**Modeling complex effects of exposure to particulate matter and extreme heat during pregnancy on congenital heart defects**

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***Supplemental Tables***

Table S1. Distribution of residential distance (km) to EPA PM2.5 monitor, among NBDPS congenital heart defect cases and controls

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Mean** | **25th percentile** | **Median** | **75th percentile** |
| Cases | 14.1669237 | 5.3380992 | 10.6224229 | 20.2889932 |
| Controls | 14.3695001 | 5.2208361 | 10.2387574 | 20.9932030 |

No statistically significant differences between cases and controls at a Type I error rate of 0.05.

Table S2. Distribution of extreme heat day (EHD) count among specific NBDPS congenital heart defect cases and controls

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Control** | **LVOTO** | **RVOTO** | **Conotruncal** | **Septal** | **VSDpm** | **ASD-II** |
| EHDs |  |  |  |  |  |  |  |
| 0 | 1034 (26%) | 153 (26%) | 114 (26%) | 173 (27%) | 268 (28%) | 107 (26%) | 118 (28%) |
| 1 | 430 (11%) | 55 (9.4%) | 43 (9.6%) | 71 (11%) | 93 (9.7%) | 34 (8.4%) | 49 (12%) |
| 2 | 478 (12%) | 62 (11%) | 54 (12%) | 76 (12%) | 130 (14%) | 48 (12%) | 63 (15%) |
| 3 | 388 (9.6%) | 60 (10%) | 36 (8.1%) | 43 (6.7%) | 126 (13%) | 63 (15%) | 43 (10%) |
| 4 | 347 (8.6%) | 54 (9.2%) | 34 (7.6%) | 50 (7.8%) | 68 (7.1%) | 26 (6.4%) | 27 (6.4%) |
| 5 | 305 (7.6%) | 56 (9.5%) | 32 (7.2%) | 56 (8.8%) | 64 (6.7%) | 35 (8.6%) | 25 (6.0%) |
| 6 | 287 (7.1%) | 32 (5.4%) | 30 (6.7%) | 45 (7.0%) | 49 (5.1%) | 23 (5.7%) | 22 (5.2%) |
| 7 | 254 (6.3%) | 33 (5.6%) | 42 (9.4%) | 41 (6.4%) | 57 (5.9%) | 27 (6.6%) | 20 (4.8%) |
| 8 | 248 (6.1%) | 42 (7.1%) | 34 (7.6%) | 43 (6.7%) | 49 (5.1%) | 20 (4.9%) | 24 (5.7%) |
| 9 | 160 (4.0%) | 28 (4.8%) | 21 (4.7%) | 26 (4.1%) | 27 (2.8%) | 11 (2.7%) | 15 (3.6%) |
| 10 | 38 (0.9%) | 7 (1.2%) | 2 (0.4%) | 10 (1.6%) | 9 (0.9%) | 5 (1.2%) | 4 (1.0%) |
| 11 | 23 (0.6%) | 3 (0.5%) | 3 (0.7%) | 0 | 7 (0.7%) | 3 (0.7%) | 4 (1.0%) |
| 12 | 18 (0.4%) | 1 (0.2%) | 0 | 2 (0.3%) | 4 (0.4%) | 2 (0.5%) | 2 (0.5%) |
| 13 | 11 (0.3%) | 1 (0.2%) | 1 (0.2%) | 1 (0.2%) | 3 (0.3%) | 1 (0.2%) | 2 (0.5%) |
| 14 | 4 (<0.1%) | 0 | 0 | 1 (0.2%) | 3 (0.3%) | 1 (0.2%) | 2 (0.5%) |
| 15 | 5 (0.1%) | 1 (0.2%) | 1 (0.2%) | 1 (0.2%) | 1 (0.1%) | 1 (0.2%) | 0 |
| 16 | 1 (<0.1%) | 0 | 0 | 0 | 0 | 0 | 0 |
| 17 | 2 (<0.1%) | 0 | 0 | 0 | 0 | 0 | 0 |

