Air Pollution and Human Reproduction: What do we know?

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Why Study Air Pollution and Pregnancy?

- Developing organism is uniquely sensitive to environmental toxins within a short time window

- Adverse outcomes are common
  - in US:

  ~10% are preterm

  ~ 5% are low weight

- Immediate and long term health effects
  - Infant morbidity and mortality
  - Adverse effects on adult health; fetal programming hypothesis

Research Advantages

- Electronic birth registry records widely available
  - Source of information on outcomes (LBW/preterm birth), common confounders, and residential location at birth
- Networks of government monitoring stations exist
- Large number of births in metropolitan areas
  - E.g.,125,000 births in a 5-year period in 37 LA zip code areas near government air monitors

Diverse Outcomes Studied

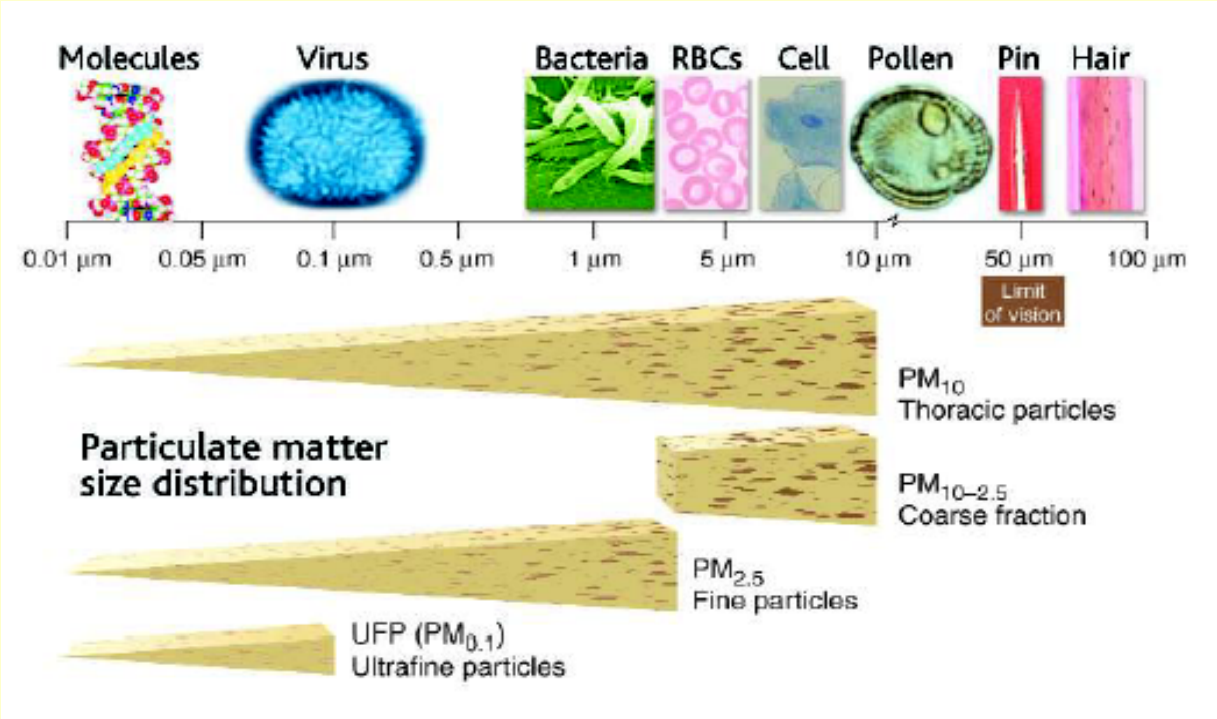
- Low birth weight (LBW)
  - Weight at birth <2500g
  - Born LBW at term *vs.* preterm
  - Small for gestational age (SGA; <10th %tile)
  - Repeated ultrasound measures during pregnancy
  - Reduction in mean birth weight
- Length and head circumference
- Preterm birth (<37 weeks of gestation)
- Malformations (mostly cardiac)
  - Spontaneous abortions
  - Pre-eclampsia

Ambient Air Pollution

Mostly:

Criteria air pollutants measured at ambient monitoring stations: CO, NO_2, PM_{10}, $PM_{2.5}$, SO_2, O_3

