**Supplemental Material**

**Maternal exposure to common air pollutants during pregnancy and asthma risk in early childhood: consideration of phases of fetal lung development**

Marnie F. Hazlehurst, Kecia N. Carroll, Christine T. Loftus, Adam A. Szpiro, Paul E. Moore, Joel D. Kaufman, Kipruto Kirwa, Kaja Z. LeWinn, Nicole R. Bush, Sheela Sathyanarayana, Frances A. Tylavsky, Emily S. Barrett, Ruby H.N. Nguyen, Catherine J. Karr.

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**Figure S2.** Sensitivity analysis using constrained distributed lag models for associations between two-week PM2.5 across the entire prenatal period and child airway outcomes at age 4.

**Table S1.** Characteristics of the analytic sample by cohort and site.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|   | **CANDLE** | **TIDES** | **TIDES-UCSF** | **TIDES-UMN** | **TIDES-URMC** | **TIDES-SCRI** |
| ***Total N*** | *1009* | *460* | *125* | *128* | *117* | *90* |
| ***Maternal Age (years), mean (SD)*** | 26.6 | (5.5) | 31.4 | (5.3) | 34.4 | (4.1) | 31.5 | (4.2) | 27.6 | (5.8) | 32.2 | (4.2) |
| ***Maternal Education, n (%)*** |  |  |  |  |  |  |  |  |  |  |  |  |
| Less than high school | 114 | (11) | 28 | (6) | 0 | (0) | 2 | (2) | 26 | (22) | 0 | (0) |
| High school completion | 473 | (47) | 72 | (16) | 12 | (10) | 9 | (7) | 48 | (41) | 3 | (3) |
| Graduated college or technical school | 304 | (30) | 142 | (31) | 33 | (26) | 46 | (37) | 22 | (19) | 41 | (46) |
| Some graduate work or degree  | 117 | (12) | 215 | (47) | 80 | (64) | 69 | (55) | 21 | (18) | 45 | (51) |
| ***Maternal Race, n (%)*** |  |  |  |  |  |  |  |  |  |  |  |  |
| Black/African American | 625 | (62) | 44 | (10) | 2 | (2) | 3 | (2) | 37 | (32) | 2 | (2) |
| White or Other | 384 | (38) | 411 | (89) | 123 | (98) | 123 | (98) | 78 | (68) | 87 | (98) |
| ***Maternal Asthma, n (%)*** |  |  |  |  |  |  |  |  |  |  |  |  |
| No | 820 | (82) | 392 | (86) | 106 | (86) | 118 | (93) | 89 | (77) | 79 | (88) |
| Yes | 176 | (18) | 64 | (14) | 17 | (14) | 9 | (7) | 27 | (23) | 11 | (12) |
| ***Prior live births***  |  |  |  |  |  |  |  |  |  |  |  |  |
| 1+ | 610 | (60) | 214 | (47) | 50 | (40) | 54 | (43) | 70 | (60) | 40 | (46) |
| 0 | 399 | (40) | 240 | (53) | 75 | (60) | 71 | (57) | 47 | (40) | 47 | (54) |
| ***Pre-pregnancy BMI, mean (SD)*** | 27.9 | (7.8) | 26 | (6.2) | 24.6 | (4.5) | 25.3 | (4.9) | 28.6 | (7.9) | 25.4 | (6.4) |
| ***Prenatal Smoking, n (%)*** |  |  |  |  |  |  |  |  |  |  |  |  |
| No | 914 | (91) | 435 | (95) | 123 | (99) | 126 | (99) | 98 | (84) | 88 | (99) |
| Yes | 94 | (9) | 21 | (5) | 1 | (1) | 1 | (1) | 18 | (16) | 1 | (1) |
| ***Postnatal secondhand smoke, n (%)*** |  |  |  |  |  |  |  |  |  |  |  |  |
| No | 704 | (70) | 394 | (94) | 111 | (99) | 121 | (98) | 87 | (80) | 75 | (99) |
| Yes | 301 | (30) | 27 | (6) | 1 | (1) | 3 | (2) | 22 | (20) | 1 | (1) |
| ***Pets in the home, n (%)*** |  |  |  |  |  |  |  |  |  |  |  |  |
| No | 585 | (58) | 226 | (49) | 74 | (59) | 57 | (45) | 51 | (44) | 44 | (49) |
| Yes | 422 | (42) | 232 | (51) | 51 | (41) | 71 | (55) | 64 | (56) | 46 | (51) |
| ***Child sex, n (%)*** |  |  |  |  |  |  |  |  |  |  |  |  |
| Male | 505 | (50) | 213 | (46) | 53 | (42) | 63 | (49) | 58 | (50) | 39 | (43) |
| Female | 504 | (50) | 247 | (54) | 72 | (58) | 65 | (51) | 59 | (50) | 51 | (57) |

