Association of prenatal exposure to air pollutants with select birth defects using the case-cohort approach

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Objective & rationale

Objective:

To assess the association between pregnant women's exposure to fine particulate matter ($PM_{2.5}$) and ozone (O_3) and the risk that their fetuses will develop clubfoot, oral clefts, or craniosynostosis in New York State (NYS) over the years 2002-2015 using a case-cohort design

Rationale

- Birth defects may be caused by oxidative stress via smoking
- Smoking contains many components of $PM_{2.5}$
- Insufficient research on air pollutants and birth defects

Study aims

1. Is there an association between select air pollutants and select birth defects?
2. Does green space alter the effects of select air pollutants on select birth defects?
3. Does a multi-pollutant model vs single-pollutant model alter the effects of each air pollutant on select birth defects?

Select air pollutants: $PM_{2.5}$ or O_3
Select birth defects: clubfoot, oral clefts, and craniosynostosis

Outcome definitions

Birth defects: Abnormalities that form in the developing fetus

Of interest for this study

- Clubfoot
- Cleft lip
- Cleft palate
- Craniosynostosis

Infant with cleft lip and palate[1]

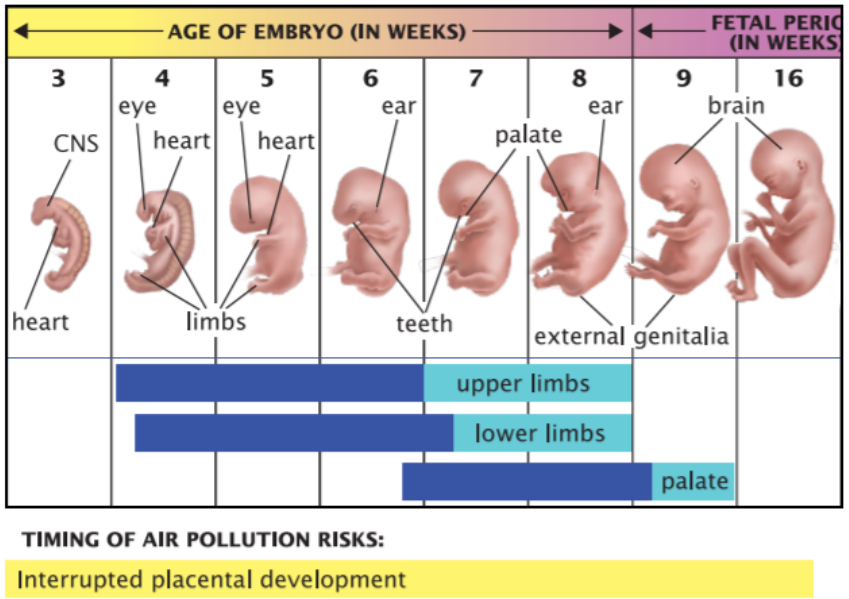
Critical windows of development

Clubfoot: gestational weeks 4-12 when limbs develop

Cleft lip: gestational weeks 3-9 when jaw develops

Cleft palate: gestational weeks 5-12 when face develops

Craniosynostosis: gestational weeks 4-12 when skull develops



Weeks of development for relevant birth defects[2]

Known or suspected causes of birth defects

- ~30%-40% causes known[3]
- Suspected gene-environment-health interaction[4,5]

Fig. 1 Bilateral talipes equinovarus.

Infant with clubfoot[6]

Known risk factors for birth defects

Demographic: parents' age; mother's race, ethnicity, education, and socio-economic status (SES); infant sex; parity

Health: mother's body-mass index (BMI), pre-gestational diabetes

Environment: parents' smoking; mother's alcohol and folate use

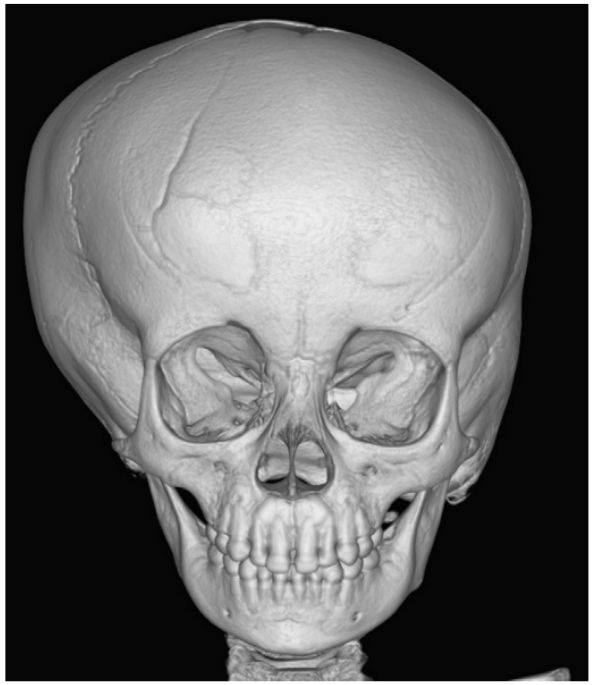


Figure 15 Unilateral lambdoid synostosis. 3D CT reconstruction, anterior view. The lambdoid synostosis causes bulging on the contralateral side.

