HHS Public Access

Author manuscript

Sci Total Environ. Author manuscript; available in PMC 2023 February 20.

Published in final edited form as:

Sci Total Environ. 2022 February 20; 808: 152150. doi:10.1016/j.scitotenv.2021.152150.

Modeling complex effects of exposure to particulate matter and extreme heat during pregnancy on congenital heart defects: A U.S. population-based case-control study in the National Birth Defects Prevention Study

Will Simmons[a], **Shao Lin**[b,c], **Thomas J. Luben**[d], **Scott C. Sheridan**[e], **Peter H. Langlois**[f], **Gary M. Shaw**[g], **Jennita Reefhuis**[h], **Paul A. Romitti**[i], **Marcia L. Feldkamp**[j], **Wendy N. Nembhard**[k], **Tania A. Desrosiers**[l], **Marilyn L. Browne**[b,m], **Jeanette A. Stingone**[a], **National Birth Defects Prevention Study**

[a]Department of Epidemiology, Columbia University, 722 West 168th Street, New York, New York, 10032, USA

[b]Department of Epidemiology and Biostatistics, University at Albany, 1 University Place, Rensselaer, New York, 12144, USA

[c]Department of Environmental Health Sciences, University at Albany, 1 University Place, Rensselaer, New York, 12144, USA

[d]Office of Research and Development, U.S. Environmental Protection Agency, 109 T.W. Alexander Drive, RTP, North Carolina, 27711, USA

[e]Department of Geography, Kent State University, 325 S. Lincoln Street, Kent, Ohio, 44242, USA

[f]Department of Epidemiology, Human Genetics, and Environmental Science, University of Texas School of Public Health, 1616 Guadalupe Street, Austin, Texas, 78701, USA

[g]Stanford School of Medicine, 453 Quarry Road, Stanford, California, 94305, USA

[h]National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, 1600 Clifton Road, Atlanta, Georgia, 30333, USA

[i]Department of Epidemiology, The University of Iowa, 145 N. Riverside Drive, Iowa City, Iowa, 52242, USA

[j]Department of Pediatrics, University of Utah School of Medicine, 295 Chipeta Way, Salt Lake City, Utah, 84108, USA

Corresponding author: Jeanette Stingone, Department of Epidemiology, Columbia University, 722 West 168th Street, Room 1608, New York, New York, 10032, USA. j.stingone@columbia.edu.

[k]Departments of Pediatrics and Epidemiology, University of Arkansas for Medical Sciences, 4301 W Markham Street, Little Rock, Arkansas, 72205, USA

[l]Department of Epidemiology, University of North Carolina, 135 Dauer Drive, Chapel Hill, North Carolina, 27599, USA

[m]Birth Defects Registry, New York State Department of Health, Corning Tower, Empire State Plaza, Albany, New York, 12237, USA

Abstract

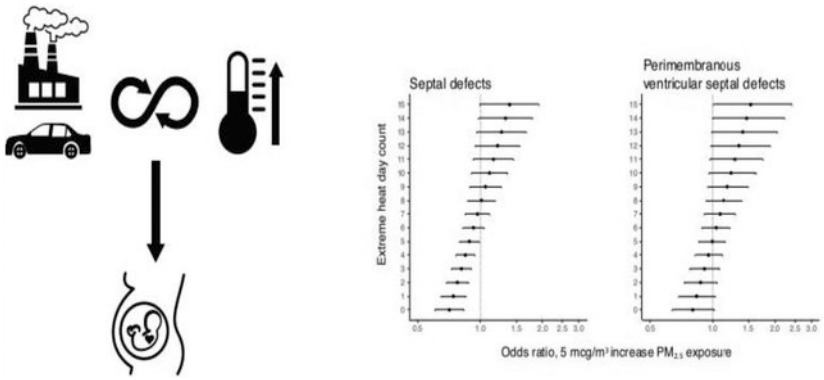
Background/Objective.—Research suggests gestational exposure to particulate matter ≤ 2.5 μm ($PM_{2.5}$) and extreme heat may independently increase risk of birth defects. We investigated whether duration of gestational extreme heat exposure modifies associations between $PM_{2.5}$ exposure and specific congenital heart defects (CHDs). We also explored nonlinear exposure-outcome relationships.

Methods.—We identified CHD case children (n = 2,824) and non-malformed live-birth control children (n = 4,033) from pregnancies ending between 1999 and 2007 in the National Birth Defects Prevention Study, a U.S. population-based multicenter case-control study. We assigned mothers 6-week averages of $PM_{2.5}$ exposure during the cardiac critical period (postconceptional weeks 3–8) using the closest monitor within 50 kilometers of maternal residence. We assigned a count of extreme heat days (EHDs, days above the 90th percentile of daily maximum temperature for year, season, and weather station) during this period using the closest weather station. Using generalized additive models, we explored logit-nonlinear exposure-outcome relationships, concluding logistic models were reasonable. We estimated joint effects of $PM_{2.5}$ and EHDs on six CHDs using logistic regression models adjusted for mean dewpoint and maternal age, education, and race/ethnicity. We assessed multiplicative and additive effect modification.

Results.—Conditional on the highest observed EHD count (15) and at least one critical period day during spring/summer, each 5 μg/m³ increase in average $PM_{2.5}$ exposure was significantly associated with perimembranous ventricular septal defects (VSDpm; OR: 1.54 [95% CI: 1.01, 2.41]). High EHD counts (8+) in the same population were positively, but non-significantly, associated with both overall septal defects and VSDpm. Null or inverse associations were observed for lower EHD counts. Multiplicative and additive effect modification estimates were consistently positive in all septal models.

Conclusions.—Results provide limited evidence that duration of extreme heat exposure modifies the $PM_{2.5}$-septal defects relationship. Future research with enhanced exposure assessment and modeling techniques could clarify these relationships.

Graphical Abstract



Keywords

particulate matter; temperature extremes; birth outcomes; congenital heart defects

1. Introduction

Congenital heart defects (CHDs) are the most commonly reported group of birth defects (van der Linde et al., 2011), broadly defined as developmental abnormalities present at birth in the heart or nearby blood vessels (American Heart Association, 2020). Global prevalence estimates for CHDs range from 9 to 18 per 1,000 live births (Liu et al., 2019; Zimmerman et al., 2020), with estimates in the U.S. and Canada around 12 per 1,000 (Zimmerman et al., 2020). CHDs have complex etiologies: only 20 percent of cases are attributable to known genetic and environmental factors (Blue et al., 2012).

Few potential risk factors for CHDs are as widespread as exposure to airborne pollutants, although ambient concentrations vary spatially and temporally (Bell et al., 2007), leading to heterogeneity in maternal exposure levels. Associations between $PM_{2.5}$ and specific CHDs have been reported previously, but estimates are inconsistent across studies. CHDs with observed, positive relationships with $PM_{2.5}$ include transposition of the great arteries (Padula et al., 2013), hypoplastic left heart syndrome (Stingone et al., 2014), interrupted aortic arch, non-isolated truncus arteriosus, total anomalous pulmonary venous return, coarctation of the aorta (Tanner et al., 2015), atrial septal defects, endocardial cushion defect, and pulmonary artery and valve stenosis (Huang et al., 2019). However, studies have also reported less consistent findings. A recent meta-analysis found little evidence of associations between ambient pollutants—including $PM_{2.5}$—and CHDs, but studies included were geographically and methodologically heterogenous (Ma et al., 2021). Studies have also found inverse associations between $PM_{2.5}$ and certain CHDs. In samples distinct from those in this study, Agay-Shay et al. (2013) reported inverse $PM_{2.5}$ associations with isolated patent ductus arteriosus; Schembari (2014) with ventricular septal defects; and Vinikoor-Imler et al. (2015) with septal and obstructive defects. Prior analyses within the National Birth Defects Prevention Study (NBDPS)—the source of our study population—have also reported inverse associations between $PM_{2.5}$ and atrial septal defects (Padula et al., 2013; Stingone et al., 2014).

Research has also explored maternal exposure to high ambient temperature as a risk factor for CHDs. Broadly, unusually high temperatures and extreme heat events (EHEs) have both been linked to negative health outcomes, including adverse birth outcomes (He et al., 2016; Zhang et al., 2017; Haghighi et al., 2021) and mortality (Gasparrini and Armstrong, 2011; Mora et al., 2017). A small number of recent studies have specifically investigated exposure to EHEs as a potential risk factor for CHDs, a biologically plausible relationship given the well-documented teratogenic effects of fetal heat exposure (Bennett, 2010; Edwards et al., 2003; Milunsky et al., 1992). Studies linking EHEs and CHDs have consistently reported positive associations with septal defects (K Agay-Shay et al., 2013; Auger et al., 2017; Lin et al., 2018), with one also reporting positive associations with conotruncal defects (Lin et al., 2018).

As global mean temperatures rise and extreme climatic events become more common (Jones et al., 2015; Watts et al., 2021), prevalence of CHDs resulting from extreme heat may increase (Zhang et al., 2019). Complex relationships between air pollution, climate, and health are of concern, having been noted widely in research and high-level policy (WHO, 2018). Synergistic effects between $PM_{2.5}$ and temperature have been reported, with extreme temperatures worsening the effects of ambient pollution exposure on health outcomes (Chen et al., 2018; Kioumourtzoglou et al., 2015; Stafoggia et al., 2008; Zanobetti and Peters, 2015; Zhang et al., 2018). However, there is uncertainty as to the mechanisms underlying modification of pollutant-related health effects by meteorological factors. Some suggest this is mainly due to changes in population behavior between warmer and colder seasons, which leads to variations in personal exposure (Hänninen and Jantunen, 2007). Particulate matter has also been shown to vary in composition by season, which may contribute to this modification (Bell et al., 2007). Others have suggested that physiological stress responses to extreme heat may increase susceptibility to ambient pollutants (Gordon, 2003). Finally, biological pathways of synergy remain feasible because particulate matter and extreme heat may share teratogenic pathways (Bennett, 2010; Tanwar et al., 2017; Wu et al., 2019).

Most published research on interactions between air pollution and extreme heat has focused on associations with aggregate health outcomes, such as emergency department visits (Chen et al., 2018) or mortality count (Chen et al., 2018; Kioumourtzoglou et al., 2015; Stafoggia et al., 2008; Zanobetti and Peters, 2015; Zhang et al., 2018). A recent U.S.-based study from our research group (Stingone et al., 2019) was the first to analyze $PM_{2.5}$-EHE interactions with respect to CHDs, finding that ventricular septal defects were associated with $PM_{2.5}$ exposure only among mothers exposed to an EHE. Another recent study based in Changsha, China (Jiang et al., 2021) also reported interaction effects between ambient heat exposure and multiple pollutants, including $PM_{2.5}$, on overall CHDs. However, a limitation of both studies was their use of dichotomized measures of maternal $PM_{2.5}$ and/or heat exposure, whereas research has demonstrated complex dose-response relationships between $PM_{2.5}$, heat, and various health outcomes (Chen et al., 2018; Daniels, 2000; Dejmek et al., 1999; Gasparrini et al., 2015; Vodonos et al., 2018; Zanobetti and Peters, 2015). To capture these complexities, the current study analyzes the same sample used in Stingone et al.'s 2019 research, expanding on this prior study in two ways. First, we use continuous operationalizations for maternal $PM_{2.5}$ and extreme heat exposures (see Section 2.2), which avoids loss of power and potential bias introduced by categorization of explanatory variables

(Royston et al., 2006). Second, we investigate whether logit-linearity assumptions imposed by logistic regression models are reasonable in estimating $PM_{2.5}$-heat-CHD relationships (see Section 2.4), because the independent and joint effects of these exposures on CHDs may be more accurately estimated using more flexible models.

Thus, our objective in this study was to further characterize the complex relationships and potential interactions between $PM_{2.5}$ and extreme heat in two ways: first, by exploring nonlinear relationships between these exposures and CHDs using generalized additive models (GAMs); and second, by modeling the joint effects of these exposures operationalized as continuous measures.