**Table S2.** Pearson correlations between PM2.5 exposures.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Fetal Lung Development Phase** | **Entire pregnancy** | **Trimester** | **Postnatal** |
|  | **5-16 wks** | **16-24 wks** | **24-36 wks** | **36+ wks** | **1** | **2** | **3** |
| **5-16 weeks:** Pseudoglandular phase | 1 |  |  |  |  |  |  |  |  |
| **16-24 weeks:** Canalicular phase | 0.61 | 1 |  |  |  |  |  |  |  |
| **24-36 weeks:** Saccular phase | 0.45 | 0.58 | 1 |  |  |  |  |  |  |
| **36+ weeks:** Alveolar phase | 0.36 | 0.31 | 0.64 | 1 |  |  |  |  |  |
| **Entire pregnancy** | 0.82 | 0.78 | 0.84 | 0.63 | 1 |  |  |  |  |
| **1st trimester** (1-13 wks) | 0.95 | 0.52 | 0.46 | 0.34 | 0.82 | 1 |  |  |  |
| **2nd trimester** (14-27 wks) | 0.62 | 0.96 | 0.73 | 0.37 | 0.85 | 0.54 | 1 |  |  |
| **3rd trimester** (28 wks-birth) | 0.42 | 0.42 | 0.89 | 0.87 | 0.77 | 0.42 | 0.51 | 1 |  |
| **Postnatal** (year prior to age 4 study visit) | 0.62 | 0.60 | 0.64 | 0.53 | 0.78 | 0.64 | 0.64 | 0.62 | 1 |

**Figure S1.** Associations between prenatal PM2.5 exposure during fetal lung developmental windows and child airway outcomes at age 4, by pre-pregnancy BMI. a



Risk ratios (95% confidence intervals) shown for a 2 µg/m3 higher PM2.5 exposure during each phase in each group (N=425 with pre-pregnancy BMI ≥30, N=1039 with pre-pregnancy BMI <30). P-values are shown for the multiplicative interaction term. Models are adjusted for child age, sex, date of birth, study site, maternal characteristics, and postnatal child home and neighborhood environment.

**Table S3.** Sensitivity analyses using varying exposure windows and mutually adjusted models to assess the association (risk ratios [95% confidence intervals]) between prenatal PM2.5 exposure and child airway outcomes at age 4.a