Skull exhibiting craniosynostosis[7]

Cigarette smoke

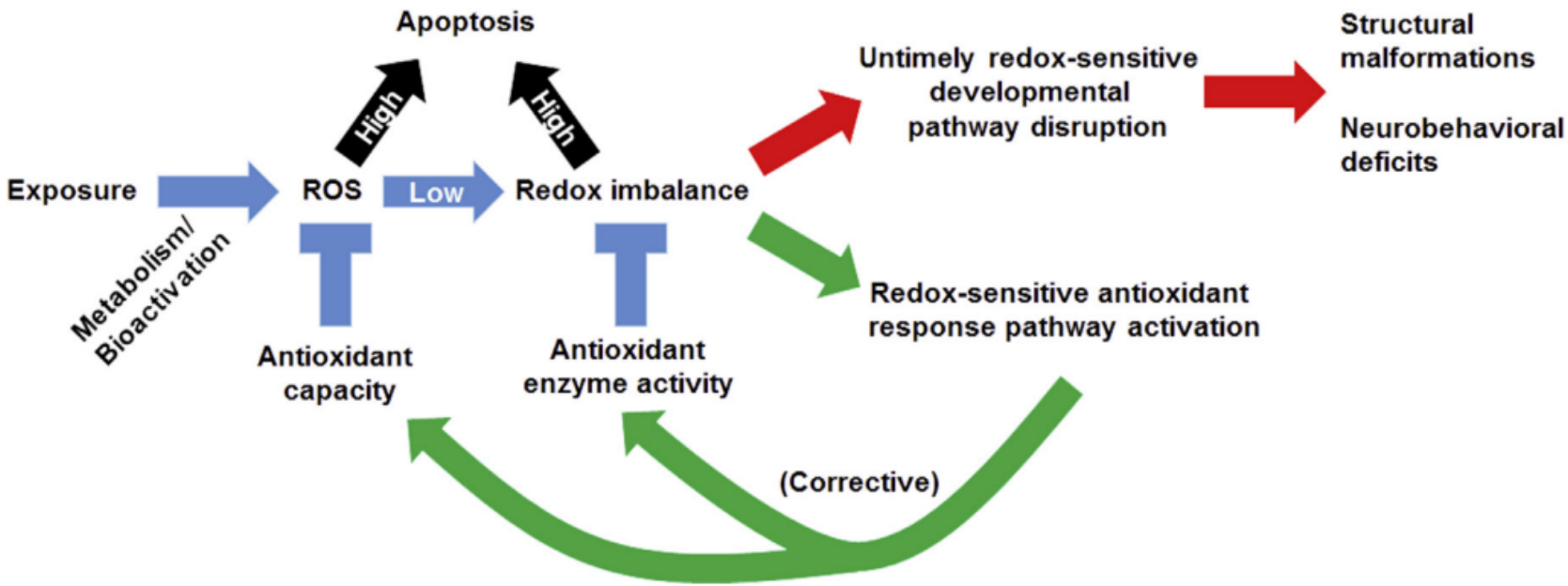
Maternal smoke exposure due to smoking herself or to secondhand smoke

Smoke components of concern

- Benzene
- 1,3-Butadiene
- Acetaldehyde
- Toluene
- Chromium VI

Teratogenic mechanism

Teratogenic mechanism: Oxidative stress - imbalance of antioxidants and reactive oxygen species (ROS) in the cell, reducing its ability to remove chemicals that can damage deoxyribonucleic acid (DNA)



Proposed mechanism by which oxidative stress disrupts the fetus[8]

Purpose of the study

To assess the association between pregnant women's exposure to $PM_{2.5}$ and O_3 and the risk that their fetuses will develop clubfoot, oral clefts, or craniosynostosis in NYS over the years 2002-2015 using a case-cohort design

Air pollutant definitions

Air pollution: Composite of chemicals suspended in the air

- **$PM_{2.5}$:** Particles less than 2.5μm diameter created by combustion
- **O_3:** Oxygen molecule created by chemical reactions in sunlight

Green space: Presence of plants such as grass or trees

Research on these exposures and birth defects to date is sparse and inconclusive.

Green space is of interest because it can reduce $PM_{2.5}$ and O_3.

Case-cohort study design

Strengths of case-cohort over case-control

- Lower selection bias: non-cases drawn from full population
- Lower information bias: exposures assessed without considering case status

Population: infants born in 2002-2015 in NYS with NYS birth residence outside New York City (NYC)

Cases: 4 case definitions, identified by British Pediatric Association (BPA) code diagnosis from CMR (n = 5,587)

Cohort: randomly selected from population, 3 births per case matched on birth year (n = 18,153)

Data sources: NYS Vital Records, Congenital Malformations Registry (CMR)

Air pollutant exposure classification

Exposure: O_3 or $PM_{2.5}$

- Weekly O_3 and $PM_{2.5}$ means and peaks calculated by tract
  - Means: weekly averages to smooth possibly spurious estimates
  - Peaks: weekly maximums to capture short bursts of higher exposure
- Births assigned exposure of maternal residence tract during weeks of interest

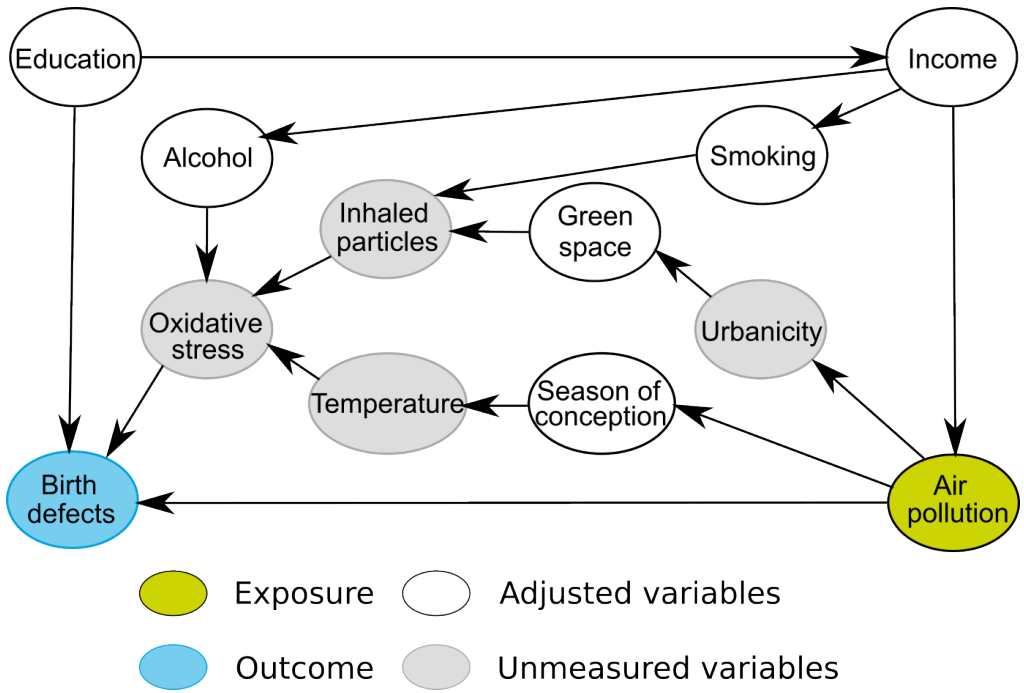
Data source: Downscaler air pollutant model