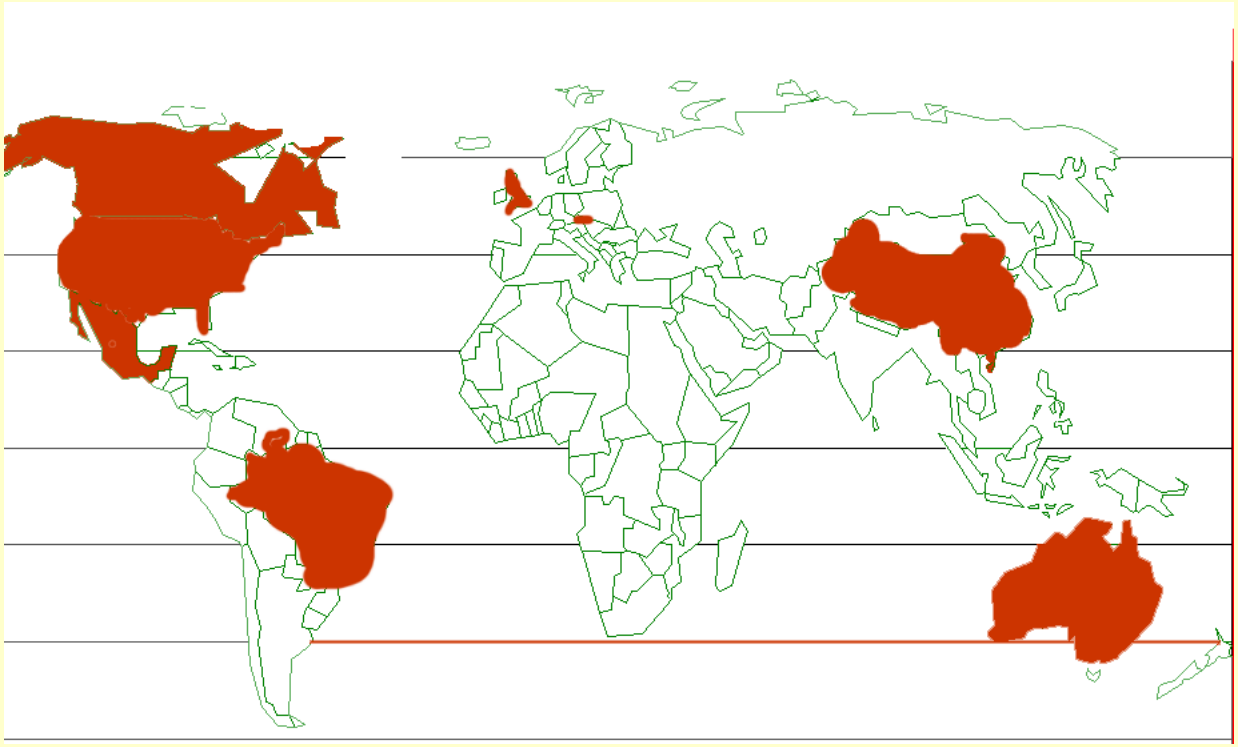
- Annual or daily area-wide averages
- Averaged over gestational period of greatest interest
- Some choose monitor closest to maternal residence



Pregnancy and ambient air pollution recently has become a focus of studies worldwide

Studies were conducted in

Australia, Brazil, Canada, China, Czech Republic, Great Britain, S. Korea, Mexico, United States…



Studies of Preterm Birth

Study	Dates	Location	Pollutants studied
Xu et al. (1995)	1988-91	Beijing, China	TSP, SO_2 (time-series)
Ritz et al. (2000)	1989-93	Southern CA, USA	CO, PM_{10}, NO_2, O_3
Bobak (2000)	1991	Czech Republic	TSP, SO_2, NO_x
Vassilev et al. (2001)	1990-91	New Jersey, USA	POM (including PAHs)
Maroziene & Grazuleviciene (2002)	1998	Kaunas, Lithuania	NO_2, formaldehyde
Woodruff et al. (2003)	1998-99	USA	CO, PM_{10}, NO_2, O_3, SO_2
Liu et al. (2003)	1985-98	Vancouver, Canada	CO, NO_2, O_3, SO_2
Wilhelm & Ritz (2005)	1994-00	Southern CA, USA	CO, PM_{10}, NO_2, O_3