2. Methods

2.1 Study design and population.

We used data from study participants in the National Birth Defects Prevention Study (NBDPS), a U.S. population-based multicenter case-control study aimed at understanding causes of birth defects. Details of the NBDPS design and methods have been described elsewhere (Reefhuis et al., 2015). Briefly, NBDPS case children included infants, stillbirths (gestational age > 20 weeks or fetal weight > 500 grams), and induced termination pregnancies with a diagnosis of at least one of 37 eligible birth defects. Case children with disorders of known etiology were excluded, as the primary goal of the NBDPS is to find causes of birth defects. Control children were randomly selected infants without birth defects and located at the same study site (i.e., an entire U.S. state or selected counties within one U.S. state) as case children. Control children were sampled from the same at-risk populations from which case children originated, using birth hospital records or vital records. Monthly totals for selected control children were proportional in size to the number of same-month, prior-year births.

The subpopulation we drew from the NBDPS for this study has been described previously (Stingone et al., 2019). We included case and control children from eight of the ten NBDPS study centers with estimated dates of delivery between January 1, 1999 (U.S. states Arkansas, California, Georgia, Iowa, New York, and Texas) or January 1, 2003 (U.S. states North Carolina and Utah) and December 31, 2007. Our study population included all control children observed during this period and case children with an isolated (single) CHD and no extracardiac malformations.

CHDs were classified in the NBDPS by a team of clinicians with expertise in pediatric cardiology, genetics, and epidemiology. The classification process is described in detail elsewhere (Botto et al., 2007). Given the developmental, clinical, and epidemiological differences among CHDs, the goal of classification was to obtain reasonably large subgroups with minimal morphological heterogeneity. Thus, case children were classified according to heart defect type, complexity, and presence of non-CHD anomalies, with a detailed cardiac phenotype assigned to each case. From this phenotype, case children were mapped to complex multilevel CHD groupings.

In this study, we examined four broad groups of CHDs as outcomes of interest: left ventricular outflow tract obstructive defects (LVOTO), right ventricular outflow tract obstructive defects (RVOTO, in this study excluding Ebstein's anomaly), conotruncal defects, and septal defects. The number of septal defects among case children was such that we were able to include two septal defect phenotypes as specific outcome categories: secundum atrial septal defects (ASD-II) and perimembranous ventricular septal defects (VSDpm). We conducted separate analyses for each of these six outcomes (four broad defect groups and two septal subgroups) to maximize within-group etiologic homogeneity.

In alignment with NBDPS protocols, we use the term "mother" to refer to the parent of a case or control child with a biological and gestational relationship to that child. Mothers of case and control children participated in structured telephone interviews from 6 weeks to 24 months after delivery. These were administered in English or Spanish and collected data on relevant demographic, health, and other pregnancy-related topics. Participant response for our study's population was 69% among case mothers and 65% among control mothers.

2.2 Exposure and covariate assignment.

During the NBDPS interview, each mother reported a history of residential addresses from three months prior to estimated conception until delivery. Addresses reported from the entire history of the pregnancy were centrally geocoded for consistency across study centers by the Geospatial Research, Analysis, and Services Program of the United States Agency for Toxic Substances and Disease Registry. We then assigned environmental exposure levels to each mother using each address and corresponding dates of residence reported for postconceptional weeks 3 to 8, a recognized critical period for prenatal cardiac development (Schoenwolf et al., 2020). To estimate postconceptional weeks, we used the estimated due date provided by a physician and reported by each mother to calculate each infant's gestational age at birth. Using gestational age at birth, we then estimated the date of conception and assigned corresponding calendar dates to each subsequent week.

We obtained data for our primary exposure of interest, ambient $PM_{2.5}$, from the United States Environmental Protection Agency (EPA) Air Quality System. Assignment of $PM_{2.5}$ exposure levels to NBDPS participants is detailed in previous research (Stingone et al., 2014) and described here. Briefly, we mapped geocoded maternal residences during postconceptional weeks 3 to 8 to the nearest EPA $PM_{2.5}$ monitor within 50 km (see Table S1 for distribution of distances to EPA $PM_{2.5}$ monitor by case status). We averaged 24-hour $PM_{2.5}$ measurements for each mother from weeks 3 to 8 of pregnancy, which yielded a single $PM_{2.5}$ exposure estimate for the 6-week critical exposure period. $PM_{2.5}$ records varied in temporal measurement density but were recorded, on average, approximately once every other day across $PM_{2.5}$ monitors assigned to study participants.

Extreme heat exposure assignment is also detailed in prior NBDPS studies (Lin et al., 2018; Van Zutphen et al., 2012). We used geocoded maternal residences to map mothers to the closest weather station, with meteorological data for each station obtained from the National Oceanic and Atmospheric Administration's (NOAA) National Centers for Environmental Information (U.S. NOAA, 2020). We gathered data on daily maximum temperature and dewpoint temperature for this study. To assign maternal exposure to extreme heat days

(EHDs), we totaled the number of days above the 90th percentile for daily maximum temperature in the exposure window (postconceptional weeks 3 to 8) with respect to the maximum temperature distribution within a specific year, season, and weather station. We then used the number of days above the 90th percentile for maximum temperature as a cumulative measure of critical period EHD exposure based on relative heat.

In addition to our primary measure of extreme heat, we calculated three other metrics: our primary EHD measure calculated at the 95th percentile; a continuous measure in days of a mother's longest exposure to an extreme heat event at the 90th percentile (EHE90, defined as ≥ 3 days above the 90th percentile for maximum temperature); and a continuous measure in days of a mother's longest exposure to an EHE defined at the 95th percentile (EHE95, defined as ≥ 2 days above the 95th percentile for maximum temperature). We refit our models using these alternative heat measures as sensitivity analyses to assess the potential effects of cumulative heat exposure across consecutive days.

To account for humidity's effect on apparent temperature, we included mean dewpoint temperature during the critical period as a covariate in all multivariable analyses that included EHDs as a covariate.

2.3 Confounder identification.

Potential confounders of the relationships between $PM_{2.5}$, extreme heat, and CHDs have been considered in similar studies (Lin et al., 2018; Stingone et al., 2019, 2014; Van Zutphen et al., 2012). Our causal model included maternal $PM_{2.5}$ exposure as the exposure of interest and offspring CHDs as the outcomes of interest, with maternal EHD exposure included as a potential confounder (Buckley et al., 2014). In interaction models, EHD exposure was also evaluated as a potential effect modifier of the $PM_{2.5}$-CHD relationship (Stingone et al., 2019; Zanobetti and Peters, 2015). For consistency across studies, we constructed a directed acyclic graph (DAG) (Greenland et al., 1999) using the same set of potential confounders evaluated in Stingone et al. (2019) and Lin et al. (2018): maternal race/ethnicity; maternal age at delivery; maternal education at delivery; maternal pre-pregnancy body mass index; maternal use of alcohol, caffeine, and/or tobacco during pregnancy; maternal use of hot baths, hot tubs, or saunas during pregnancy; maternal medical conditions during pregnancy, including fever, hypertension, and/or pregestational and gestational diabetes; maternal folic acid intake; parity; plurality; multiple birth; prenatal care; family history of CHDs; and regional mean dewpoint during the critical period. (See Supplemental Figures S1 and S2.)

As in Stingone et al. (2019), we identified maternal age at delivery (≤ 19, 20 to 34, ≥ 35 years), maternal race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, other), maternal education level at delivery (< 12 or ≥ 12 years), and regional mean dewpoint during the critical period as confounders. We included these confounders, in addition to maternal EHD exposure, as covariates in all adjusted models.

2.4 Statistical analysis.

We analyzed our full study population in all statistical models. To account for seasonal differences among observations, we included an indicator of having at least one critical period day during the hot seasons (defined as March through August, i.e., spring and

summer) in adjusted full population models. Additionally, we fit models that included only the subpopulation of mothers with at least one critical exposure period day during spring or summer. Analyses of this subpopulation allowed us to focus on mothers most likely to experience exposure to extreme heat across study regions.

First, covariate-adjusted logistic regression models were fit to estimate the total effect of maternal exposure to $PM_{2.5}$ on each CHD. Both $PM_{2.5}$ in $\mu g/m^3$ and EHDs (a potential confounder) were included as continuous terms, along with the covariates mentioned previously. From these models, we estimated odds ratios (ORs) and 95% confidence intervals (CIs) for the total effect of $PM_{2.5}$ on odds of CHD in offspring.

Complex, potentially nonlinear relationships between $PM_{2.5}$, temperature, and a range of health outcomes have been reported previously (Gasparrini et al., 2015; Zanobetti and Peters, 2015). Thus, we next constructed generalized additive models (GAMs), which allowed us to relax assumptions of logit-linearity imposed by logistic regression. Generalized linear models (GLMs), including logistic regression models, assume the mean of a response variable depends on a linear combination of model covariates via a link function. GAMs are more flexible, semi-parametric expansions of GLMs, in which model covariates may include smooth terms (Hastie and Tibshirani, 1986). We used the *mgcv* package (version 1.8) (Wood, 2017) in R to fit nonlinear penalized thin plate regression splines to both $PM_{2.5}$ and EHD terms using GAMs, adjusted for the same parametric confounding terms used in our logistic models. Spline smoothing parameters for each model were estimated via minimization of an unbiased risk estimator (UBRE) (Wood, 2004). Effective degrees of freedom (EDF), an indicator of a spline's complexity, were calculated for each penalized thin plate regression spline term, which were used to assess potential logit-nonlinear relationships between $PM_{2.5}$, EHDs, and CHDs. A statistically significant spline term with EDF > 1 was interpreted to indicate a potential logit-nonlinear relationship, with p-values testing a null hypothesis of spline term equivalence to a null term.

To investigate nonlinear exposure-outcome relationships, we implemented a two-stage model selection process, similar to one outlined by Wood (Marra and Wood, 2011; Wood, 2019). First, if a spline term was not significantly different than a null term at an alpha level of 0.05 (Wood, 2013), it was replaced with a parametric linear term. If, however, we estimated plausible nonlinearity as outlined above for any spline term, it was kept in the GAM. Second, we compared GAMs containing significant spline terms to their fully parametric (i.e., logistic regression) counterparts. To do this, we visually compared the predicted log-odds of CHD and 95% CIs in both GAMs and logistic models across values of the exposure of interest, $PM_{2.5}$. Predicted log-odds were used to assess nonlinearity—as opposed to, e.g., ORs—because logistic models assume linearity on the log-odds scale. (Note that the difference between two log-odds is equivalent to a log-OR.) Therefore, potential nonlinearity in a GAM that includes spline terms will be most apparent on the log-odds scale because its spline-free GLM counterpart will be linear on this scale. If the predicted values of the two models did not significantly differ (i.e., there was no $PM_{2.5}$ value at which the CIs for the models' predicted log-odds of CHD did not overlap), we designated the logistic model as the final model to prioritize interpretability.

Finally, we assessed interactions between $PM_{2.5}$ and EHD exposure for each final model. Because there were no departures from logit-linearity that were significantly different from a parametric model, we estimated interaction effects using adjusted logistic regression models. We assessed interaction on the multiplicative scale by including a cross-product term between continuous measures of $PM_{2.5}$ and EHD exposure. We tested cross-product terms for statistical significance using likelihood ratio tests (LRT). To visually represent multiplicative interaction in models with a significant cross-product term, we plotted conditional ORs at each observed EHD count, displaying the conditional effect of $PM_{2.5}$ on each CHD outcome. These plots were produced using the *interplot* package (Solt and Hu, 2019). Corresponding conditional parameter estimates and 95% CIs were estimated via the *arm* package, using 10,000 independent posterior model simulations (Gelman and Hill, 2007).