Covariates

- Season of conception
- Maternal smoking
- Maternal education
- Median census tract income
- Green space

Data source:

- NYS Vital Records
- US Census



Directed acyclic graph

Aim 1

Is there an association between select air pollutants and select birth defects?

Statistical analysis

- Univariate
- Bivariate
- Multivariate
- Sensitivity

Distribution of comparison and case groups

Distribution of maternal and infant characteristics by case status, New York State outside New York City, 2002 to 2015

	Non-cases (n=18,153)		Clubfoot (n=2423)		Cleft lip w/wo cleft palate (n=1281)		Cleft palate (n=952)		Craniosynostosis (n=931)	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Maternal education										
Some high school	2842	(15.86)	414	(17.32)	262	(20.71)	154	(16.47)	137	(14.86)
High school graduate	4119	(22.99)	611	(25.56)	341	(26.96)	251	(26.84)	218	(23.64)
Some college	4832	(26.97)	697	(29.16)	332	(26.25)	250	(26.74)	248	(26.90)
College graduate	3028	(16.90)	353	(14.77)	170	(13.44)	136	(14.55)	177	(19.20)
Advanced education	3096	(17.28)	315	(13.18)	160	(12.65)	144	(15.40)	142	(15.40)
Smoked tobacco at all during pregnancy										
No	15204	(84.65)	1869	(77.71)	987	(78.02)	747	(79.05)	751	(81.45)
Yes	2758	(15.35)	536	(22.29)	278	(21.98)	198	(20.95)	171	(18.55)
Tract-level median household income										
Low	4536	(24.99)	701	(28.95)	371	(28.96)	229	(24.05)	232	(24.92)
Medium-low	4546	(25.05)	671	(27.72)	365	(28.49)	277	(29.10)	260	(27.93)
Medium-high	4527	(24.94)	535	(22.10)	302	(23.58)	219	(23.00)	233	(25.03)
High	4541	(25.02)	514	(21.23)	243	(18.97)	227	(23.84)	206	(22.13)
Season of conception										
Winter	4567	(25.16)	610	(25.18)	295	(23.03)	279	(29.31)	241	(25.89)
Spring	4252	(23.42)	541	(22.33)	317	(24.75)	202	(21.22)	209	(22.45)
Summer	4578	(25.22)	629	(25.96)	330	(25.76)	195	(20.48)	230	(24.70)
Autumn	4756	(26.20)	643	(26.54)	339	(26.46)	276	(28.99)	251	(26.96)

Aim 1 study design

Case-cohort study with time-varying exposure

$$logit(RR_{bd}) = \beta_0 + \sum(\alpha_j Air) + \beta_1 Education + \beta_2 Season + \beta_3 Smoking + \beta_4 Income$$

$\alpha_j Air$ = series of betas for each air pollutant and week of estimates
bd = birth defect case group

Two models:

- Three-month: 4 weeks pre-conception to gestation week 8
- Four-month: 4 weeks pre-conception to gestation week 12

Aim 1 cumulative effect

Cumulative risk ratios for covariate models of air pollutant and birth defects pairs, New York State outside New York City, 2002 to 2015

	Clubfoot	Cleft lip w/wo palate		Cleft palate		Craniosynostosis	
Pollutant	4-month RR (95% CI)	3-month RR (95% CI)	4-month RR (95% CI)	3-month RR (95% CI)	4-month RR (95% CI)	3-month RR (95% CI)	4-month RR (95% CI)
Ozone mean	0.99 (0.90-1.09)	0.94 (0.83-1.07)	0.98 (0.88-1.08)	1.01 (0.91-1.13)	1.03 (0.91-1.17)	0.99 (0.87-1.13)	0.95 (0.82-1.09)
Ozone peak	0.99 (0.93-1.05)	0.95 (0.87-1.04)	0.96 (0.87-1.06)	1.00 (0.91-1.11)	1.01 (0.94-1.10)	0.98 (0.88-1.08)	0.94 (0.84-1.04)
$PM_{2.5}$ mean	0.98 (0.82-1.17)	0.86 (0.71-1.05)	0.85 (0.69-1.04)	0.81 (0.57-1.14)	0.77 (0.55-1.09)	0.88 (0.67-1.16)	0.89 (0.65-1.22)
$PM_{2.5}$ peak	0.96 (0.87-1.06)	0.91 (0.81-1.03)	0.94 (0.85-1.05)	0.91 (0.76-1.08)	0.92 (0.78-1.08)	0.99 (0.82-1.20)	0.95 (0.81-1.11)

Models adjusted for maternal education & smoking, tract-level median income, and conception season. risk ratio (RR) applies to a 10-unit increase over two standard deviations above the mean. For clubfoot, only the four-month model was run.