Table S3. Multiplicative interaction model results: odds ratios and 95% confidence intervals, PM2.5 and EHD. Sensitivity analysis: lower 99.5th percentile for PM2.5 exposure.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **LVOTO** | **RVOTO** | | **Conotruncal** | | **Septal** | | | | **VSDpm** | | | | **ASD-II** | | | |
| **Population 1: Full populationa,b** |  |  |  |  |  |  | |  | |  | |  | |  | |  | |
| PM2.5 (5-unit increase) | 1.03 (0.92, 1.14) | 1.06 (0.94, 1.19) | | 1.09 (0.99, 1.20) | | 0.82 (0.74, 0.90) | | | | 0.90 (0.79, 1.03) | | | | 0.81 (0.71, 0.94) | | | |
| EHD (1-day increase) | 1.03 (0.96, 1.10) | 1.07 (0.99, 1.16) | | 1.02 (0.95, 1.09) | | 0.92 (0.86, 0.98) | | | | 0.95 (0.87, 1.04) | | | | 0.95 (0.87, 1.04) | | | |
| PM2.5-EHD interaction (multiplicative)c | 0.99 (0.97, 1.02) | 0.98 (0.96, 1.01) | | 1.00 (0.97, 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/summera** | | | | | | |  | |  | |  | |  | |  | |  |
| PM2.5 (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) | | | |
| PM2.5-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) | | | |

aAll models adjusted for maternal age, race/ethnicity, education, and mean dew point.

bOnly full population estimates changed in this sensitivity analysis compared to Table 3, since subpopulation exposure values did not include overall 99.5th+ percentile of PM2.5 exposure distribution. Full population models also adjusted for mother having at least 1 day of early pregnancy during spring/summer.

cMultiplicative interaction estimates for 5-unit increase in PM2.5 and 1-day increase in EHD. Wald standard errors (SEs) used to calculate confidence intervals.

Abbreviations: 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 S4. Relative excess risk due to interaction (RERIOR) estimates and 95% confidence intervals: joint effects, PM2.5 and EHD. Sensitivity analysis: lower 99.5th percentile for PM2.5 exposure.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **LVOTO** | **RVOTO** | **Conotruncal** | **Septal** | **VSDpm** | **ASD-II** |
| Population 1: Full populationa,b | -0.0086 (-0.034, 0.0169 | -0.016 (-0.0422, 0.0102) | -0.0026 (-0.0228, 0.0176) | 0.0298 (-0.0014, 0.061) | 0.0199 (-0.0146, 0.0545) | 0.0161 (-0.0325, 0.0648) |
| Population 2: Mothers with 1+ day during spring/summera | -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) |

aRERIOR standard errors and 95% CIs calculated from n = 10,000 bootstrap samples. RERIOR evaluated for 5-unit increase in PM2.5 and 1-day increase in EHD exposure. All models adjusted for maternal age, race/ethnicity, education, and mean dew point.

bOnly full population estimates changed in this sensitivity analysis compared to Table 3, since subpopulation exposure values did not include overall 99.5th+ percentile of PM2.5 exposure distribution. Full population models also adjusted for mother having at least 1 day of early pregnancy during spring/summer.