We also estimated interaction on the additive scale by calculating the relative excess risk due to interaction on the OR scale ($RERI_{OR}$) for each logistic model as follows: $RERI_{OR} = OR_{11} - OR_{10} - OR_{01} + 1$. In calculating RERI on the OR scale, we assumed our OR estimates approximated risk ratios (RRs). We interpreted $RERI_{OR}$ values above 0 as superadditivity and values below 0 as subadditivity. Although RERI is typically calculated using two dichotomous interacting variables, Knol et al. (2007) provide useful considerations for calculating this measure between continuous interacting variables. We estimated 95% CIs for each model's $RERI_{OR}$ measure using 10,000 nonparametric bootstrap samples.

Parametric effect estimates for $PM_{2.5}$ (including interaction terms) were calculated per 5 $\mu g/m^3$ increase in maternal exposure, an approximately interquartile range (IQR) increase for the study population. EHD exposure, when included in models as a potential confounder and/or effect modifier, was parameterized per 1-day increase in maternal exposure during the cardiac critical period. We conducted several sensitivity analyses to assess our final models' robustness to outliers and confounding bias: (1) we refit our final GAMs and logistic interaction models excluding $PM_{2.5}$ values above the 99.5^{th} percentile for our data; (2) to address spatial variation and clustering effects, we refit each of our final interaction models as a generalized linear mixed effects model including a random intercept term for study center; and (3) we refit our models using the three alternative extreme heat measures described in Section 2.2.

Analyses were performed using R version 3.6 (R Core Team, 2020).

The NBDPS was approved by the Institutional Review Board of the Centers for Disease Control and Prevention and by each constituent study center. All subjects provided informed consent prior to participation. Consistent with NBDPS protocol, replication of selected analyses was performed and results compared to ensure data quality.

3. Results

3.1 Descriptive results.

Full population analyses included a total of 4,033 control and 2,824 case children. For the subpopulation of mothers with at least one critical period day during spring or summer,

analyses included 2,487 (62%) control and 1,747 (62%) case mothers. Case children were subdivided into broad CHD groups, with case numbers ranging from 447 (RVOTO) to 958 (septal defects). We also analyzed two septal defect phenotypes, VSDpm and ASD-II. Table 1 describes our analytic population by CHD outcome and demographic factors. (Tables were created using the R packages *gtsummary* (Sjoberg et al., 2020) and *gt* (Iannone et al., 2020).

Our maternal study population was predominantly non-Hispanic white (54.1%), with more than 12 years of education (58.6%) and an average age of 26.9 years at offspring conception. Mean maternal $PM_{2.5}$ exposure across postconceptional weeks 3 to 8 was 13.7 $\mu g/m^3$. This exceeds the annual exposure guidelines set by the World Health Organization (WHO, 10 $\mu g/m^3$) and the U.S. Environmental Protection Agency (EPA, 12 $\mu g/m^3$) (U.S. EPA, 2012; WHO, 2006), although maternal averages occurred over a shorter timespan than these annual guidelines. Mothers experienced an average of 3.35 days above the 90^{th} percentile for maximum temperature during postconceptional weeks 3 to 8, with approximately 75% exposed to at least one EHD.

3.2 Logistic and generalized additive models.

Figure 1 displays adjusted ORs and 95% CIs for associations between maternal $PM_{2.5}$ exposure and CHDs, estimated using separate covariate-adjusted logistic regression models without interaction terms. We estimated ORs for both the full study population and the subpopulation described previously. Results did not differ appreciably across population analyzed or after adjustment for EHDs as a potential confounder. However, effect estimates differed by CHD, as expected given their divergent etiologies.

In Table 2, we present nonparametric results for GAMs by CHD and analytic population, adjusted for parametric covariate terms. For each model, the EDF and p-value for each spline term are presented (see Section 2.4). Models presented in Table 2 each included an EHD spline term as a potential nonlinear confounder; adjusted models without EHD spline terms did not differ appreciably from those presented (data not shown). Visual inspection of these splines aided in determining whether observed logit-nonlinearity appeared meaningful in this context (i.e., whether nonlinear models would appreciably improve our estimates of these relationships). Five of twelve fitted GAMs contained significant $PM_{2.5}$ spline terms (see Table 2), which are plotted against log-odds of CHDs in Figure 2. (See Supplemental Figure S3 for other model plots.) Although the $PM_{2.5}$ spline term in each of the models in Figure 2 significantly differed from a null term, none differed appreciably from its logistic counterpart, i.e., from the EHD-adjusted models presented in Figure 1 (comparison data not shown). Visual inspection of Figure 2 suggests that, in most instances, the non-linearity appears most evident at high and low $PM_{2.5}$ concentrations where data are sparse. Thus, although the possibility of logit-nonlinearity in the relationship between $PM_{2.5}$ and CHDs remains, we did not investigate further. Instead, we prioritized model parsimony and interpretability by using fully parametric models in subsequent analyses, which we demonstrated to be comparable in estimating associations between $PM_{2.5}$ and CHDs.

3.3 Interaction models.

Table 3 details multiplicative interaction results from covariate-adjusted logistic regression models. In Table 3, interaction odds ratio estimates are not interpreted as effect estimates but are used to assess departures from multiplicativity. Values greater than 1 indicate positive multiplicative interaction between $PM_{2.5}$ and EHDs. We observed slightly positive multiplicative interaction in the full population, and when we restricted to mothers with at least one critical period day during spring or summer, interaction point estimates moved further from the null.

Plots in Figure 3 display estimated $PM_{2.5}$ coefficients conditional on EHD exposure, modelled separately against the two outcomes that exhibited significant multiplicative interaction between $PM_{2.5}$ and EHDs in our subpopulation (see model results in Table 3). Note that VSDpm in this study comprises a subset (42%) of overall septal defects.

We observed that among our subpopulation of mothers with at least one critical period day during spring or summer, at low levels of EHD exposure, conditional log-odds of septal defects and VSDpm decreased with increasing maternal exposure to $PM_{2.5}$ (i.e., an OR less than 1). However, at higher levels of EHD exposure, this association reversed. In Figure 3, we observed that the conditional estimated OR for VSDpm given a 5 μg/m3 increase in $PM_{2.5}$ exposure among those with zero EHDs was 0.80 (95% CI: 0.64, 1.02), but among mothers with the highest number of EHDs (15 days), the conditional estimated OR was 1.54 (95% CI: 1.01, 2.41), holding adjusted covariates constant. Positive $PM_{2.5}$-VSDpm associations were seen above EHD counts of 5 days. We observe a similar pattern in overall septal defects: among mothers experiencing zero EHDs, the conditional estimated OR given a 5 $\mu g/m^3$ increase in $PM_{2.5}$ exposure was 0.71 (95% CI: 0.61, 0.83), but among mothers experiencing 15 EHDs, the conditional estimated OR was 1.39 (95% CI: 1.00, 1.93), holding adjusted covariates constant. Positive $PM_{2.5}$-septal associations were seen above EHD counts of 8 days. However, these conditional results should be interpreted with caution, as only a small proportion of mothers experienced high numbers of EHDs (see Table S2).

In Table 4, we detail additive interaction estimates for adjusted logistic models, assessed via $RERI_{OR}$. We derived these $RERI_{OR}$ estimates from the same models presented in Table 3. Among mothers in our overall population, the estimated $RERI_{OR}$ for septal defects was 0.0316 (95% CI: 0.0014, 0.0617). In other words, the odds ratio of a mother delivering a child with a septal defect was estimated to be 0.0316 units greater than if interaction were absent. The observed magnitude was greater in our subpopulation ($RERI_{OR}$: 0.0676, 95% CI: 0.0214, 0.1137). Thus, we observed significant and positive departures from additivity between $PM_{2.5}$ and EHDs for overall septal defects among both populations analyzed (see Table 4).

3.4 Sensitivity analyses.

We conducted several sensitivity analyses. First, to ensure our interaction models were robust to removal of extreme $PM_{2.5}$ values, we refit them excluding the top 0.5^{th} percentile of $PM_{2.5}$ values (exposure levels above 45.5 $\mu g/m^3$). This only altered our effect estimates

for our full population analyses, because our subpopulation already excluded these extreme $PM_{2.5}$ values. We observed no appreciable changes in multiplicative interaction results (Supplemental Table S3), but $RERI_{OR}$ estimates were slightly attenuated for septal defects (Supplemental Table S4). Given the sensitivity of nonparametric splines to outliers, we also refit our GAMs without extreme $PM_{2.5}$ values and observed no appreciable changes (Supplemental Table S5).

We analyzed data from eight state-level study centers for this study, each with varying exposure and outcome levels. To check robustness of our results to factors related to exposure and outcome that may covary across study centers, we fit generalized linear mixed effects models that included a random intercept for study center. Although some results changed slightly (e.g., the cross-product term in our final septal defects model decreased by approximately 17 percent, and some non-interaction point estimates were slightly changed), we observed the same direction and approximate magnitude of multiplicative interaction effect estimates (Supplemental Table S6). Like our sensitivity analyses with high $PM_{2.5}$ values removed, both multiplicative and additive interaction effect estimates were slightly attenuated for septal defects (Supplemental Table S7).

Finally, we refit each of our models using three alternative measures of extreme heat (see Section 2.2). For each measure, the magnitude and direction of $PM_{2.5}$-extreme heat associations with CHDs was consistent with primary analyses (data not shown), although in some instances, there was a loss of precision. Conditional OR plots fit using these alternative heat measures can be found in Supplemental Figures S4–S6.

4. Discussion

4.1 Description and interpretation of results.

Our study provides evidence that duration of extreme heat and magnitude of $PM_{2.5}$ exposure —not simply presence or absence of these exposures—may be important considerations for offspring congenital heart defects. Although both environmental exposures are likely risk factors, our results suggest their joint effect may be disproportionately harmful to offspring health. Our results should be cautiously interpreted, as our study sample contained very few individuals exposed to the highest levels of extreme heat (e.g., only five case children and five control children were exposed to 15 days of extreme heat at the 90^{th} percentile; see Table S2). However, global exposure to extreme heat will likely increase due to worsening climate change, thus increasing the number of pregnancies affected by extreme heat (Jones et al., 2015; Watts et al., 2021).

GAMs showed limited evidence of nonlinearity in the relationship between $PM_{2.5}$ and log-odds of CHDs. Although further research is necessary to fully characterize potentially nonlinear relationships, our analyses provided evidence that logistic models were likely comparable in estimating these associations. Prior studies investigating environmental exposures and birth outcomes have adjusted for temperature or have estimated effects for both pollutants and temperature independently (Arroyo et al., 2016; Ebisu and Bell, 2012; Schifano et al., 2016). However, only a few studies (Stingone et al., 2019) have explicitly investigated interactions between these two exposures. The results of our study provide

limited evidence of such interactions between $PM_{2.5}$ and extreme heat during pregnancy and provide justification for further analyses. Our results also suggest that lower, cumulative extreme temperatures for longer durations can modify the association between $PM_{2.5}$ and septal defects, demonstrating the potential utility of a cumulative extreme heat measure alongside more established metrics such as EHEs.

Our results were generally consistent with prior literature. We built upon Stingone et al.'s analyses (Stingone et al., 2019) by using more robust, non-categorized measures to assign maternal exposure levels and by investigating and supporting assumptions of logit-linearity underlying logistic models. The previous study observed effect modification of $PM_{2.5}$-CHD relationships by extreme heat when using a more restrictive operationalization, defined as occurrence of at least two consecutive days above the 95th percentile for daily maximum temperature during early pregnancy. In our study, we observed such effect modification using a less stringent definition, namely the total number of early pregnancy days above the 90th percentile for daily maximum temperature. We observed multiplicative effect modification in models with VSDpm and overall septal defects as outcomes, consistent with the previous study's findings of effect modification with VSDpm. Greater than additive interaction was observed for all septal defects (overall septal defects, VSDpm, and ASD-II) in both populations analyzed, with $RERI_{OR}$ magnitudes greater among a subpopulation of mothers with at least one critical period day during spring or summer. $RERI_{OR}$ estimates in covariate-adjusted case-control studies should be interpreted cautiously, however, because RERI values may vary across covariate strata (Skrondal, 2003). Because septal defects were most common CHD in our sample, statistical power to detect effect modification may have been greater for models with this outcome.