Aim 1 weeks with highest effect

Weekly risk ratios for covariate models of air pollutant and birth defects pairs, New York State outside New York City, 2002 to 2015

		Three-month model		Four-month model	
Birth defect	Pollutant	Week	RR (95% CI)	Week	RR (95% CI)
Clubfoot	Ozone mean			-2	1.03 (1.00-1.06)
	Ozone peak			2	**1.04 (1.00-1.09)**
	$PM_{2.5}$ mean			11	1.01 (0.96-1.06)
	$PM_{2.5}$ peak			5	1.04 (0.98-1.11)
Cleft lip w/wo cleft palate	Ozone mean	-1	**1.12 (1.01-1.26)**	12	1.19 (0.93-1.53)
	Ozone peak	-1	**1.08 (1.00-1.16)**	12	1.09 (0.97-1.22)
	$PM_{2.5}$ mean	8	1.07 (0.72-1.59)	12	0.90 (0.59-1.37)
	$PM_{2.5}$ peak	5	1.07 (0.86-1.33)	12	0.96 (0.77-1.19)
Cleft palate	Ozone mean	7	1.07 (0.88-1.29)	11	1.16 (0.98-1.37)
	Ozone peak	0	**1.13 (1.00-1.27)**	10	1.04 (0.92-1.17)
	$PM_{2.5}$ mean	8	1.03 (0.99-1.06)	6	1.02 (1.00-1.05)
	$PM_{2.5}$ peak	8	1.03 (0.99-1.08)	7	1.04 (1.00-1.08)
Craniosynostosis	Ozone mean	7	**1.16 (1.02-1.31)**	6	**1.34 (1.14-1.58)**
	Ozone peak	7	**1.19 (1.04-1.36)**	7	**1.08 (1.01-1.17)**
	$PM_{2.5}$ mean	7	1.08 (0.99-1.17)	6	1.07 (0.98-1.17)
	$PM_{2.5}$ peak	-1	**1.09 (1.02-1.16)**	11	1.02 (0.93-1.12)

Models were adjusted for maternal education level, maternal smoking, tract-level median income, and conception season. RR applies to a 10-unit increase over two standard deviations above the mean. Week 0 is week of conception; week 12 is end of the first trimester. For clubfoot, only the four-month model was run.

Aim 1 take-aways

Highest effects:

- Clubfoot
  - Pre-conception: O_3 mean & peak
  - Post-conception: $PM_{2.5}$ mean (week 11) & peak (week 5)
- Cleft lip with or without cleft palate
  - Pre-conception: O_3 mean & peak
  - Post-conception: $PM_{2.5}$ mean (week 8) & peak (week 5)
- Cleft palate
  - Pre-conception: O_3 peak
  - Post-conception: O_3 mean, $PM_{2.5}$ mean & peak (~week 8)
- Craniosynostosis
  - Pre-conception: $PM_{2.5}$ peak
  - Post-conception: O_3 mean & peak, $PM_{2.5}$ mean (~week 7)

Aim 2

Does green space alter the effects of select air pollutants on select birth defects?

Aim 2 exposure classification

Exposure: $PM_{2.5}$ or O_3, and green space:

- Aim 1, plus ...
- proportions of area in 50m, 100m, 200m, 300m, 400m, 500m buffers around mother's residence at birth classified as grasses, trees, or water

Data source: Downscaler air pollutant model, National Land Cover Database (NLCD)

Aim 2 study design

Case-cohort study with time-varying exposure

$$logit(RR_{bd}) = \beta_0 + \sum(\alpha_j Air) + \beta_1 Education + \beta_2 Season + \beta_3 Smoking + \beta_4 Income + \beta_5 Green$$

$\alpha_j Air =$ series of betas for each air pollutant and week of estimates
$bd =$ birth defect case group
$Green =$ green space measure

Aim 2 cumulative effect

Cumulative risk ratios for covariate models of air pollutant and birth defects pairs with 300m buffer of grasses and trees, New York State outside New York City, 2002 to 2015

	Clubfoot	Cleft lip w/wo palate		Cleft palate		Craniosynostosis	
Pollutant	4-month RR (95% CI)	3-month RR (95% CI)	4-month RR (95% CI)	3-month RR (95% CI)	4-month RR (95% CI)	3-month RR (95% CI)	4-month RR (95% CI)
Proportion of grasses and trees within 300m buffer							
Ozone mean	0.99 (0.90-1.10)	0.93 (0.82-1.06)	0.97 (0.88-1.08)	1.01 (0.91-1.12)	1.03 (0.91-1.17)	0.98 (0.86-1.12)	0.94 (0.81-1.07)
Ozone peak	0.99 (0.93-1.06)	0.96 (0.87-1.05)	0.97 (0.88-1.06)	1.00 (0.91-1.11)	1.02 (0.92-1.13)	0.98 (0.88-1.09)	0.94 (0.84-1.04)
$PM_{2.5}$ mean	1.00 (0.84-1.19)	0.88 (0.72-1.08)	0.87 (0.70-1.07)	0.81 (0.57-1.14)	0.77 (0.55-1.10)	0.92 (0.70-1.21)	1.12 (0.76-1.64)
$PM_{2.5}$ peak	0.97 (0.88-1.07)	0.93 (0.82-1.04)	0.96 (0.86-1.06)	0.91 (0.76-1.08)	0.91 (0.77-1.08)	1.03 (0.85-1.25)	0.97 (0.83-1.14)
Proportion of green space and water within 300m buffer							
Ozone mean	0.99 (0.90-1.09)	0.93 (0.82-1.06)	0.97 (0.88-1.08)	1.01 (0.91-1.13)	1.03 (0.91-1.17)	0.98 (0.86-1.12)	0.94 (0.82-1.08)
Ozone peak	0.99 (0.93-1.05)	0.96 (0.87-1.04)	0.96 (0.88-1.06)	1.00 (0.91-1.11)	1.01 (0.94-1.10)	0.98 (0.88-1.09)	0.94 (0.84-1.04)
$PM_{2.5}$ mean	1.01 (0.84-1.20)	0.88 (0.72-1.07)	0.86 (0.70-1.07)	0.81 (0.57-1.14)	0.78 (0.55-1.10)	0.91 (0.69-1.19)	1.09 (0.74-1.60)
$PM_{2.5}$ peak	0.97 (0.88-1.08)	0.92 (0.82-1.04)	0.95 (0.86-1.06)	0.91 (0.76-1.08)	0.92 (0.78-1.08)	1.02 (0.84-1.23)	0.96 (0.82-1.13)

Models adjusted for maternal education & smoking, tract-level median income, conception season, and green space. RR applies to a 10-unit increase over two standard deviations above the mean. For clubfoot, only the four-month model was run because limb formation finishes around week 12.