|  |  |  |  |
| --- | --- | --- | --- |
| **PM2.5 Exposure**  | **Ever asthma** | **Current wheeze** | **Current asthma** |
| Entire pregnancy | 1.13 (0.66, 1.94) | 0.81 (0.53, 1.24) | 1.20 (0.72, 2.01) |
| *Exposures by trimester* |  |  |  |
|  1st trimester (1-13 weeks) | 0.80 (0.61, 1.04) | 0.79 (0.64, 0.98) | 0.82 (0.64, 1.04) |
|  2nd trimester (14-27 weeks) | 1.10 (0.87, 1.40) | 1.15 (0.93, 1.41) | 1.26 (0.99, 1.61) |
|  3rd trimester (28 weeks-birth) | 1.27 (1.05, 1.55) | 1.00 (0.84, 1.20) | 1.15 (0.94, 1.41) |
| *Exposure by fetal lung developmental window b* |  |  |  |
|  Pseudoglandular phase: 5-16 weeks | 0.90 (0.71, 1.14) | 0.91 (0.76, 1.10) | 0.97 (0.79, 1.21) |
|  Canalicular phase: 16-24 weeks | 1.01 (0.82, 1.25) | 1.06 (0.89, 1.28) | 1.09 (0.88, 1.36) |
|  Saccular phase: 24-36 weeks | 1.29 (1.06, 1.58) | 1.11 (0.92, 1.33) | 1.27 (1.04, 1.54) |
|  Alveolar phase: 36+ weeks | 1.15 (0.99, 1.34) | 0.98 (0.86, 1.12) | 1.08 (0.92, 1.26) |
| *Mutually-adjusted model* |  |  |  |
|  Pseudoglandular phase: 5-16 weeks | 0.98 (0.75, 1.29) | 0.92 (0.75, 1.13) | 1.06 (0.83, 1.35) |
|  Canalicular phase: 16-24 weeks | 1.04 (0.83, 1.29) | 1.06 (0.88, 1.28) | 1.10 (0.89, 1.37) |
|  Saccular phase: 24-36 weeks | 1.24 (0.99, 1.55) | 1.10 (0.89, 1.36) | 1.27 (1.01, 1.60) |
|  Alveolar phase: 36+ weeks | 1.09 (0.92, 1.30) | 0.95 (0.82, 1.10) | 1.04 (0.87, 1.25) |
| *Adjusted for postnatal exposure c* |  |  |  |
|  Pseudoglandular phase: 5-16 weeks | 0.93 (0.72, 1.20) | 0.94 (0.77, 1.14) | 0.99 (0.79, 1.23) |
|  Canalicular phase: 16-24 weeks | 0.99 (0.79, 1.24) | 1.06 (0.86, 1.31) | 1.11 (0.88, 1.42) |
|  Saccular phase: 24-36 weeks | 1.25 (1.01, 1.54) | 1.18 (0.98, 1.43) | 1.33 (1.08, 1.63) |
|  Alveolar phase: 36+ weeks | 1.13 (0.96, 1.33) | 0.97 (0.84, 1.13) | 1.06 (0.90, 1.26) |

aModels are adjusted for child age, sex, birth in warm versus cold season, cubic splines for date of birth (1 degree of freedom/year), study site, maternal age, maternal race, maternal education, pre-pregnancy BMI, prenatal smoking, parity, postnatal secondhand smoke, pets in the home, and Childhood Opportunity Index.

bPrimary analysis reported in Figure 1.

cYear prior to the outcome ascertainment.

**Table S4.** Sensitivity analyses with varying confounder adjustment in models of the association (risk ratios [95% confidence intervals]) between prenatal PM2.5 exposure and child airway outcomes at age 4.a

|  |  |  |  |
| --- | --- | --- | --- |
| **PM2.5 Exposure**  | **Ever asthma** | **Current wheeze** | **Current asthma** |
| **Reduced models** |  |  |  |
| *Without adjustment for study site, season, or year of birth* b |  |  |  |
|  Pseudoglandular phase: 5-16 weeks | 1.09 (0.94, 1.26) | 1.10 (0.97, 1.24) | 1.19 (1.04, 1.36) |
|  Canalicular phase: 16-24 weeks | 1.19 (1.03, 1.37) | 1.20 (1.07, 1.35) | 1.26 (1.10, 1.43) |
|  Saccular phase: 24-36 weeks | 1.36 (1.17, 1.58) | 1.23 (1.08, 1.40) | 1.38 (1.19, 1.59) |
|  Alveolar phase: 36+ weeks | 1.17 (1.05, 1.31) | 1.06 (0.96, 1.17) | 1.15 (1.03, 1.28) |
| *Without adjustment for covariates assessed at age 4 (secondhand smoke, pets in the home)* c |  |  |  |
|  Pseudoglandular phase: 5-16 weeks | 0.85 (0.66, 1.08) | 0.88 (0.73, 1.06) | 0.93 (0.75, 1.15) |
|  Canalicular phase: 16-24 weeks | 1.01 (0.83, 1.24) | 1.07 (0.89, 1.27) | 1.10 (0.89, 1.35) |
|  Saccular phase: 24-36 weeks | 1.28 (1.05, 1.55) | 1.09 (0.91, 1.31) | 1.25 (1.03, 1.51) |
|  Alveolar phase: 36+ weeks | 1.16 (1.01, 1.34) | 0.98 (0.86, 1.12) | 1.08 (0.93, 1.25) |
| **Extended models** |  |  |  |
| *Additional adjustment for birthweight* d |  |  |  |
|  Pseudoglandular phase: 5-16 weeks | 0.90 (0.71, 1.14) | 0.91 (0.76, 1.10) | 0.97 (0.79, 1.21) |
|  Canalicular phase: 16-24 weeks | 1.00 (0.81, 1.24) | 1.06 (0.89, 1.28) | 1.09 (0.88, 1.35) |
|  Saccular phase: 24-36 weeks | 1.30 (1.07, 1.59) | 1.11 (0.92, 1.34) | 1.28 (1.04, 1.56) |
|  Alveolar phase: 36+ weeks | 1.15 (0.99, 1.34) | 0.98 (0.86, 1.12) | 1.08 (0.92, 1.26) |
| *Additional adjustment for exact gestational age* d |  |  |  |
|  Pseudoglandular phase: 5-16 weeks | 0.91 (0.71, 1.15) | 0.91 (0.76, 1.10) | 0.98 (0.79, 1.21) |
|  Canalicular phase: 16-24 weeks | 1.01 (0.82, 1.25) | 1.06 (0.89, 1.28) | 1.10 (0.88, 1.36) |
|  Saccular phase: 24-36 weeks | 1.29 (1.05, 1.57) | 1.11 (0.92, 1.33) | 1.26 (1.03, 1.54) |
|  Alveolar phase: 36+ weeks | 1.15 (0.99, 1.34) | 0.98 (0.86, 1.12) | 1.08 (0.92, 1.26) |