Temperature modified some of our study's effect estimates for $PM_{2.5}$, which may provide clues as to why conflicting results are seen among studies. Prior studies that did not account for meteorological factors have reported inverse associations between $PM_{2.5}$ and septal defects (Padula et al., 2013; Schembari et al., 2014; Vinikoor-Imler et al., 2015; Yang et al., 2021). However, even when accounting for modification by extreme heat in our models, we still observed an inverse conditional association between $PM_{2.5}$ and septal defects given low EHD levels. There are several potential explanations for this. Ito et al. (2007) discussed multicollinearity among air pollution and meteorological variables, with interrelationships sometimes changing by season. Although we conducted subanalyses during the spring/summer season, collinearity between $PM_{2.5}$ and other important, unmeasured exposures —or with varying subcomponents of $PM_{2.5}$ itself—could still account for these inverse relationships. Case ascertainment bias may also partially explain inverse $PM_{2.5}$-septal defect relationships, by which wealthier areas with lower pollution levels have better healthcare and diagnostics to detect CHDs. This bias could persist despite adjustment for meteorological variables. Finally, by using logistic regression models, we are imposing linearity on our exposure covariates. If the dose-response curve for $PM_{2.5}$ and septal defects is flatter at low EHD levels, a linear model could create the appearance of an inverse $PM_{2.5}$-septal relationship at low EHD levels. Although our GAMs did not exhibit strong nonlinearity, complexities in these relationships may still exist and may clarified by more precise studies.

Our findings of positive interaction on both the multiplicative and additive scales are consistent with Stingone et al.'s (2019) findings in the same study population. Although their measures of $PM_{2.5}$ and extreme heat were dichotomized, they observed increased odds of VSDpm only among mothers experiencing both high average $PM_{2.5}$ (> 17.1 μg/m^3) and an extreme heat event (2+ days above the 95th maximum temperature percentile) during postconceptional weeks 3 to 8. Other research supports the potential for heat to modify the negative health effects of pollutant exposure. Jiang et al. (2021) reported additive interaction between ambient heat exposure defined at the 75th and 90th percentiles and $PM_{2.5}$ on overall CHDs. Zhang et al. (2018) reported positive interactions between $PM_{2.5}$ and increased ambient temperature on emergency department visits in Beijing, and in a large study of U.S. Medicare enrollees, Kioumourtzoglou et al. (2015) reported that $PM_{2.5}$ had a stronger effect on mortality in warmer cities.

Research on heat-$PM_{2.5}$ interactions is supported by prior research separately investigating associations of $PM_{2.5}$ and extreme heat with CHDs. A recent study of the NBDPS population by Lin et al. (2018) reported an association between a greater number of maternal critical period EHDs and VSDs. Outside the NBDPS, Auger et al. (2017) reported positive associations between measures of maternal extreme heat exposure and ASDs in Quebec, as did Agay-Shay et al. (2013) in Israel. Our results also coincide in part with two recent registry-based studies reporting $PM_{2.5}$-CHD associations: a Toronto-based study reported positive associations between critical period $PM_{2.5}$ and VSDs (Lavigne et al., 2019), and a Taiwan-based study reported positive associations between $PM_{2.5}$ and ASDs, in addition to endocardial cushion defect and pulmonary artery and valve stenosis (Huang et al., 2019).

Prior research also supports the biological plausibility of our findings. Experimental laboratory and epidemiological studies have consistently linked maternal air pollution (Huang et al., 2019; Kavlock et al., 1980; Longo, 1977; Padula et al., 2013; Stingone et al., 2019, 2014; Tanner et al., 2015) and extreme heat (Bennett, 2010; Edwards et al., 2003; He et al., 2016; Milunsky et al., 1992; Zhang et al., 2017) exposure with a range of birth defects in offspring. Research as early as the 1960s demonstrated dose-response relationships between severity of neural tube and other congenital defects and *in utero* extreme heat exposure in rats and guinea pigs (Edwards et al., 2003). However, exact biological mechanisms remain unclear, with evidence suggesting multiple complex pathways, including inflammation, cell death, inhibited cell proliferation, and placental and circulatory disruption (Bennett, 2010). Air pollution has been similarly studied with respect to birth defects, with potential disease pathways including acute *in utero* inflammation, extracellular matrix remodeling (Tanwar et al., 2017), impaired organogenesis, and placental dysfunction (Wu et al., 2019). As noted above (see Section 1), synergistic effects between these two environmental exposures have been previously reported, but the underlying mechanisms of interaction remain unclear. Potential explanations relevant to this study include seasonal changes in particulate matter composition, increased susceptibility to ambient pollutants due to heat stress, and shared teratogenic pathways (Bell et al., 2007; Gordon, 2003; Hänninen and Jantunen, 2007).

4.2 Study strengths.

A strength of this study was its use of a standardized CHD classification system. The system allowed us to analyze case groups of reasonable size and etiologic homogeneity, which may not be true for studies observing diagnoses from a range of facilities and clinicians. In a recent meta-analysis of studies investigating $PM_{2.5}$ and CHDs, Hu et al. (2020) reported strong evidence of heterogeneity among effect estimates, most consistently for septal defect outcomes. Although some of this heterogeneity could be due to differences in study populations, published literature varies widely in CHD classification methodologies (Botto et al., 2007), as well as inclusion criteria, which may lead to differing effect estimates among studies. Another strength of this study, and of the NBDPS overall, was its geographic diversity. Unlike studies based in a single city, ours evaluated data from across eight U.S. states, representing six of the country's nine climate regions. Maternal addresses were centrally geocoded and matched to environmental exposures for each address and timeframe of residence, decreasing potential measurement error by accounting for changes of address during pregnancy.

4.3 Study limitations.

Our effect estimates may have been affected by assignment of exposure levels to mothers. We aggregated maternal $PM_{2.5}$ exposure estimates across postconceptional weeks 3 to 8, assigning a single value to each mother. This aggregate operationalization reduced precision and may have resulted in exposure misclassification, given that temporality of exposure is an important consideration within the embryonic cardiac critical period (Stingone et al., 2014). The difference between actual and measured $PM_{2.5}$ concentrations could have introduced bias, in addition to residential distance from a mother's assigned $PM_{2.5}$ monitoring station. We used a maximum distance of 50 km between maternal residence and $PM_{2.5}$ monitor to balance tradeoffs inherent to nearest-monitor methods: smaller distances introduce sample size concerns, and larger distances may increase exposure misclassification. Median distance from maternal residence to $PM_{2.5}$ monitor was approximately 10 km (see Table S1). Prior research in our sample demonstrated overall consistent $PM_{2.5}$-CHD relationships when data were limited to $PM_{2.5}$ monitors within 10 km of mothers' residences, with some increases in effect size (Stingone et al., 2014). Other sources of potential exposure misclassification include spatial variation in $PM_{2.5}$ and its component subchemicals (Bell et al., 2007) and maternal time spent indoors or away from home. Even indoors, exposure levels may have differed spatially and by maternal socioeconomic status, e.g., via prevalence of or access to air conditioning. Certain maternal occupations could also confer additional risk through increased exposure to both air pollution and extreme heat, but due to low prevalence of such occupations within the NBDPS, we were unable to investigate this in our study.

These limitations similarly apply to our assignment of EHDs. First, it is important to reiterate that our measure of extreme heat was relative, based on temperature percentiles calculated with respect to year, season, and weather station. In future studies, other factors (e.g., spatial considerations, or relative versus absolute heat) may also be important in determining how extreme heat is operationalized because the utility of different measures may differ by geography and relevant research question (Vaidyanathan et al., 2016). Mean residential distance to the nearest weather station also differed by region, with mothers

in the northeast closest (15.75 km for cases and 16.67 km for controls) and those in the southeast farthest (60.61 km for cases and 58.11 km for controls), which may have introduced bias. Sensitivity analyses conducted in the NBDPS population demonstrated only small differences in extreme heat effect estimates when maximum residential distance from weather station was varied (Lin et al., 2018). Overall, there is ongoing debate as to the optimal means of ambient exposure assessment for individuals, and researchers must consider the potential for bias with each method (Weisskopf and Webster, 2017). Despite tradeoffs between aggregate and personal exposure assessment, we believe that more refined exposure assessment techniques than the standard nearest-monitor methods would have decreased measurement error (and potentially bias) in our study (Yu et al., 2018).

Despite the advantageous system of CHD classification implemented by the NBDPS, it is important to consider differential case distribution and its potential to bias our results. If, for example, hospitals in geographic regions with relatively high levels of $PM_{2.5}$ or EHD exposure reported relatively more septal defects—the most common CHD in our sample—then unmeasured confounding or differential outcome misclassification could have biased our results away from the null. Bias at the study center (i.e., state) level may be less likely to have affected our results, as a sensitivity analysis of final models that included a random intercept term for study center yielded estimates of similar direction and magnitude. However, it is important to note that our exposures of interest vary across study centers. Thus, adjusting for this variation by including random intercept for study center as we did in our sensitivity analyses (Supplemental Tables S6 and S7) may have masked some of the meaningful exposure effects. Studies with larger sample sizes that can include both a random intercept for study site and random slopes, thereby even more fully accounting for both within-state and between-state variation, may address this limitation more effectively. Although we partially accounted for between-state variation in sensitivity analyses, within-state spatial variation still exists for many factors such as income, racial and ethnic makeup, residential and transportation access and infrastructure, relevant policies, and access to health services. If such uncontrolled spatially varying factors increased likelihood of both offspring CHD and maternal exposure to $PM_{2.5}$ or EHDs, they could have spuriously contributed to our observed associations. Issues of selection also could have influenced our results, e.g., due to differential participation rates among participant subgroups dependent on one or more exposures (Reefhuis et al., 2015). Finally, we analyzed six CHD outcomes among two subpopulations, producing many analytic results. Thus, we cannot discount random error as a contributor to our findings.

4.4 Conclusions and future research.

This study adds to existing knowledge regarding $PM_{2.5}$, extreme heat, and CHDs. It provides some evidence of positive effect modification by extreme heat of the $PM_{2.5}$-CHD relationship and emphasizes the potential importance of cumulative extreme heat exposure. However, some results merit further investigation, including inverse conditional effect estimates with certain CHDs. Future studies should prioritize more accurate and precise measurement of maternal exposures, with consideration given to $PM_{2.5}$ variability and extremes, multiple exposures, and exposure mixtures with respect to risk of CHDs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The authors would like to thank the NBDPS for its support with this study, in addition to all participants in the NBDPS. We thank Kathy Wisniewski for her data management support and reviewers at CDC, EPA, and NBDPS for their helpful comments. This work was supported by the National Institutes of Health and National Institute of Environmental Health Sciences [grant numbers ES021359, ES027022]; the Centers for Disease Control and Prevention (CDC) [grant number U01DD001231]; and CDC cooperative agreements [PA #96043, PA #02081, FOA #DD09-001, FOA #DD13-003, and NOFO #DD18-001].

Abbreviations:

NBDPS	National Birth Defects Prevention Study
$PM_{2.5}$	fine particulate matter with aerodynamic diameter ≤ 2.5 μm
CHD	congenital heart defect
EHD	extreme heat day
LVOTO	left ventricular outflow tract obstruction
RVOTO	right ventricular outflow tract obstruction
VSDpm	perimembranous ventricular septal defect
ASD-II	secundum atrial septal defect
OR	odds ratio
CI	confidence interval
GAM	generalized additive model
$RERI_{OR}$	relative excess risk due to interaction on the odds ratio scale

5. References

Agay-Shay K, Friger M, Linn S, Peled A, Amitai Y, Peretz C, 2013a. Air pollution and congenital heart defects. Environ. Res 124, 28–34. 10.1016/j.envres.2013.03.005 [PubMed: 23623715]

Agay-Shay K, Friger M, Linn S, Peled A, Amitai Y, Peretz C, 2013b. Ambient temperature and congenital heart defects. Hum. Reprod 28, 2289–2297. 10.1093/humrep/det244 [PubMed: 23739216]

American Heart Association, 2020. Congenital Heart Defects [WWW Document] URL https://www.heart.org/en/health-topics/congenital-heart-defects (accessed 2.5.20).