Aim 2 weeks with highest effect

Weekly risk ratios for covariate models of air pollutant and birth defects pairs with 300m buffer of grasses and trees, New York State outside New York City, 2002 to 2015

		Three-month model		Four-month model	
Birth defect	Pollutant	Week	RR (95% CI)	Week	RR (95% CI)
Clubfoot	Ozone mean			-4	1.01 (1.00-1.03)
	Ozone peak			2	**1.02 (1.00-1.04)**
	$PM_{2.5}$ mean			11	1.03 (0.93-1.14)
	$PM_{2.5}$ peak			5	1.04 (0.98-1.12)
Cleft lip w/wo cleft palate	Ozone mean	-1	**1.06 (1.00-1.11)**	12	1.08 (0.97-1.21)
	Ozone peak	-1	**1.03 (1.00-1.07)**	12	1.04 (0.99-1.10)
	$PM_{2.5}$ mean	8	1.04 (0.87-1.24)	12	0.96 (0.79-1.16)
	$PM_{2.5}$ peak	5	1.03 (0.94-1.14)	12	0.99 (0.89-1.09)
Cleft palate	Ozone mean	7	1.04 (0.92-1.17)	11	1.10 (0.99-1.22)
	Ozone peak	0	**1.06 (1.00-1.11)**	1	1.07 (1.00-1.15)
	$PM_{2.5}$ mean	8	1.05 (0.99-1.13)	6	1.04 (0.99-1.10)
	$PM_{2.5}$ peak	8	1.04 (0.99-1.08)	7	1.03 (0.99-1.08)
Craniosynostosis	Ozone mean	7	**1.09 (1.01-1.18)**	6	**1.21 (1.09-1.34)**
	Ozone peak	7	**1.08 (1.02-1.15)**	7	**1.04 (1.00-1.07)**
	$PM_{2.5}$ mean	7	1.16 (0.99-1.36)	-1	**1.15 (1.03-1.28)**
	$PM_{2.5}$ peak	-3	**1.10 (1.03-1.18)**	11	1.03 (0.92-1.14)

Models were adjusted for maternal education level, maternal smoking, tract-level median income, green space, and conception season. RR applies to a 10-unit increase over two standard deviations above the mean. Week 0 is week of conception; week 12 is end of the first trimester. For clubfoot, only the four-month model was run.

Aim 2 take-aways

Effects altered by including green space:

- Cleft palate:
  - Weekly O_3 peak highest around conception
- Craniosynostosis:
  - Cumulative effect of $PM_{2.5}$ mean much higher than in model without green space
  - Weekly $PM_{2.5}$ mean highest around conception

Aim 3

Does a multi-pollutant model vs single-pollutant model alter the effects of each air pollutant on select birth defects?

Aim 3 exposure classification

Exposure: $PM_{2.5}$ and O_3, and green space:

- Aims 1 and 2, except ...
- $PM_{2.5}$ and O_3 are included in the same model

Data source:

- Downscaler air pollutant model
- NLCD

Aim 3 study design

Case-cohort study with time-varying exposure

$$logit(RR_{bd}) = \beta_0 + \sum(\alpha_a O_3) + \sum(\alpha_b PM_{2.5}) + \beta_1 Education + \beta_2 Season + \beta_3 Smoking + \beta_4 Income + \beta_5 Green$$

$\alpha_a O_3$ and $\alpha_b PM_{2.5}$ = series of betas for each air pollutant and week of estimates

bd = birth defect case group

$Green$ = green space measure

Aim 3 cumulative effect

Cumulative risk ratios for covariate multi-pollutant models of air pollutants and birth defects with 300m buffer of grasses and trees, New York State outside New York City, 2002 to 2015

		Three-month model		Four-month model	
Birth Defect	Measure	O_3 RR (95% CI)	PM_{25} RR (95% CI)	O_3 RR (95% CI)	PM_{25} RR (95% CI)
Clubfoot	mean			**0.92 (0.85-1.00)**	1.06 (0.88-1.27)
	peak			0.99 (0.93-1.05)	0.99 (0.89-1.11)
Cleft lip w/wo cleft palate	mean	0.97 (0.87-1.09)	0.86 (0.67-1.11)	0.99 (0.89-1.10)	0.84 (0.65-1.09)
	peak	1.01 (0.92-1.10)	0.92 (0.80-1.06)	0.98 (0.91-1.06)	0.94 (0.82-1.08)
Cleft palate	mean	1.00 (0.90-1.12)	1.08 (0.86-1.36)	1.03 (0.91-1.16)	0.90 (0.67-1.21)
	peak	1.01 (0.91-1.13)	0.94 (0.78-1.13)	1.03 (0.94-1.13)	0.90 (0.77-1.06)
Craniosynostosis	mean	0.98 (0.86-1.12)	0.92 (0.68-1.24)	0.93 (0.81-1.07)	1.04 (0.76-1.44)
	peak	0.98 (0.89-1.09)	0.96 (0.81-1.14)	0.96 (0.87-1.06)	1.01 (0.85-1.19)

Models adjusted for maternal education & smoking, tract-level median income, green space, and conception season. RR applies to a 10-unit increase over two standard deviations above the mean. For clubfoot, only the four-month model was run.