Associations most consistently reported for CO, particles (TSP, PM_{10}), and SO_2 in early and end of pregnancy

Studies of Low Birth Weight

Study	Dates	Location	Pollutants studied
Alderman et al. (1987)	1978-83	Denver, USA	CO
Wang et al. (1997)	1988-91	Beijing, China	TSP, SO_2
Ritz and Yu (1999)	1989-93	Southern CA, USA	CO, PM_{10}, NO_2, O_3
Gouveia (2000)	2000	Sao Paulo, Brazil	CO, PM_{10}, NO_2, O_3
Maisonet et al. (2001)	1994-96	6 NE cities, USA	CO, PM_{10}, SO_2
Ha et al. (2001) Lee et al. (2003)	1996-97 1996-98	Seoul, South Korea	CO, PM_{10}, NO_2, SO_2, O_3
Wilhelm & Ritz (2005)	1994-00	Southern CA, USA	CO, PM_{10}, NO_2, O_3

Associations most consistently reported for CO, particles (TSP, PM_{10}), SO_2 averaged over 3rd trimester

Studies of SGA

Study	Dates	Location	Pollutants studied
Dejmek et al. (1999)	1994-96	Czech Republic	PM_{10}, $PM_{2.5}$
Dejmek et al. (2000)	1994-98	Czech Republic	PM_{10}, $PM_{2.5}$, PAHs
Vassilev et al. (2001)	1990-91	New Jersey, USA	POM (including PAHs)
Liu et al. (2003)	1985-98	Vancouver, Canada	CO, NO_2, O_3, SO_2

- Largest increases reported for PM_{10} exposures during first month of pregnancy
  - 264% increase for $\geq$50 ug/m^3 vs. <40 ug/m^3 PM_{10}, 211% increase for $\geq$37 ug/m^3 vs. <27 ug/m^3 $PM_{2.5}$

Limited Comparability of Studies

- Differences for
  - Outcome definition
  - Air pollutants measured: sources and mixes; scaling of units for pollutants
  - Timing of exposure (targeting the correct pregnancy period?)
  - Covariates adjusted for in models

Air Pollution and Adverse Birth Outcomes in Los Angeles and the South Coast Air Basin (SoCAB)

Summary of Research

Ritz B, Yu F. The effect of ambient carbon monoxide on low birth weight among children born in southern California between 1989 and 1993. Environmental Health Perspectives 1999, 107(1):17-25

Ritz B, Yu F, Chapa G, Fruin S. Effect of air pollution on preterm birth among children born in Southern California between 1989 and 1993. Epidemiology, 2000; 11:502-511.

Ritz B, Yu F, Chapa G, Fruin S, Shaw G, Harris J. Ambient air pollution and birth defects. Am J Epidemiol 2002;155:17–25.

Wilhelm M, Ritz B. Residential proximity to traffic and adverse birth outcomes in Los Angeles County, California, 1994-1996. Environ Health Perspect. 2003 Feb; 111(2):207-16.

Ponce NA, Hoggatt KJ, Wilhelm M, Ritz B. Preterm Birth: The interaction of traffic-related air pollution with economic hardship In Los Angeles neighborhoods. Am J Epidemiol. 2005 Jul 15;162(2):140-8.

Wilhelm M, Ritz, B. Local variations in CO and particulate air pollution and adverse birth outcomes in Los Angeles County, California. Environ Health Perspect; 2005 Sep;113(9):1212-21.

