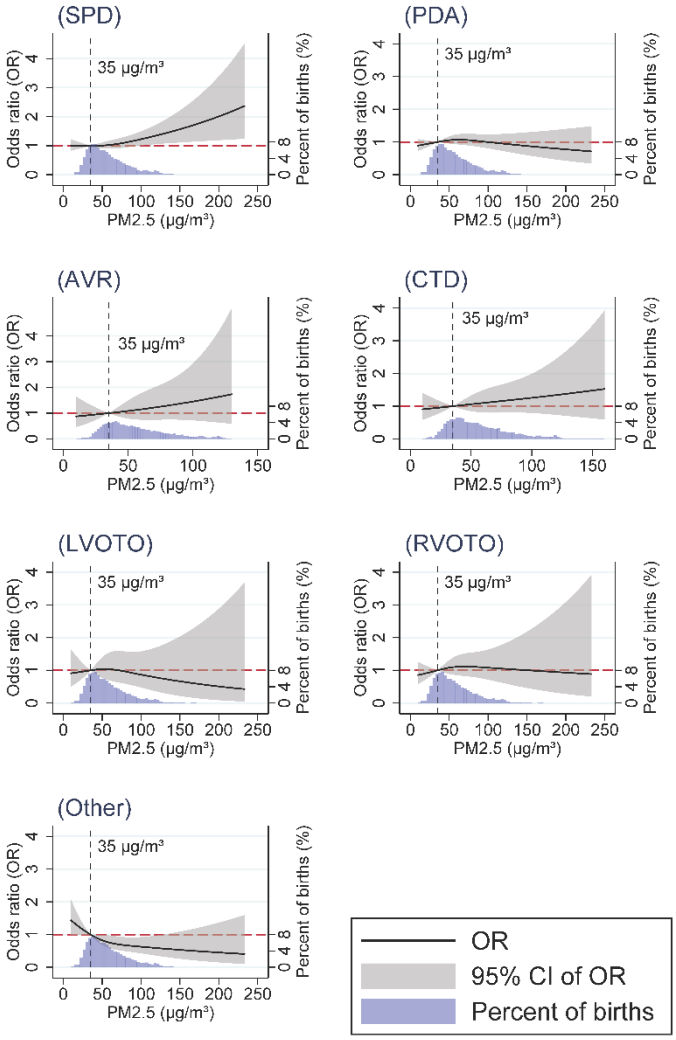

Figure S6. Exposure-response association of maternal exposure to $PM_{2.5}$ in the first trimester and CHDs in offspring. Restricted cubic spline analysis was used to evaluate the shape of the association between $PM_{2.5}$ and the prevalence of CHDs. Odds ratios were estimated by comparing to a reference value of 35 μg/m³, which is the China Class II standard of the annual mean of $PM_{2.5}$. Percentages of births were calculated over all births during the period from 2014 to 2017 per unit of $PM_{2.5}$. Solid line represents point estimates and gray area represents 95% confidence intervals. AVR, anomalous venous return; CTD, conotruncus defect; LVOTO, left ventricular outflow tract obstruction; PDA, patent ductus arteriosus; Other, cardiac structure abnormalities not classified into the other types; RVOTO, right ventricular outflow tract obstruction; SPD, septal defect.