Aim 3 weeks with highest effect

Weekly risk ratios for covariate models of air pollutant and birth defects pairs with 300m buffer of grasses and trees, New York State outside New York City, 2002 to 2015

			Three-month model		Four-month model	
Birth defect	Measure	Pollutant	Week	RR (95% CI)	Week	RR (95% CI)
Clubfoot	mean	Ozone			9	1.05 (0.98-1.13)
		$PM_{2.5}$			12	1.06 (0.91-1.23)
	peak	Ozone			5	**1.03 (1.00-1.06)**
		$PM_{2.5}$			10	1.04 (1.00-1.09)
Cleft lip w/wo cleft palate	mean	Ozone	4	1.04 (0.93-1.17)	12	1.09 (0.97-1.23)
		$PM_{2.5}$	3	0.98 (0.85-1.13)	7	0.98 (0.86-1.12)
	peak	Ozone	4	1.03 (0.96-1.11)	12	**1.09 (1.00-1.18)**
		$PM_{2.5}$	8	1.01 (0.92-1.12)	8	1.01 (0.94-1.09)
Cleft palate	mean	Ozone	7	1.04 (0.91-1.18)	11	1.10 (0.96-1.25)
		$PM_{2.5}$	8	1.04 (0.83-1.31)	7	1.17 (0.96-1.44)
	peak	Ozone	0	**1.06 (1.01-1.12)**	10	1.03 (0.97-1.10)
		$PM_{2.5}$	8	1.04 (0.99-1.10)	8	1.08 (0.96-1.22)
Craniosynostosis	mean	Ozone	11	**1.16 (1.03-1.32)**	7	1.09 (0.94-1.26)
		$PM_{2.5}$	4	1.02 (0.80-1.30)	7	1.07 (0.82-1.38)
	peak	Ozone	6	1.06 (0.98-1.14)	8	1.04 (0.95-1.14)
		$PM_{2.5}$	7	1.06 (0.93-1.21)	12	1.06 (0.93-1.20)

Models were adjusted for maternal education level, maternal smoking, tract-level median income, and conception season. RR applies to a 10-unit increase over two standard deviations above the mean. Week 0 is week of conception; week 12 is end of the first trimester. For clubfoot, only the four-month model was run.

Aim 3 take-aways

Effects altered by using a multi-pollutant model:

- Clubfoot:
  - Cumulative effect of O_3 mean lower and $PM_{2.5}$ mean higher than in single-pollutant model
  - Weekly O_3 mean and peak highest post-conception (not before), higher than in single-pollutant model
- Cleft lip with or without cleft palate:
  - Weekly O_3 mean and peak highest post-conception (not before), lower than in single-pollutant model
  - Weekly $PM_{2.5}$ mean highest earlier post-conception, lower than in single-pollutant model
- Cleft palate:
  - Cumulative effect of O_3 mean higher than in single-pollutant model
- Craniosynostosis:
  - Cumulative effect of $PM_{2.5}$ mean higher than in single-pollutant model
  - Weekly O_3 and $PM_{2.5}$ peak lower than in single-pollutant model, no longer significant

Sensitivity analyses

Conducted 3 analyses

1. Under-reporting of maternal smoking:
   - Reported: non-cases 15%, case groups 20-22%
   - Even if under-reported, difference between non-cases & cases would likely still exist
   - 1% missing smoking would not impact difference
2. Misclassification of clubfoot:
   - Estimated 95% talipes equinovarus
   - Modeling tests for 5% misclassification non-significant
3. Misclassification of ungeocoded records:
   - Results comparable with and without ungeocoded records (n=507)

Limitations

Unknowns:

- Maternal time spent outside at home
- Maternal residential mobility
- Second-hand smoke exposure
- Occupational exposure to $PM_{2.5}$ & O_3
- Indoor exposure to $PM_{2.5}$ & O_3

Assumptions:

- $PM_{2.5}$ composition is comparable across locations
- Median tract income reflects mother's income
- Green space is relatively consistent over time

Strengths

- Case-cohort study design
- Well defined, easily identified birth defects
- Statewide (excluding NYC) birth records over 14 years joined to CMR
- Birthdate and residence point coordinates for precise exposure estimates
- Statewide daily air pollutant exposure data
- Statewide land cover data that differentiate between trees and grass

Findings: air pollutants only

O_3

- Pre-conception exposure:
  - Peak only: cleft palate
  - Mean & peak: cleft lip with or without cleft palate, clubfoot
- Post-conception exposure:
  - Mean only: cleft lip with or without cleft palate, cleft palate
  - Mean & peak: craniosynostosis

$PM_{2.5}$

- Pre-conception exposure:
  - Mean & peak: craniosynostosis
- Post-conception exposure:
  - Peak only: clubfoot
  - Mean & peak: cleft lip with or without cleft palate, cleft palate

Findings: air pollutants & green space

Estimates altered by including green space

- O_3 peak: cleft palate
- $PM_{2.5}$ mean: craniosynostosis
- No effect: cleft lip with or without cleft palate, clubfoot

Estimates altered by using a multi-pollutant model

- O_3 peak: clubfoot
- O_3 mean & peak: cleft lip with or without cleft palate
- $PM_{2.5}$ mean & peak: clubfoot, cleft lip with or without cleft palate, craniosynostosis
- No effect: cleft palate

Next steps

- Research on exposure around conception
- Research evaluating multiple exposures at once
- Improved spatial & temporal granularity
- Evaluate different models of air pollution data
- Research that incorporates neighborhood characteristics

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https://github.com/ajstamm/apcmpkg