Arroyo V, Díaz J, Carmona R, Ortiz C, Linares C, 2016. Impact of air pollution and temperature on adverse birth outcomes: Madrid, 2001–2009. Environ. Pollut 218, 1154–1161. 10.1016/j.envpol.2016.08.069 [PubMed: 27589893]

Auger N, Fraser WD, Sauve R, Bilodeau-Bertrand M, Kosatsky T, 2017. Risk of Congenital Heart Defects after Ambient Heat Exposure Early in Pregnancy. Environ. Health Perspect 125, 8–14. 10.1289/EHP171 [PubMed: 27494594]

Bell ML, Dominici F, Ebisu K, Zeger SL, Samet JM, 2007. Spatial and Temporal Variation in PM $_{2.5}$ Chemical Composition in the United States for Health Effects Studies. Environ. Health Perspect 115, 989–995. 10.1289/ehp.9621 [PubMed: 17637911]

Bennett GD, 2010. Hyperthermia: malformations to chaperones. Birth Defects Res. B. Dev. Reprod. Toxicol 89, 279–288. 10.1002/bdrb.20254 [PubMed: 20803688]

Blue GM, Kirk EP, Sholler GF, Harvey RP, Winlaw DS, 2012. Congenital heart disease: current knowledge about causes and inheritance. Med. J. Aust 197, 155–159. 10.5694/mja12.10811 [PubMed: 22860792]

Botto LD, Lin AE, Riehle-Colarusso T, Malik S, Correa A, The National Birth Defects Prevention Study, 2007. Seeking causes: Classifying and evaluating congenital heart defects in etiologic studies. Birt. Defects Res. A. Clin. Mol. Teratol 79, 714–727. 10.1002/bdra.20403

Buckley JP, Samet JM, Richardson DB, 2014. Commentary: Does Air Pollution Confound Studies of Temperature? Epidemiology 25, 242–245. 10.1097/EDE.0000000000000051 [PubMed: 24487206]

Chen K, Wolf K, Breitner S, Gasparrini A, Stafoggia M, Samoli E, Andersen ZJ, Bero-Bedada G, Bellander T, Hennig F, Jacquemin B, Pekkanen J, Hampel R, Cyrys J, Peters A, Schneider A, 2018. Two-way effect modifications of air pollution and air temperature on total natural and cardiovascular mortality in eight European urban areas. Environ. Int 116, 186–196. 10.1016/j.envint.2018.04.021 [PubMed: 29689465]

Daniels MJ, 2000. Estimating Particulate Matter-Mortality Dose-Response Curves and Threshold Levels: An Analysis of Daily Time-Series for the 20 Largest US Cities. Am. J. Epidemiol 152, 397–406. 10.1093/aje/152.5.397 [PubMed: 10981451]

Dejmek J, Selevan SG, Benes I, Solanský I, Srám RJ, 1999. Fetal growth and maternal exposure to particulate matter during pregnancy. Environ. Health Perspect 107, 475–480. 10.1289/ehp.99107475 [PubMed: 10339448]

Ebisu K, Bell ML, 2012. Airborne PM $_{2.5}$ Chemical Components and Low Birth Weight in the Northeastern and Mid-Atlantic Regions of the United States. Environ. Health Perspect 120, 1746–1752. 10.1289/ehp.1104763 [PubMed: 23008268]

Edwards MJ, Saunders RD, Shiota K, 2003. Effects of heat on embryos and foetuses. Int. J. Hyperthermia 19, 295–324. 10.1080/0265673021000039628 [PubMed: 12745973]

Gasparrini A, Armstrong B, 2011. The Impact of Heat Waves on Mortality. Epidemiology 22, 68–73. 10.1097/EDE.0b013e3181fdcd99 [PubMed: 21150355]

Gasparrini A, Guo Y, Hashizume M, Lavigne E, Zanobetti A, Schwartz J, Tobias A, Tong S, Rocklöv J, Forsberg B, Leone M, De Sario M, Bell ML, Guo Y-LL, Wu C, Kan H, Yi S-M, de Sousa Zanotti Stagliorio Coelho M, Saldiva PHN, Honda Y, Kim H, Armstrong B, 2015. Mortality risk attributable to high and low ambient temperature: a multicountry observational study. The Lancet 386, 369–375. 10.1016/S0140-6736(14)62114-0

Gelman A, Hill J, 2007. Data analysis using regression and multilevel/hierarchical models, Analytical methods for social research Cambridge University Press, Cambridge ; New York.

Gordon CJ, 2003. Role of environmental stress in the physiological response to chemical toxicants. Environ. Res 92, 1–7. 10.1016/S0013-9351(02)00008-7 [PubMed: 12706749]

Greenland S, Pearl J, Robins JM, 1999. Causal Diagrams for Epidemiologic Research. Epidemiology 10, 37–48. 10.1097/00001648-199901000-00008 [PubMed: 9888278]

Haghighi M, Wright C, Ayer J, Urban M, Pham M, Boeckmann M, Areal A, Wernecke B, Swift C, Robinson M, Hetem R, Chersich M, Climate Change and Heat-Health Study Group, 2021. Impacts of High Environmental Temperatures on Congenital Anomalies: A Systematic Review. Int. J. Environ. Res. Public. Health 18, 4910. 10.3390/ijerph18094910 [PubMed: 34063033]

Hänninen O, Jantunen M, 2007. Response to findings on association between temperature and dose–response coefficient of inhalable particles (PM_{10}). J. Epidemiol. Community Health 61, 838. [PubMed: 17699541]

Hastie T, Tibshirani R, 1986. Generalized Additive Models. Stat. Sci 1, 15.

He J-R, Liu Y, Xia X-Y, Ma W-J, Lin H-L, Kan H-D, Lu J-H, Feng Q, Mo W-J, Wang P, Xia H-M, Qiu X, Muglia LJ, 2016. Ambient Temperature and the Risk of Preterm Birth in Guangzhou,

China (2001–2011). Environ. Health Perspect 124, 1100–1106. 10.1289/ehp.1509778 [PubMed: 26672059]

Hu C-Y, Huang K, Fang Y, Yang X-J, Ding K, Jiang W, Hua X-G, Huang D-Y, Jiang Z-X, Zhang X-J, 2020. Maternal air pollution exposure and congenital heart defects in offspring: A systematic review and meta-analysis. Chemosphere 253, 126668. 10.1016/j.chemosphere.2020.126668 [PubMed: 32278917]

Huang C, Chen B, Pan S, Ho Y, Guo YL, 2019. Prenatal exposure to PM2.5 and Congenital Heart Diseases in Taiwan. Sci. Total Environ 655, 880–886. 10.1016/j.scitotenv.2018.11.284 [PubMed: 30481714]

Iannone R, Cheng J, Schloerke B, 2020. R package gt: Easily Create Presentation-Ready Display Tables R package version.

Ito K, Thurston GD, Silverman RA, 2007. Characterization of PM2.5, gaseous pollutants, and meteorological interactions in the context of time-series health effects models. J. Expo. Sci. Environ. Epidemiol 17, S45–S60. 10.1038/sj.jes.7500627 [PubMed: 18079764]

Jiang W, Liu Z, Ni B, Xie W, Zhou H, Li X, 2021. Independent and interactive effects of air pollutants and ambient heat exposure on congenital heart defects. Reprod. Toxicol 104, 106–113. 10.1016/j.reprotox.2021.07.007 [PubMed: 34311057]

Jones B, O'Neill BC, McDaniel L, McGinnis S, Mearns LO, Tebaldi C, 2015. Future population exposure to US heat extremes. Nat. Clim. Change 5, 652–655. 10.1038/nclimate2631

Kavlock RJ, Meyer E, Grabowski CT, 1980. Studies on the developmental toxicity of ozone: Postnatal effects. Toxicol. Lett 5, 3–9. 10.1016/0378-4274(80)90141-1 [PubMed: 7376198]

Kioumourtzoglou M-A, Schwartz J, James P, Dominici F, Zanobetti A, 2015. PM2.5 and mortality in 207 US cities: Modification by temperature and city characteristics. Epidemiology 1. 10.1097/EDE.0000000000000422

Knol MJ, van der Tweel I, Grobbee DE, Numans ME, Geerlings MI, 2007. Estimating interaction on an additive scale between continuous determinants in a logistic regression model. Int. J. Epidemiol 36, 1111–1118. 10.1093/ije/dym157 [PubMed: 17726040]

Lavigne E, Lima I, Hatzopoulou M, Van Ryswyk K, Decou ML, Luo W, van Donkelaar A, Martin RV, Chen H, Stieb DM, Crighton E, Gasparrini A, Elten M, Yasseen AS, Burnett RT, Walker M, Weichenthal S, 2019. Spatial variations in ambient ultrafine particle concentrations and risk of congenital heart defects. Environ. Int 130, 104953. 10.1016/j.envint.2019.104953 [PubMed: 31272016]

Lin S, Lin Z, Ou Y, Soim A, Shrestha S, Lu Y, Sheridan S, Luben TJ, Fitzgerald E, Bell E, Shaw GM, Reefhuis J, Langlois PH, Romitti P, Feldkamp ML, Malik S, Pantea C, Nayak S, Hwang S-A, Browne M, 2018. Maternal ambient heat exposure during early pregnancy in summer and spring and congenital heart defects – A large US population-based, case-control study. Environ. Int 118, 211–221. 10.1016/j.envint.2018.04.043 [PubMed: 29886237]

Liu Y, Chen S, Zühlke L, Black GC, Choy M, Li N, Keavney BD, 2019. Global birth prevalence of congenital heart defects 1970–2017: updated systematic review and meta-analysis of 260 studies. Int. J. Epidemiol 48, 455–463. 10.1093/ije/dyz009 [PubMed: 30783674]

Longo LD, 1977. The biological effects of carbon monoxide on the pregnant woman, fetus, and newborn infant. Am. J. Obstet. Gynecol 129, 69–103. 10.1016/0002-9378(77)90824-9 [PubMed: 561541]

Ma Z, Cao X, Chang Y, Li W, Chen X, Tang N jun, 2021. Association between gestational exposure and risk of congenital heart disease: A systematic review and meta-analysis. Environ. Res 197, 111014. 10.1016/j.envres.2021.111014 [PubMed: 33716027]

Marra G, Wood SN, 2011. Practical variable selection for generalized additive models. Comput. Stat. Data Anal 55, 2372–2387. 10.1016/j.csda.2011.02.004

Milunsky A, Ulcickas M, Rothman KJ, Jick SS, Jick H, 1992. Maternal Heat Exposure and Neural Tube Defects. JAMA J. Am. Med. Assoc 268, 882. 10.1001/jama.1992.03490070064043

Mora C, Dousset B, Caldwell IR, Powell FE, Geronimo RC, Bielecki CR, Counsell CWW, Dietrich BS, Johnston ET, Louis LV, Lucas MP, McKenzie MM, Shea AG, Tseng H, Giambelluca TW, Leon LR, Hawkins E, Trauernicht C, 2017. Global risk of deadly heat. Nat. Clim. Change 7, 501–506. 10.1038/nclimate3322

Padula AM, Tager IB, Carmichael SL, Hammond SK, Yang W, Lurmann F, Shaw GM, 2013. Ambient Air Pollution and Traffic Exposures and Congenital Heart Defects in the San Joaquin Valley of California: Air pollution and congenital heart defects. Paediatr. Perinat. Epidemiol 27, 329–339. 10.1111/ppe.12055 [PubMed: 23772934]

R Core Team, 2020. R: A language and environment for statistical computing R Foundation for Statistical Computing, Vienna, Austria.