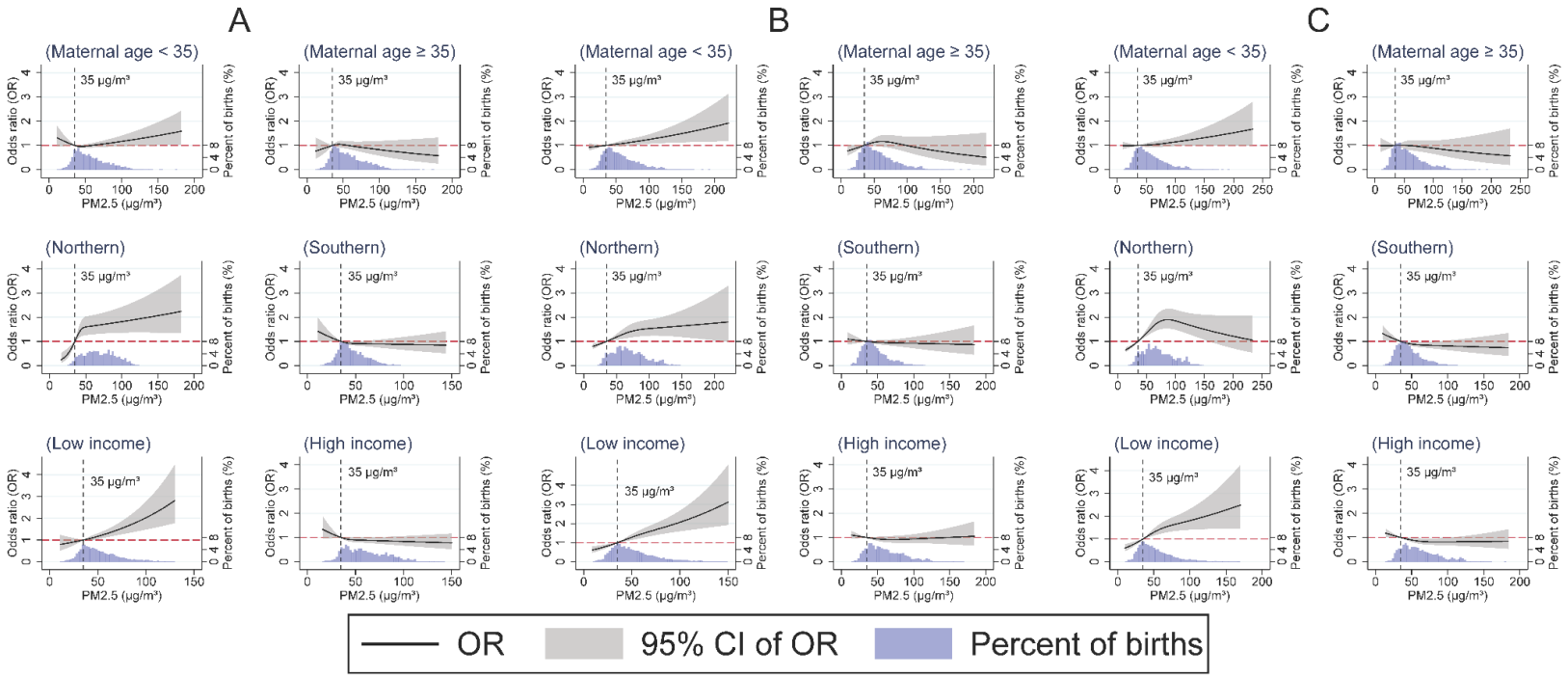

Figure S7. Exposure-response association of maternal exposure to $PM_{2.5}$ by maternal characteristics, in the periconception period, preconception period, and the first trimester. **A**: periconception period, **B**: preconception period, **C**: the first trimester. Restricted cubic spline analysis was used to evaluate the shape of the association between $PM_{2.5}$ and the prevalence of CHDs. Odds ratios were estimated by comparing to a reference value of 35 μg/m³, which is the China Class II standard of the annual mean of $PM_{2.5}$. Percentages of births were calculated over all births during the period from 2014 to 2017 per unit of $PM_{2.5}$. Solid line represents point estimates and gray area represents 95% confidence intervals.

Appendix S1—Checklist of items that should be included in reports of case-control studies.

	Item No	Recommendation	Location
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Pages 3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Pages 5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 6
Methods			
Study design	4	Present key elements of study design early in the paper	Page 7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Pages 7-8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	Page 9
		(*b*) For matched studies, give matching criteria and the number of controls per case	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Pages 9-11
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Pages 9-12

Bias	9	Describe any efforts to address potential sources of bias	Pages 9, 11
Study size	10	Explain how the study size was arrived at	Page 8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Pages 10-11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Pages 10-13
		(*b*) Describe any methods used to examine subgroups and interactions	Page 12
		(*c*) Explain how missing data were addressed	Pages 8-9
		(*d*) If applicable, explain how matching of cases and controls was addressed	-
		(*e*) Describe any sensitivity analyses	Page 12
Results			
Participants	13	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Pages 8-9, 13
		(b) Give reasons for non-participation at each stage	Pages 8-9
		(c) Consider use of a flow diagram	Page 9
Descriptive data	14	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Page 13
		(b) Indicate number of participants with missing data for each variable of interest	-
Outcome data	15	Report numbers in each exposure category, or summary measures of exposure	Page 13
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Pages 11, 13, 14
		(*b*) Report category boundaries when continuous variables were categorized	Pages 10-11

		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Page 14
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Pages 14-15
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Pages 18-19
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Pages 15-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	Pages 18-19
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 19