Abbreviations: RERIOR, relative excess risk due to interaction on the odds ratio scale; 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 S5. Generalized additive model (GAM) estimates for nonparametric penalized thin-plate regression splines. Sensitivity analysis: lower 99.5th percentile for PM2.5 exposure.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **LVOTO** | | **RVOTO** | | **Conotruncal** | | **Septal** | | | | **VSDpm** | | | | **ASD-II** | | | |
|  | **EDF** | **p** | **EDF** | **p** | **EDF** | **p** | **EDF** | | **p** | | **EDF** | | **p** | | **EDF** | | **p** | |
| **Population 1: Full populationa,b** |  |  |  |  |  |  |  | |  | |  | |  | |  | |  | |
| PM2.5 penalized spline | 3.71 | 0.22 | 1.67 | 0.56 | 1.26 | 0.06 | 4.82 | | 0.00 | | 1.94 | | 0.34 | | 3.01 | | 0.00 | |
| EHE penalized spline | 1.00 | 0.73 | 2.98 | 0.32 | 1.00 | 0.63 | 3.22 | | 0.03 | | 1.00 | | 0.68 | | 3.19 | | 0.09 | |
| **Population 2: Mothers with 1+ day during spring/summera** | | | | | | | |  | |  | |  | |  | |  | |  | |
| PM2.5 penalized spline | 2.55 | 0.01 | 1.87 | 0.41 | 1.00 | 0.41 | 4.35 | | 0.00 | | 1.24 | | 0.67 | | 3.17 | | 0.01 | |
| EHE penalized spline | 1.22 | 0.82 | 3.11 | 0.53 | 1.00 | 0.77 | 3.20 | | 0.04 | | 3.17 | | 0.27 | | 2.61 | | 0.04 | |

aAll models fit with penalized thin-plate regression spline terms for PM2.5 and EHD. All models adjusted for maternal age, race/ethnicity, education, and mean dew point.

bOnly full population estimates changed in this sensitivity analysis compared to Table 3, since subpopulation exposure values did not include overall 99.5th+ percentile of PM2.5 exposure distribution. Full population models also adjusted for mother having at least 1 day of early 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 S6. Multiplicative interaction model results: odds ratios and 95% confidence intervals, PM2.5 and EHD. Sensitivity analysis: generalized linear mixed model with study center (U.S. state) included as a random intercept term.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **LVOTO** | **RVOTO** | | **Conotruncal** | | **Septal** | | | | **VSDpm** | | | | **ASD-II** | | | |
| **Population 1: Full populationa,b** |  |  |  |  |  |  | |  | |  | |  | |  | |  | |
| PM2.5 (5-unit increase) | 0.99 (0.91 1.09) | 1.04 (0.93 1.15) | | 1.04 (0.95 1.13) | | 0.84 (0.76 0.93) | | | | 0.87 (0.75 1.00) | | | | 0.86 (0.75 0.98) | | | |
| EHD (1-day increase) | 1.01 (0.94 1.08) | 1.05 (0.97 1.14) | | 1.01 (0.95 1.08) | | 0.94 (0.88 1.00) | | | | 0.96 (0.87 1.05) | | | | 0.95 (0.87 1.04) | | | |
| PM2.5-EHD interaction (multiplicative)c | 1.00 (0.97 1.02) | 0.99 (0.96 1.01) | | 1.00 (0.98 1.02) | | 1.01 (0.99 1.04) | | | | 1.02 (0.98 1.05) | | | | 1.01 (0.98 1.04) | | | |
| **Population 2: Mothers with 1+ day during spring/summera** | | | | | | |  | |  | |  | |  | |  | |  |
| PM2.5 (5-unit increase) | 1.17 (1.00 1.38) | 1.04 (0.83 1.30) | | 1.00 (0.82 1.23) | | 0.70 (0.58 0.84) | | | | 0.72 (0.55 0.94) | | | | 0.80 (0.62 1.02) | | | |
| EHD (1-day increase) | 1.01 (0.93 1.11) | 1.06 (0.95 1.18) | | 1.01 (0.92 1.12) | | 0.89 (0.82 0.96) | | | | 0.90 (0.80 1.01) | | | | 0.92 (0.83 1.03) | | | |
| PM2.5-EHD interaction (multiplicative)c | 0.99 (0.96 1.02) | 0.98 (0.94 1.02) | | 1.00 (0.96 1.03) | | 1.04 (1.01 1.07) | | | | 1.04 (1.00 1.09) | | | | 1.02 (0.98 1.07) | | | |

aAll models included study center (state-level) as a random intercept and were adjusted for maternal age, race/ethnicity, education, and mean dew point.

bFull population models also adjusted for mother having at least 1 day of early pregnancy during spring/summer.

cMultiplicative interaction estimates for 5-unit increase in PM2.5 and 1-day increase in EHD. Wald standard errors (SEs) used to calculate confidence intervals.