Reefhuis J, Gilboa SM, Anderka M, Browne ML, Feldkamp ML, Hobbs CA, Jenkins MM, Langlois PH, Newsome KB, Olshan AF, Romitti PA, Shapira SK, Shaw GM, Tinker SC, Honein MA, the National Birth Defects Prevention Study, 2015. The national birth defects prevention study: A review of the methods. Birt. Defects Res. A. Clin. Mol. Teratol 103, 656–669. 10.1002/bdra.23384

Royston P, Altman DG, Sauerbrei W, 2006. Dichotomizing continuous predictors in multiple regression: a bad idea. Stat. Med 25, 127–141. 10.1002/sim.2331 [PubMed: 16217841]

Schembari A, Nieuwenhuijsen MJ, Salvador J, de Nazelle A, Cirach M, Dadvand P, Beelen R, Hoek G, Basagaña X, Vrijheid M, 2014. Traffic-Related Air Pollution and Congenital Anomalies in Barcelona. Environ. Health Perspect 122, 317–323. 10.1289/ehp.1306802 [PubMed: 24380957]

Schifano P, Asta F, Dadvand P, Davoli M, Basagana X, Michelozzi P, 2016. Heat and air pollution exposure as triggers of delivery: A survival analysis of population-based pregnancy cohorts in Rome and Barcelona. Environ. Int 88, 153–159. 10.1016/j.envint.2015.12.013 [PubMed: 26760712]

Schoenwolf GC, Bleyl SB, Brauer PR, Francis-West PH, Larsen WJ, 2020. Development of the Heart, in: Larsen's Human Embryology Elsevier, Philadelphia, PA.

Sjoberg DD, Hannum M, Whiting K, Zabor EC, 2020. R package gtsummary: Presentation-Ready Data Summary and Analytic Result Tables

Skrondal A, 2003. Interaction as Departure from Additivity in Case-Control Studies: A Cautionary Note. Am. J. Epidemiol 158, 251–258. 10.1093/aje/kwg113 [PubMed: 12882947]

Solt F, Hu Y, 2019. R package interplot: Plot the Effects of Variables in Interaction Terms

Stafoggia M, Schwartz J, Forastiere F, Perucci CA, 2008. Does Temperature Modify the Association between Air Pollution and Mortality? A Multicity Case-Crossover Analysis in Italy. Am. J. Epidemiol 167, 1476–1485. 10.1093/aje/kwn074 [PubMed: 18408228]

Stingone JA, Luben TJ, Daniels JL, Fuentes M, Richardson DB, Aylsworth AS, Herring AH, Anderka M, Botto L, Correa A, Gilboa SM, Langlois PH, Mosley B, Shaw GM, Siffel C, Olshan AF, the National Birth Defects Prevention Study, 2014. Maternal Exposure to Criteria Air Pollutants and Congenital Heart Defects in Offspring: Results from the National Birth Defects Prevention Study. Environ. Health Perspect 122, 863–872. 10.1289/ehp.1307289 [PubMed: 24727555]

Stingone JA, Luben TJ, Sheridan SC, Langlois PH, Shaw GM, Reefhuis J, Romitti PA, Feldkamp ML, Nembhard WN, Browne ML, Lin S, 2019. Associations between fine particulate matter, extreme heat events, and congenital heart defects: Environ. Epidemiol 3, e071. 10.1097/EE9.0000000000000071 [PubMed: 32091506]

Tanner JP, Salemi JL, Stuart AL, Yu H, Jordan MM, DuClos C, Cavicchia P, Correia JA, Watkins SM, Kirby RS, 2015. Associations between exposure to ambient benzene and PM2.5 during pregnancy and the risk of selected birth defects in offspring. Environ. Res 142, 345–353. 10.1016/j.envres.2015.07.006 [PubMed: 26196779]

Tanwar V, Gorr MW, Velten M, Eichenseer CM, Long VP, Bonilla IM, Shettigar V, Ziolo MT, Davis JP, Baine SH, Carnes CA, Wold LE, 2017. In Utero Particulate Matter Exposure Produces Heart Failure, Electrical Remodeling, and Epigenetic Changes at Adulthood. J. Am. Heart Assoc 6. 10.1161/JAHA.117.005796

US Environmental Protection Agency (EPA), 2012. Federal Register: National Ambient Air Quality Standards for Particulate Matter; Final Rule

US National Oceanic and Atmospheric Administration (NOAA), 2020. National Centers for Environmental Information (NCEI) [WWW Document] URL https://www.ncdc.noaa.gov/ (accessed 4.10.20).

Vaidyanathan A, Kegler SR, Saha SS, Mulholland JA, 2016. A Statistical Framework to Evaluate Extreme Weather Definitions from a Health Perspective: A Demonstration Based on Extreme

Heat Events. Bull. Am. Meteorol. Soc 97, 1817–1830. 10.1175/BAMS-D-15-00181.1 [PubMed: 28883666]

van der Linde D, Konings EEM, Slager MA, Witsenburg M, Helbing WA, Takkenberg JJM, Roos-Hesselink JW, 2011. Birth Prevalence of Congenital Heart Disease Worldwide. J. Am. Coll. Cardiol 58, 2241–2247. 10.1016/j.jacc.2011.08.025 [PubMed: 22078432]

Van Zutphen AR, Lin S, Fletcher BA, Hwang S-A, 2012. A Population-Based Case–Control Study of Extreme Summer Temperature and Birth Defects. Environ. Health Perspect 120, 1443–1449. 10.1289/ehp.1104671 [PubMed: 23031822]

Vinikoor-Imler LC, Stewart TG, Luben TJ, Davis JA, Langlois PH, 2015. An exploratory analysis of the relationship between ambient ozone and particulate matter concentrations during early pregnancy and selected birth defects in Texas. Environ. Pollut 202, 1–6. 10.1016/j.envpol.2015.03.001 [PubMed: 25782177]

Vodonos A, Awad YA, Schwartz J, 2018. The concentration-response between long-term PM2.5 exposure and mortality; A meta-regression approach. Environ. Res 166, 677–689. 10.1016/j.envres.2018.06.021 [PubMed: 30077140]

Watts N, Amann M, Arnell N, Ayeb-Karlsson S, Beagley J, Belesova K, Boykoff M, Byass P, Cai W, Campbell-Lendrum D, Capstick S, Chambers J, Coleman S, Dalin C, Daly M, Dasandi N, Dasgupta S, Davies M, Napoli CD, Dominguez-Salas P, Drummond P, Dubrow R, Ebi KL, Eckelman M, Ekins P, Escobar LE, Georgeson L, Golder S, Grace D, Graham H, Haggar P, Hamilton I, Hartinger S, Hess J, Hsu S-C, Hughes N, Mikhaylov SJ, Jimenez MP, Kelman I, Kennard H, Kiesewetter G, Kinney PL, Kjellstrom T, Kniveton D, Lampard P, Lemke B, Liu Y, Liu Z, Lott M, Lowe R, Martinez-Urtaza J, Maslin M, McAllister L, McGushin A, McMichael C, Milner J, Moradi-Lakeh M, Morrissey K, Munzert S, Murray KA, Neville T, Nilsson M, Sewe MO, Oreszczyn T, Otto M, Owfi F, Pearman O, Pencheon D, Quinn R, Rabbaniha M, Robinson E, Rocklöv J, Romanello M, Semenza JC, Sherman J, Shi L, Springmann M, Tabatabaei M, Taylor J, Triñanes J, Shumake-Guillemot J, Vu B, Wilkinson P, Winning M, Gong P, Montgomery H, Costello A, 2021. The 2020 report of The Lancet Countdown on health and climate change: responding to converging crises. The Lancet 397, 129–170. 10.1016/S0140-6736(20)32290-X

Weisskopf MG, Webster TF, 2017. Trade-offs of Personal Versus More Proxy Exposure Measures in Environmental Epidemiology: Epidemiology 28, 635–643. 10.1097/EDE.0000000000000686 [PubMed: 28520644]

WHO, 2018. COP24 special report: Health and climate change

Wood S, 2019. Generalized Additive Model Selection [WWW Document] Doc. Package 'mgcv' Version 18–31. URL https://stat.ethz.ch/R-manual/R-devel/library/mgcv/html/gam.selection.html (accessed 4.11.20).

Wood SN, 2017. Generalized Additive Models: An Introduction with R, 2nd ed. Chapman and Hall/CRC. 10.1201/9781315370279

Wood SN, 2013. On p-values for smooth components of an extended generalized additive model. Biometrika 100, 221–228. 10.1093/biomet/ass048

Wood SN, 2004. Stable and Efficient Multiple Smoothing Parameter Estimation for Generalized Additive Models. J. Am. Stat. Assoc 99, 673–686. 10.1198/016214504000000980

World Health Organization (WHO), 2006. WHO Air quality guidelines for particulate matter, ozone, nitrogen dioxide and sulfur dioxide: Global update 2005

Wu G, Brown J, Zamora ML, Miller A, Satterfield MC, Meininger CJ, Steinhauser CB, Johnson GA, Burghardt RC, Bazer FW, Li Y, Johnson NM, Molina MJ, Zhang R, 2019. Adverse organogenesis and predisposed long-term metabolic syndrome from prenatal exposure to fine particulate matter. Proc. Natl. Acad. Sci 201902925. 10.1073/pnas.1902925116

Yang B-Y, Qu Y, Guo Y, Markevych I, Heinrich J, Bloom MS, Bai Z, Knibbs LC, Li S, Chen G, Jalaludin B, Morawska L, Gao M, Han B, Yu Y, Liu X-X, Ou Y, Mai J, Gao X, Wu Y, Nie Z, Zeng X-W, Hu L-W, Shen X, Zhou Y, Lin S, Liu X, Dong G-H, 2021. Maternal exposure to ambient air pollution and congenital heart defects in China. Environ. Int 153, 106548. 10.1016/j.envint.2021.106548 [PubMed: 33838617]

Yu H, Russell A, Mulholland J, Odman T, Hu Y, Chang HH, Kumar N, 2018. Cross-comparison and evaluation of air pollution field estimation methods. Atmos. Environ 179, 49–60. 10.1016/j.atmosenv.2018.01.045

Zanobetti A, Peters A, 2015. Disentangling interactions between atmospheric pollution and weather. J. Epidemiol. Community Health 69, 613–615. 10.1136/jech-2014-203939 [PubMed: 25452456]

Zhang W, Spero TL, Nolte CG, Garcia VC, Lin Z, Romitti PA, Shaw GM, Sheridan SC, Feldkamp ML, Woomert A, Hwang S, Fisher SC, Browne ML, Hao Y, Lin S, the National Birth Defects Prevention Study, Hobbs C, Carmichael S, Reefhuis J, Tinker S, Anderka M, Druschel C, Bell E, Olshan A, Meyer R, Canfield M, Langlois P, Botto L, 2019. Projected Changes in Maternal Heat Exposure During Early Pregnancy and the Associated Congenital Heart Defect Burden in the United States. J. Am. Heart Assoc 8. 10.1161/JAHA.118.010995

Zhang Y, Wang S, Fan X, Ye X, 2018. Temperature modulation of the health effects of particulate matter in Beijing, China. Environ. Sci. Pollut. Res 25, 10857–10866. 10.1007/s11356-018-1256-3

Zhang Y, Yu C, Wang L, 2017. Temperature exposure during pregnancy and birth outcomes: An updated systematic review of epidemiological evidence. Environ. Pollut 225, 700–712. 10.1016/j.envpol.2017.02.066 [PubMed: 28284544]

Zimmerman MS, Smith AGC, Sable CA, Echko MM, Wilner LB, Olsen HE, Atalay HT, Awasthi A, Bhutta ZA, Boucher JL, Castro F, Cortesi PA, Dubey M, Fischer F, Hamidi S, Hay SI, Hoang CL, Hugo-Hamman C, Jenkins KJ, Kar A, Khalil IA, Kumar RK, Kwan GF, Mengistu DT, Mokdad AH, Naghavi M, Negesa L, Negoi I, Negoi RI, Nguyen CT, Nguyen HLT, Nguyen LH, Nguyen SH, Nguyen TH, Nixon MR, Noubiap JJ, Patel S, Peprah EK, Reiner RC, Roth GA, Temsah M-H, Tovani-Palone MR, Towbin JA, Tran BX, Tran TT, Truong NT, Vos T, Vosoughi K, Weintraub RG, Weldegwergs KG, Zaidi Z, Zheleva B, Zuhlke L, Murray CJL, Martin GR, Kassebaum NJ, 2020. Global, regional, and national burden of congenital heart disease, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Child Adolesc. Health 4, 185–200. 10.1016/S2352-4642(19)30402-X [PubMed: 31978374]

Highlights

- Duration of extreme heat during pregnancy may modify the impact of air pollutants.
- Potential nonlinear associations were assessed using generalized additive models.
- Longer-duration heat exposure increased some $PM_{2.5}$-heart defect associations.