Oral clefts, PM, and O_3

Monitoring station data

- 6 averaged over critical window, 1 significant:
  - $PM_{2.5}$: cleft palate odds ratio (OR) 0.69 (0.50-0.93) $4\frac{\mu g}{m^3}$ change[9]
- 5 averaged monthly, 4 significant:
  - O_3: cleft lip with or without cleft palateadjusted odds ratio (aOR) 1.17 (1.01-1.36) month 1; aOR 1.22 (1.03-1.46) month 2[10]
  - $PM_{2.5}$: cleft palate RR 1.09 (1.01-1.17) month 1; cleft lip with or without cleft palateRR 1.05 (1.01-1.08) month 2[11]
  - coarse particulate matter (PM_{10}): oral clefts strong association[12]
  - PM_{10}: cleft lip with or without cleft palatespatial association[13]

Modeled data

- 1 averaged annually, not significant
- 6 averaged over critical window, 3 significant:
  - $PM_{2.5}$: oral clefts OR 0.90 (0.82-0.99) $5\frac{\mu g}{m^3}$ change[14]
  - $PM_{2.5}$: cleft palate OR 1.43 (1.11-1.86) $10\frac{\mu g}{m^3}$ increase[15]
  - $PM_{2.5}$: cleft palate aOR 1.74 (1.15-2.64)[16]

Craniosynostosis, Clubfoot, PM, and O_3

Clubfoot

- 1 averaged monitoring station data monthly, not significant

Craniosynostosis

- 1 averaged monitoring station data over 2 months, not significant
- 1 averaged modeled data over 1st trimester, significant:
  - O_3 aOR 1.38 (1.11-1.72) 13.3ppb increase[14]
  - $PM_{2.5}$ OR 0.78 (0.64-0.96) $5 \frac{\mu g}{m^3}$ increase[14]

Characteristics of prior literature

Measures of exposure

- monitoring station value applied to buffer or tract
- monitoring stations sparse
- modeled data estimated
- use residence at birth

Measures of time

- only one study considered pre-conception exposure
- most studies averaged over critical window or trimester
- no study used time shorter than one month
- averages may mask variation

Measures of outcome

- most studies used birth registries or NBDPS
- most studies were case-control

Model settings

Cross-basis settings for distributed lag logistic regression models

Birth defect	Pollutant	Measure	Four-month model settings	Three-month model settings
Clubfoot	Ozone	mean		Linear
		peak		Linear
	$PM_{2.5}$	mean		Polynomial, 2 degrees
		peak		Polynomial, 3 degrees
Cleft lip with or without cleft palate	Ozone	mean	Polynomial, 4 degrees	Polynomial, 4 degrees
		peak	Polynomial, 4 degrees	Polynomial, 3 degrees
	$PM_{2.5}$	mean	Linear	Linear
		peak	Polynomial, 2 degrees	Linear
Cleft palate	Ozone	mean	Linear	Polynomial, 4 degrees
		peak	Polynomial, 4 degrees	Polynomial, 3 degrees
	$PM_{2.5}$	mean	Linear	Polynomial, 2 degrees
		peak	Linear	Polynomial, 2 degrees
Craniosynostosis	Ozone	mean	Polynomial, 3 degrees	Polynomial, 4 degrees
		peak	Polynomial, 4 degrees	Polynomial, 2 degrees
	$PM_{2.5}$	mean	Polynomial, 2 degrees	Polynomial, 4 degrees
		peak	Polynomial, 4 degrees	Polynomial, 3 degrees

Setting refers to the relationship between exposure and outcome for the matrix containing the lag weeks. For clubfoot, only the four-month models were run.