Abbreviations: 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 S7. Relative excess risk due to interaction (RERIOR) estimates and 95% confidence intervals: joint effects, PM2.5 and EHD. Sensitivity analysis: generalized linear mixed model with study center (U.S. state) included as a random intercept term.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **LVOTO** | **RVOTO** | **Conotruncal** | **Septal** | **VSDpm** | **ASD-II** |
| Population 1: Full populationa,b | -0.0051 (-0.0299, 0.0197) | -0.0124 (-0.0378, 0.0131) | -0.0015 (-0.0226, 0.0197) | 0.0211 (-0.0076, 0.0498) | 0.0187 (-0.0203, 0.0578) | 0.0145 (-0.0253, 0.0543) |
| Population 2: Mothers with 1+ day during spring/summera | -0.0068 (-0.0328, 0.0191) | -0.0169 (-0.0587, 0.0248) | -0.0035 (-0.0404, 0.0333) | 0.0578 (0.0115, 0.104) | 0.0562 (-0.0071, 0.1195) | 0.0334 (-0.0272, 0.094) |

aRERIOR standard errors and 95% CIs calculated from n = 10,000 bootstrap samples. RERIOR evaluated for 5-unit increase in PM2.5 and 1-day increase in EHD exposure. All models included study center (state-level) as a random intercept and were adjusted for maternal age, race/ethnicity, education, and mean dew point.

bFull population models also adjusted for mother having at least 1 day of early pregnancy during spring/summer.

Abbreviations: RERIOR, relative excess risk due to interaction on the odds ratio scale; 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.

***Supplemental Figures***



Figure S1. Directed acyclic graph (DAG) of relationship between PM2.5 and congenital heart defects, with all potential confounders and pathways. Identified confounders shaded in red.



Figure S2. Directed acyclic graph (DAG) of relationship between PM2.5 and congenital heart defects, with pathways of relevant confounders blocked. Confounder adjustment in models represented by shading in white.

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Figure S3.A. Log-odds of CHDs by maternal PM2.5 exposure: penalized spline terms from covariate-adjusted generalized additive models (GAMs). Models 1 to 6 (of 12).



Figure S3.B. Log-odds of CHDs by maternal PM2.5 exposure: penalized spline terms from covariate-adjusted generalized additive models (GAMs). Models 7 to 12 (of 12).



Figure S4. Effect of maternal PM2.5 exposure on CHD outcomes, conditional on extreme heat day (EHD) exposure defined at the 95th percentile. Estimates and 95% CIs calculated using 10,000 model simulations. 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.

1+ day: Models fit in subpopulation of mothers with 1+ day of gestational weeks 3-8 during spring or summer.

Abbreviations: PM2.5, fine particulate matter; CHD, congenital heart defect; EHD, extreme heat day; VSDpm, perimembranous ventricular septal defect.



Figure S5. Effect of maternal PM2.5 exposure on CHD outcomes, conditional on length of longest extreme heat event defined at the 90th percentile, in days. Estimates and 95% CIs calculated using 10,000 model simulations. 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.

1+ day: Models fit in subpopulation of mothers with 1+ day of gestational weeks 3-8 during spring or summer.

Abbreviations: PM2.5, fine particulate matter; CHD, congenital heart defect; VSDpm, perimembranous ventricular septal defect.



Figure S6. Effect of maternal PM2.5 exposure on CHD outcomes, conditional on length of longest extreme heat event defined at the 95th percentile, in days. Estimates and 95% CIs calculated using 10,000 model simulations. 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.

1+ day: Models fit in subpopulation of mothers with 1+ day of gestational weeks 3-8 during spring or summer.

Abbreviations: PM2.5, fine particulate matter; CHD, congenital heart defect; VSDpm, perimembranous ventricular septal defect.