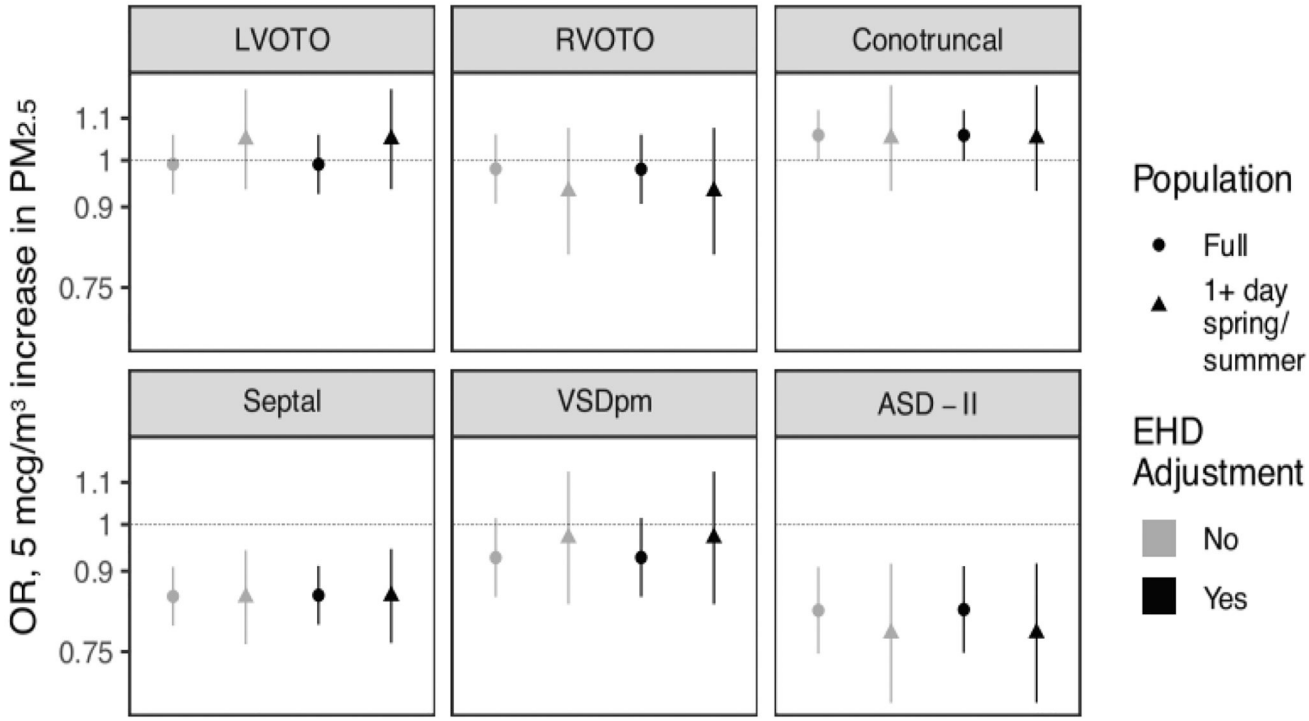


Figure 1.

Adjusted ORs and 95% confidence intervals for effect of $PM_{2.5}$ on CHDs. We fit multivariable logistic regression models across our full study population and our analytic subpopulation of mothers with 1+ day of gestational weeks 3–8 during spring/summer, and by adjustment for extreme heat days (EHDs). All models adjusted for maternal race/ethnicity, age, and education. Full-population models also adjusted for mother having at least 1 day of gestational weeks 3–8 of pregnancy during spring/summer.

Abbreviations: $PM_{2.5}$, fine particulate matter; CHD, congenital heart defect; EHD, extreme heat day; LVOTO, left ventricular outflow tract obstruction; RVOTO, right ventricular outflow tract obstruction; VSDpm, perimembranous ventricular septal defect; ASD-II, secundum atrial septal defect.

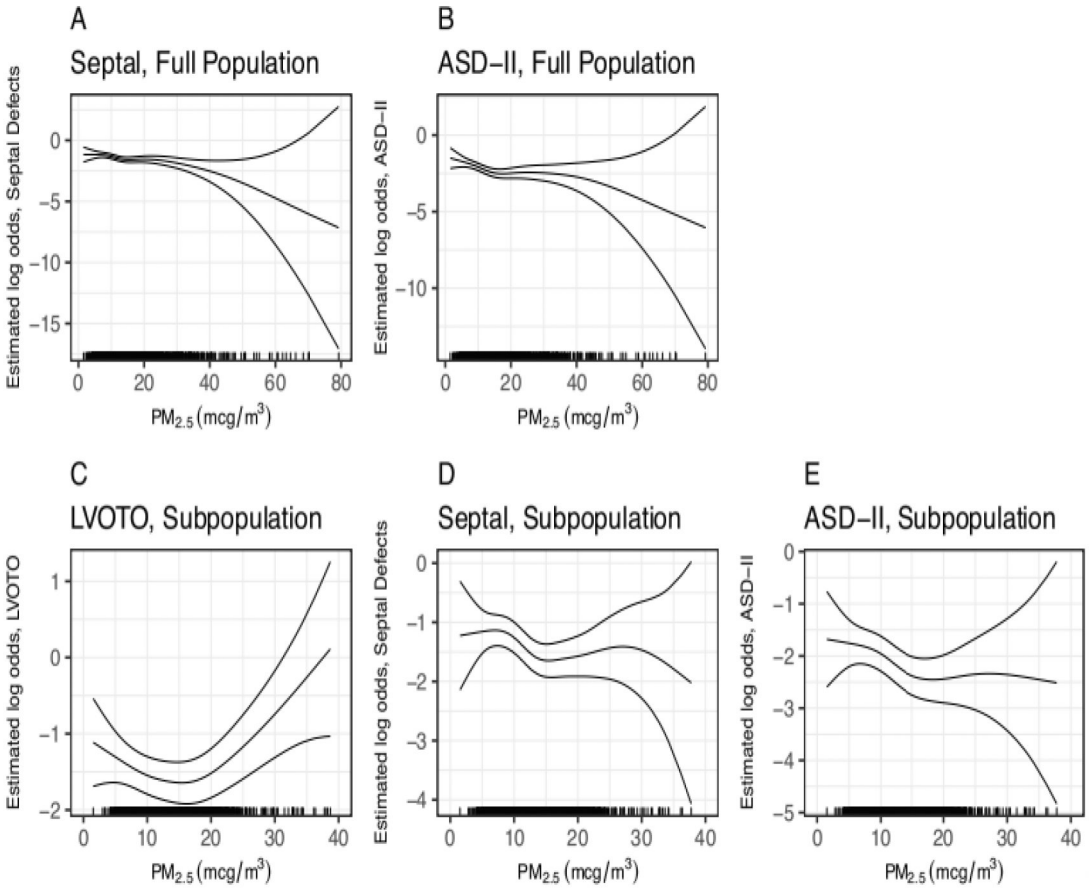


Figure 2.

Log-odds of CHDs by maternal $PM_{2.5}$ exposure: penalized spline terms from covariate-adjusted generalized additive models (GAMs). To further assess nonlinearity, log-odds and 95% confidence intervals for CHDs were plotted using penalized spline terms from each model containing a significant spline term for $PM_{2.5}$. These were compared with fully parametric logistic regression models (plots not shown). All models adjusted for maternal age, race/ethnicity, education, and mean dew point. Full-population models also adjusted for mother having at least 1 day of gestational weeks 3–8 of pregnancy during spring/summer. Change in x-axis range between full population and subpopulation due to differences in maximum $PM_{2.5}$ exposure.

Abbreviations: CHD, congenital heart defect; $PM_{2.5}$, fine particulate matter; EHD, extreme heat day; LVOTO, left ventricular outflow tract obstruction; ASD-II, secundum atrial septal defect.

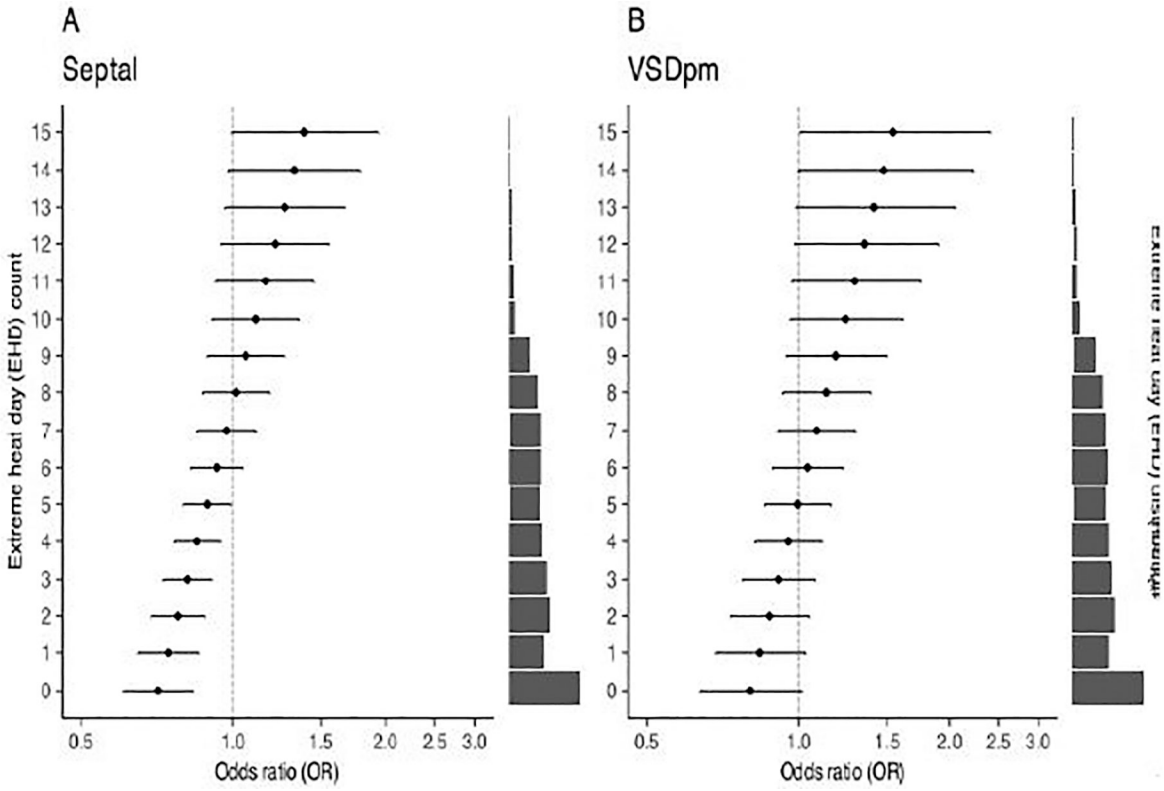


Figure 3.