a Models in the primary analysis were adjusted for child age, sex, birth in warm versus cold season, cubic splines for date of birth (1 degree of freedom/year), study site, maternal age, maternal race, maternal education, pre-pregnancy BMI, prenatal smoking, parity, postnatal secondhand smoke, pets in the home, and Childhood Opportunity Index.

b Models are adjusted for the same covariates as in primary models (a), except for the three covariates that were removed in this sensitivity analysis: birth in warm versus cold season, cubic splines for date of birth (1 degree of freedom/year), and study site.

c Models are adjusted for the same covariates as in primary models (a), except for the two covariates that were removed in this sensitivity analysis: postnatal secondhand smoke and pets in the home.

d Models are adjusted for the same covariates as in primary models (a), with the inclusion of one additional covariate in each model: either birthweight or exact gestational age.

**Table S5.** Sensitivity analyses for association between prenatal PM2.5 exposure during fetal lung developmental windows and child airway outcomes at age 4, leaving one city or one cohort out of the analysis at a time.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **PM2.5 exposure window** | **N** | **Ever asthma** | **Current wheeze** | **Current asthma** |
| *Leave out San Francisco* | 1344 |  |  |  |
|  Pseudoglandular phase: 5-16 weeks |  | 0.87 (0.68, 1.11) | 0.93 (0.76, 1.12) | 1.01 (0.82, 1.26) |
|  Canalicular phase: 16-24 weeks |  | 1.02 (0.82, 1.27) | 1.04 (0.86, 1.27) | 1.14 (0.90, 1.43) |
|  Saccular phase: 24-36 weeks |  | 1.30 (1.06, 1.59) | 1.13 (0.93, 1.36) | 1.28 (1.05, 1.56) |
|  Alveolar phase: 36+ weeks |  | 1.16 (0.98, 1.36) | 0.98 (0.85, 1.13) | 1.09 (0.92, 1.28) |
| *Leave out Minneapolis* | 1341 |  |  |  |
|  Pseudoglandular phase: 5-16 weeks |  | 0.91 (0.71, 1.16) | 0.92 (0.76, 1.12) | 0.98 (0.79, 1.21) |
|  Canalicular phase: 16-24 weeks |  | 1.05 (0.85, 1.30) | 1.07 (0.88, 1.29) | 1.13 (0.91, 1.41) |
|  Saccular phase: 24-36 weeks |  | 1.30 (1.07, 1.59) | 1.10 (0.91, 1.33) | 1.27 (1.04, 1.55) |
|  Alveolar phase: 36+ weeks |  | 1.15 (0.99, 1.35) | 0.99 (0.86, 1.14) | 1.08 (0.91, 1.27) |
| *Leave out Rochester* | 1352 |  |  |  |
|  Pseudoglandular phase: 5-16 weeks |  | 0.90 (0.70, 1.16) | 0.93 (0.77, 1.13) | 0.97 (0.77, 1.21) |
|  Canalicular phase: 16-24 weeks |  | 1.01 (0.81, 1.27) | 1.07 (0.88, 1.29) | 1.07 (0.86, 1.34) |
|  Saccular phase: 24-36 weeks |  | 1.29 (1.05, 1.58) | 1.12 (0.94, 1.35) | 1.27 (1.04, 1.56) |
|  Alveolar phase: 36+ weeks |  | 1.12 (0.96, 1.31) | 0.95 (0.83, 1.10) | 1.05 (0.89, 1.23) |
| *Leave out Seattle* | 1379 |  |  |  |
|  Pseudoglandular phase: 5-16 weeks |  | 0.91 (0.71, 1.15) | 0.91 (0.75, 1.10) | 0.98 (0.79, 1.21) |
|  Canalicular phase: 16-24 weeks |  | 1.03 (0.84, 1.28) | 1.06 (0.89, 1.27) | 1.11 (0.90, 1.38) |
|  Saccular phase: 24-36 weeks |  | 1.32 (1.08, 1.60) | 1.13 (0.94, 1.36) | 1.29 (1.05, 1.57) |