Green space calculation

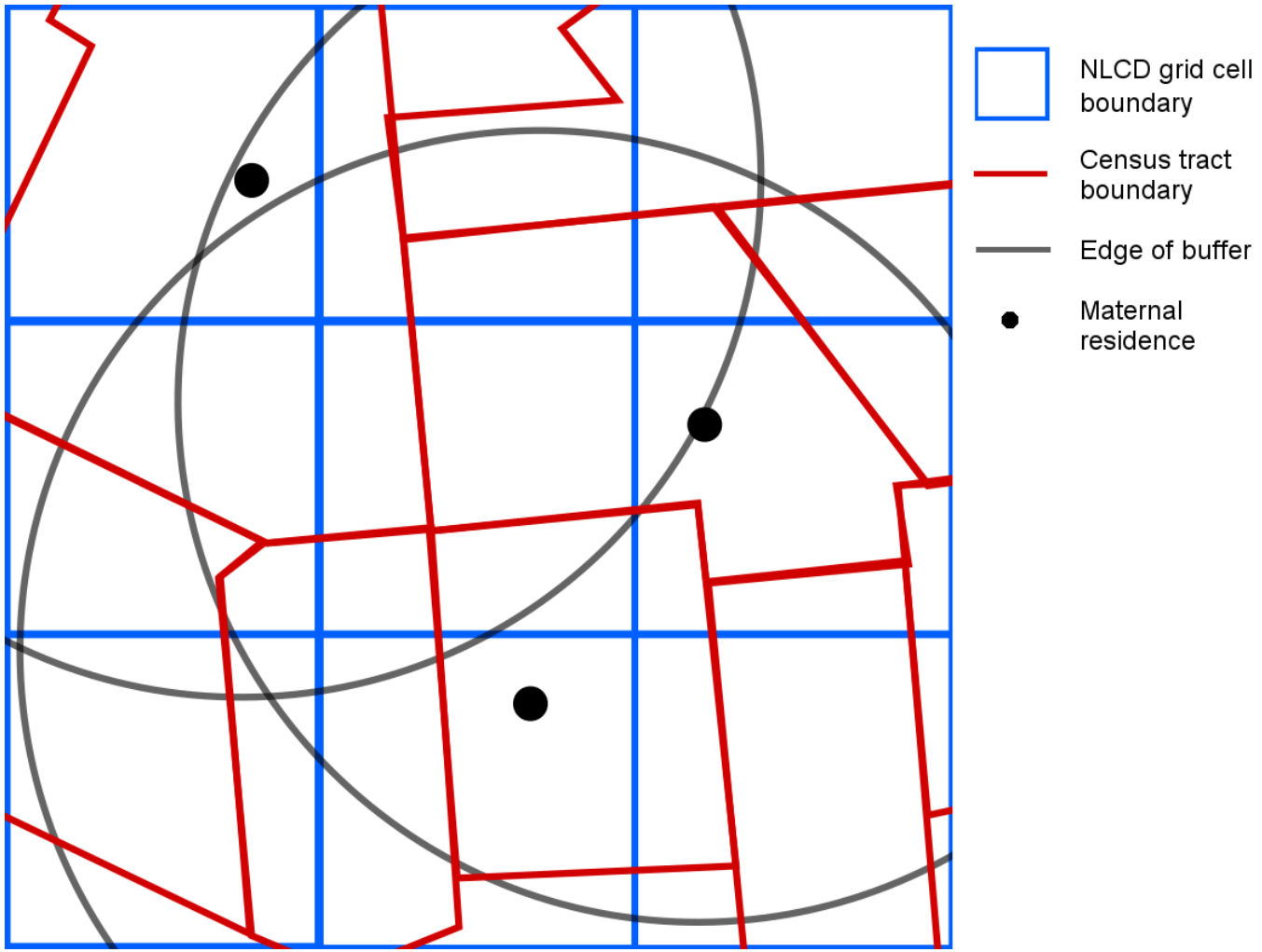

Figure 6: Data merging method

References I

1. Centers for Disease Control and Prevention. Facts about Cleft Lip and Cleft Palate. 2017. https://www.cdc.gov/ncbddd/birthdefects/cleftlip.html.
2. Ritz B, Wilhelm M. *Air Pollution Impacts on Infants and Children*. Los Angeles, CA: UCLA Institute of the Environment; 2008. https://www.ioes.ucla.edu/wp-content/uploads/air-pollution-2008.pdf.
3. Al-Hadithi TS, Al-Diwan JK, Saleh AM, Shabila NP. Birth defects in Iraq and the plausibility of environmental exposure: A review. *Conflict and Health*. 2012;6(1):1-8. doi:10.1186/1752-1505-6-3.
4. Honein MA, Paulozzi LJ, Moore CA. Family history, maternal smoking, and clubfoot: an indication of a gene-environment interaction. *American Journal of Epidemiology*. 2000;152(7):658-665. https://www.ncbi.nlm.nih.gov/pubmed/11032161.
5. Durham EL, Howie RN, Cray JJ. Gene/environment interactions in craniosynostosis: A brief review. *Orthodontics and Craniofacial Research*. 2017;20:8-11. doi:10.1111/ocr.12153.
6. Miedzybrodzka Z. Congenital talipes equinovarus (clubfoot): A disorder of the foot but not the hand. *Journal of Anatomy*. 2003;202(1):37-42. doi:10.1046/j.1469-7580.2003.00147.x.
7. Nagaraja S, Anslow P, Winter B. Craniosynostosis. *Clinical Radiology*. 2013;68(3):284-292. doi:10.1016/j.crad.2012.07.005.
8. Hansen JM, Jacob BR, Piorczynski TB. Oxidative stress during development: Chemical-induced teratogenesis. *Current Opinion in Toxicology*. 2018;7:110-115. doi:10.1016/j.cotox.2017.11.003.
9. Hansen CA, Barnett AG, Jalaludin BB, Morgan GG. Ambient air pollution and birth defects in Brisbane, Australia. *PLoS ONE*. 2009;4(4):6-13. doi:10.1371/journal.pone.0005408.
10. Hwang BF, Jaakkola JJK. Ozone and other air pollutants and the risk of oral clefts. *Environmental Health Perspectives*. 2008;116(10):1411-1415. doi:10.1289/ehp.11311.
11. Wang L, Xiang X, Mi B, et al. Association between early prenatal exposure to ambient air pollution and birth defects: evidence from newborns in Xi'an, China. *Journal of Public Health*. 2018;30. doi:10.1093/pubmed/fdy137.

References II

12. Huang X, Chen J, Zeng D, et al. The association between ambient air pollution and birth defects in five major ethnic groups in Liuzhou, China. *BMC Pediatrics*. 2021;21(1):1-12. doi:10.1186/s12887-021-02687-z.

13. Gasca-Sanchez FM, Santos-Guzman J, Elizondo-Dueñaz R, et al. Spatial clusters of children with cleft lip and palate and their association with polluted zones in the monterrey metropolitan area. *International Journal of Environmental Research and Public Health*. 2019;16(14). doi:10.3390/ijerph16142488.

14. Vinikoor-Imler LC, Stewart TG, Luben TJ, Davis JA, Langlois PH. An exploratory analysis of the relationship between ambient ozone and particulate matter concentrations during early pregnancy and selected birth defects in Texas. *Environmental Pollution*. 2015;202:1-6. doi:10.1016/j.envpol.2015.03.001.

15. Zhou Y, Gilboa SM, Herdt ML, et al. Maternal exposure to ozone and PM2.5 and the prevalence of orofacial clefts in four U.S. states. *Environmental Research*. 2017;153:35-40. doi:10.1016/j.envres.2016.11.007.

16. Zhu Y, Zhang C, Liu D, Grantz KL, Wallace M, Mendola P. Maternal ambient air pollution exposure preconception and during early gestation and offspring congenital orofacial defects. *Environmental Research*. 2015;140:714-720. doi:10.1016/j.envres.2015.06.002.