Effect of maternal $PM_{2.5}$ exposure on CHD outcomes, conditional on EHD exposure. We plotted odds ratios for the effect of $PM_{2.5}$ exposure on CHDs, conditional on EHD exposure. A histogram displays the distribution of EHDs in each model. Both models were fit in the subpopulation of mothers with 1+ day of gestational weeks 3–8 during spring or summer. Both models adjusted for maternal age, race/ethnicity, education, and mean dew point. Estimates and 95% confidence intervals calculated using 10,000 model simulations. Abbreviations: $PM_{2.5}$, fine particulate matter; CHD, congenital heart defect; EHD, extreme heat day; VSDpm, perimembranous ventricular septal defect.

Table 1.

Demographic and exposure profiles of cases and controls in the National Birth Defects Prevention Study (NBDPS), 1999–2007

	Control N = 4033	LVOTO N = 588	RVOTO N = 447	Conotruncal N = 639	Septal N = 958	VSDpm N = 407	ASD-II N = 420
Child Sex							
Female	1951 (48%)	172 (29%)	240 (54%)	248 (39%)	490 (51%)	195 (48%)	234 (56%)
Male	2077 (52%)	415 (71%)	207 (46%)	391 (61%)	468 (49%)	212 (52%)	186 (44%)
Maternal Race							
White, non-Hispanic	2145 (53%)	387 (66%)	250 (56%)	336 (53%)	499 (52%)	226 (56%)	225 (54%)
Black, non-Hispanic	500 (12%)	36 (6.1%)	73 (16%)	87 (14%)	142 (15%)	73 (18%)	51 (12%)
Hispanic	1073 (27%)	134 (23%)	83 (19%)	169 (26%)	242 (25%)	80 (20%)	110 (26%)
Asian & Pacific Islander	99 (2.5%)	15 (2.6%)	11 (2.5%)	18 (2.8%)	29 (3.0%)	12 (2.9%)	14 (3.3%)
Other	216 (5.4%)	16 (2.7%)	30 (6.7%)	29 (4.5%)	46 (4.8%)	16 (3.9%)	20 (4.8%)
Maternal Education							
High School Graduate or Less	1649 (41%)	232 (39%)	189 (42%)	268 (42%)	404 (42%)	161 (40%)	184 (44%)
More than High School	2384 (59%)	356 (61%)	258 (58%)	371 (58%)	554 (58%)	246 (60%)	236 (56%)
Maternal Age							
< 20 Years Old	516 (13%)	56 (9.5%)	46 (10%)	68 (11%)	123 (13%)	44 (11%)	61 (15%)
20–34 Years Old	3069 (76%)	466 (79%)	354 (79%)	491 (77%)	723 (75%)	305 (75%)	318 (76%)
> 34 Years Old	448 (11%)	66 (11%)	47 (11%)	80 (13%)	112 (12%)	58 (14%)	41 (9.8%)
Climate Region							
Northeast (New York)	473 (12%)	70 (12%)	44 (9.8%)	88 (14%)	64 (6.7%)	47 (12%)	11 (2.6%)
South (Arkansas, Texas)	778 (19%)	80 (14%)	104 (23%)	103 (16%)	306 (32%)	81 (20%)	156 (37%)
Southeast (Georgia, North Carolina)	1116 (28%)	122 (21%)	105 (23%)	182 (28%)	252 (26%)	135 (33%)	74 (18%)
Southwest (Utah)	505 (13%)	131 (22%)	84 (19%)	67 (10%)	125 (13%)	47 (12%)	69 (16%)
Upper Midwest (Iowa)	434 (11%)	62 (11%)	41 (9.2%)	51 (8.0%)	98 (10%)	54 (13%)	44 (10%)
West (California)	727 (18%)	123 (21%)	69 (15%)	148 (23%)	113 (12%)	43 (11%)	66 (16%)
$PM_{2.5}$ Exposure							
Avg. $PM_{2.5}$ level ≤ 12 μg/m^3	1886 (47%)	298 (51%)	207 (46%)	294 (46%)	518 (54%)	185 (45%)	250 (60%)
Avg. $PM_{2.5}$ level > 12 μg/m^3	2147 (53%)	290 (49%)	240 (54%)	345 (54%)	440 (46%)	222 (55%)	170 (40%)
Days of weeks 3–8 of pregnancy in spring/summer							
0 days	1546 (38%)	212 (36%)	173 (39%)	265 (41%)	364 (38%)	166 (41%)	163 (39%)

	Control N = 4033	LVOTO N = 588	RVOTO N = 447	Conotruncal N = 639	Septal N = 958	VSDpm N = 407	ASD-II N = 420
1+	2487 (62%)	376 (64%)	274 (61%)	374 (59%)	594 (62%)	241 (59%)	257 (61%)
EHD Exposure							
None	1034 (26%)	153 (26%)	114 (26%)	173 (27%)	268 (28%)	107 (26%)	118 (28%)
1–2 Days	908 (23%)	117 (20%)	97 (22%)	147 (23%)	223 (23%)	82 (20%)	112 (27%)
3–5 Days	1040 (26%)	170 (29%)	102 (23%)	149 (23%)	258 (27%)	124 (30%)	95 (23%)
6–9 Days	949 (24%)	135 (23%)	127 (28%)	155 (24%)	182 (19%)	81 (20%)	81 (19%)
10+ Days	102 (2.5%)	13 (2.2%)	7 (1.6%)	15 (2.3%)	27 (2.8%)	13 (3.2%)	14 (3.3%)

Statistics presented: n (%).

Abbreviations: LVOTO, left ventricular outflow tract obstruction; RVOTO, right ventricular outflow tract obstruction; VSDpm, perimembranous ventricular septal defect; ASD-II, secundum atrial septal defect; $PM_{2.5}$, fine particulate matter; EHD, extreme heat day.

Table 2.

Generalized additive model (GAM) estimates for nonparametric penalized thin-plate regression splines

	LVOTO		RVOTO		Conotruncal		Septal		VSDpm		ASD-II	
	EDF	**p**	**EDF**	**p**	**EDF**	**p**	**EDF**	**p**	**EDF**	**p**	**EDF**	**p**
Population 1: Full population [a,b]												
$PM_{2.5}$ penalized spline	3.66	0.22	3.04	0.49	1.00	0.05	4.78	0.00	2.32	0.17	3.87	0.00
EHD penalized spline	1.00	0.77	3.02	0.32	1.00	0.63	3.22	0.03	1.00	0.68	3.15	0.09
Population 2: Mothers with 1+ day during spring/summer [a]												
$PM_{2.5}$ penalized spline	2.55	0.01	1.87	0.42	1.00	0.41	4.35	0.00	1.24	0.69	3.17	0.01
EHD penalized spline	1.22	0.86	3.11	0.53	1.00	0.77	3.20	0.04	3.17	0.27	2.61	0.04

[a] All models fit with penalized thin-plate regression spline terms for $PM_{2.5}$ and EHD. All models adjusted for maternal age, race/ethnicity, education, and mean dew point.

[b] Full population models also adjusted for mother having at least 1 day of weeks 3–8 of pregnancy during spring/summer.

Abbreviations: EDF, spline effective degrees of freedom; p, approximate spline p-value (see Wood, 2013); PM2.5, fine particulate matter; EHD, extreme heat day; LVOTO, left ventricular outflow tract obstruction; RVOTO, right ventricular outflow tract obstruction; VSDpm, perimembranous ventricular septal defect; ASD-II, secundum atrial septal defect.

Table 3.

Multiplicative interaction model results: odds ratios and 95% confidence intervals, $PM_{2.5}$ and EHD

	LVOTO	RVOTO	Conotruncal	Septal	VSDpm	ASD-II
Population 1: Full population [a,b]						
$PM_{2.5}$ (5-unit increase)	1.03 (0.94, 1.12)	1.03 (0.93, 1.14)	1.06 (0.98, 1.15)	0.80 (0.73, 0.88)	0.88 (0.77, 1.00)	0.80 (0.70, 0.92)
EHD (1-day increase)	1.04 (0.97, 1.11)	1.07 (0.99, 1.15)	1.01 (0.95, 1.08)	0.92 (0.86, 0.98)	0.94 (0.87, 1.03)	0.95 (0.87, 1.04)
$PM_{2.5}$-EHD interaction (multiplicative) [c]	0.99 (0.96, 1.01)	0.98 (0.96, 1.01)	1.00 (0.98, 1.02)	1.02 (1.00, 1.04)	1.02 (0.99, 1.05)	1.01 (0.98, 1.04)
Population 2: Mothers with 1+ day during spring/summer [a]						
$PM_{2.5}$ (5-unit increase)	1.14 (0.97, 1.34)	1.00 (0.81, 1.25)	1.06 (0.88, 1.27)	0.71 (0.60, 0.83)	0.80 (0.63, 1.01)	0.70 (0.55, 0.88)
EHD (1-day increase)	1.06 (0.97, 1.16)	1.06 (0.95, 1.18)	1.01 (0.92, 1.11)	0.86 (0.80, 0.94)	0.89 (0.79, 1.00)	0.91 (0.82, 1.02)
$PM_{2.5}$-EHD interaction (multiplicative) [c]	0.98 (0.95, 1.01)	0.98 (0.94, 1.02)	1.00 (0.97, 1.03)	1.05 (1.02, 1.08)	1.04 (1.00, 1.09)	1.03 (0.99, 1.07)

[a] All models adjusted for maternal age, race/ethnicity, education, and mean dew point.

[b] Full population models also adjusted for mother having at least 1 day of weeks 3–8 of pregnancy during spring/summer.

[c] Multiplicative interaction estimates for 5-unit increase in $PM_{2.5}$ and 1-day increase in EHD. Wald standard errors (SEs) used to calculate confidence intervals.

Abbreviations: $PM_{2.5}$, fine particulate matter; EHD, extreme heat day; LVOTO, left ventricular outflow tract obstruction; RVOTO, right ventricular outflow tract obstruction; VSDpm, perimembranous ventricular septal defect; ASD-II, secundum atrial septal defect.

Table 4.

Relative excess risk due to interaction ($RERI_{OR}$) estimates and 95% confidence intervals: joint effects, $PM_{2.5}$ and EHD

	LVOTO	RVOTO	Conotruncal	Septal	VSDpm	ASD-II
Population 1: Full population[a,b]	−0.0127 (−0.0375, 0.0121)	−0.0165 (−0.0429, 0.0098)	−0.0013 (−0.0205, 0.018)	0.0316 (0.0014, 0.0617)	0.0222 (−0.0126, 0.057)	0.0179 (−0.0296, 0.0653)
Population 2: Mothers with 1+ day during spring/summer[a]	−0.0174 (−0.0466, 0.0117)	−0.0184 (−0.0616, 0.0248)	−0.0012 (−0.0324, 0.0301)	0.0676 (0.0214, 0.1137)	0.054 (−0.0024, 0.1105)	0.0449 (−0.0243, 0.1141)

[a] $RERI_{OR}$ standard errors and 95% CIs calculated from n = 10,000 bootstrap samples. $RERI_{OR}$ evaluated for 5-unit increase in $PM_{2.5}$ and 1-day increase in EHD exposure. All models adjusted for maternal age, race/ethnicity, education, and mean dew point.

[b] Full population models also adjusted for mother having at least 1 day of weeks 3–8 of pregnancy during spring/summer.

Abbreviations: $RERI_{OR}$, relative excess risk due to interaction on the odds ratio scale; $PM_{2.5}$, fine particulate matter; EHD, extreme heat day; LVOTO, left ventricular outflow tract obstruction; RVOTO, right ventricular outflow tract obstruction; VSDpm, perimembranous ventricular septal defect; ASD-II, secundum atrial septal defect.