|  Alveolar phase: 36+ weeks |  | 1.16 (0.99, 1.35) | 1.00 (0.87, 1.14) | 1.08 (0.92, 1.27) |
| *Leave out Memphis/CANDLE**(TIDES-only analysis)* | 460 |  |  |  |
|  Pseudoglandular phase: 5-16 weeks |  | 1.01 (0.62, 1.65) | 0.72 (0.47, 1.13) | 0.80 (0.49, 1.31) |
|  Canalicular phase: 16-24 weeks |  | 0.89 (0.49, 1.63) | 1.10 (0.74, 1.62) | 0.72 (0.41, 1.26) |
|  Saccular phase: 24-36 weeks |  | 0.96 (0.51, 1.83) | 0.71 (0.41, 1.22) | 0.78 (0.35, 1.71) |
|  Alveolar phase: 36+ weeks |  | 1.28 (0.89, 1.85) | 0.89 (0.65, 1.20) | 1.23 (0.81, 1.85) |
| *Leave out all TIDES sites* *(CANDLE-only analysis)* | 1009 |  |  |  |
|  Pseudoglandular phase: 5-16 weeks |  | 0.84 (0.64, 1.10) | 0.98 (0.80, 1.21) | 1.01 (0.80, 1.27) |
|  Canalicular phase: 16-24 weeks |  | 1.08 (0.85, 1.36) | 1.08 (0.87, 1.35) | 1.19 (0.93, 1.53) |
|  Saccular phase: 24-36 weeks |  | 1.36 (1.10, 1.67) | 1.21 (0.99, 1.47) | 1.35 (1.09, 1.66) |
|  Alveolar phase: 36+ weeks |  | 1.15 (0.97, 1.37) | 1.02 (0.87, 1.18) | 1.07 (0.90, 1.28) |

aModels were adjusted for child age, sex, birth in warm versus cold season, cubic splines for date of birth (1 degree of freedom/year), study site, maternal age, maternal race, maternal education, pre-pregnancy BMI, prenatal smoking, parity, postnatal secondhand smoke, pets in the home, and Childhood Opportunity Index.

**Figure S2.** Sensitivity analysis using constrained distributed lag models for associations between two-week PM2.5 across the entire prenatal period and child airway outcomes at age 4.



Two-week PM2.5 averages across pregnancy from a national spatiotemporal PM2.5 model were used in constrained distributed lag models (DLMs) for (A) ever asthma, (B) current wheeze, and (C) current asthma. Separate models were run using 4 and 5 degrees of freedom (df) for the lag effect; results using 4 df are shown by the solid gray line and dark gray 95% confidence bands while results using 5 df are shown on the same plot with a black dashed line and light gray confidence bands. When using 4 df in the lag effect, no critical windows were identified for the ever asthma outcome, while there was a suggestion of increased risk with exposure during mid-gestation (weeks 16-23) for the current asthma outcome. However, when using 5 df, critical windows late in pregnancy were observed for both ever asthma and current asthma (weeks 31-33 and weeks 29-31, respectively), similar to those identified in the primary analysis. While the model with 4 df in the lag effect suggests a different critical window than the model with 5 df, the estimate from the 4 df model lies entirely within the confidence bounds of the 5 df model and the confidence intervals are overlapping across the entire prenatal period. A protective effect was also observed for the beginning of pregnancy in all models when using 5 df. Such effects may indicate selection bias in pregnancy cohorts such as this one, in which participants were enrolled in the study during mid-pregnancy.1

**REFERENCES**

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