Ritz B, Wilhelm M, Zhao Y. Ambient air pollution and infant mortality in Los Angeles County, 1989-2000. Pediatrics 2006;118;493-502

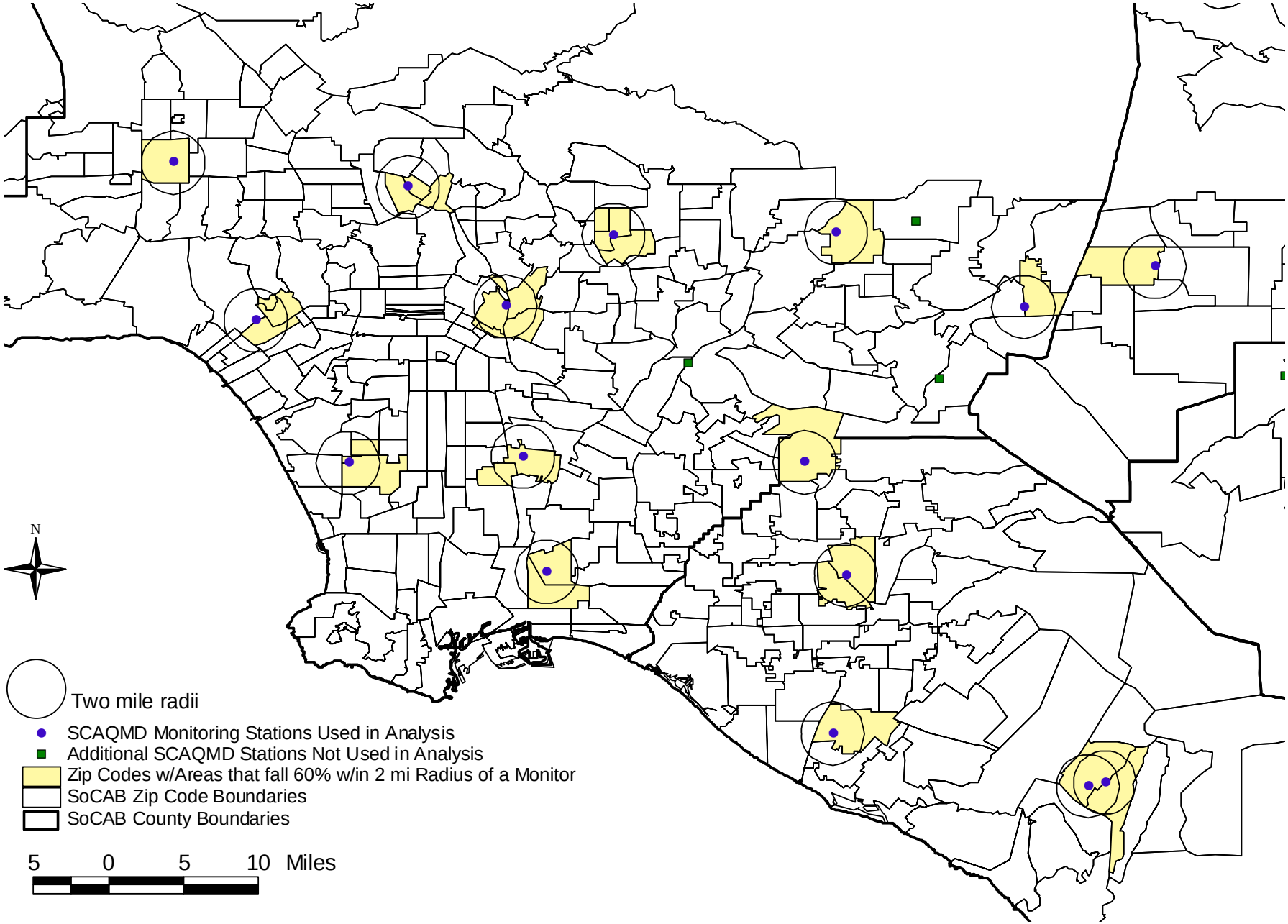
Ritz B, Wilhelm M, Hoggatt KJ, Ghosh JKC. Ambient air pollution and preterm birth in the UCLA Environment and Pregnancy Outcomes Study. In Press: Am J Epidemiol 2007

Exposure assessment 1989-1993 South Coast Air Basin

- Mothers residing within a 2-mile radius of stationary ambient monitors at the time of birth (relaxed this criterion for birth defects)

- For each child, calculated the trimester or last 6 week averages for CO, PM_{10} (O_3, NO_2) using the closest ambient monitoring station

Map of SCAQMD Monitoring Stations and Zip Codes Included in Analysis



Adjusted Odds Ratios (95%CI) for Term LBW

Ambient CO levels at LA station, 1989-1993

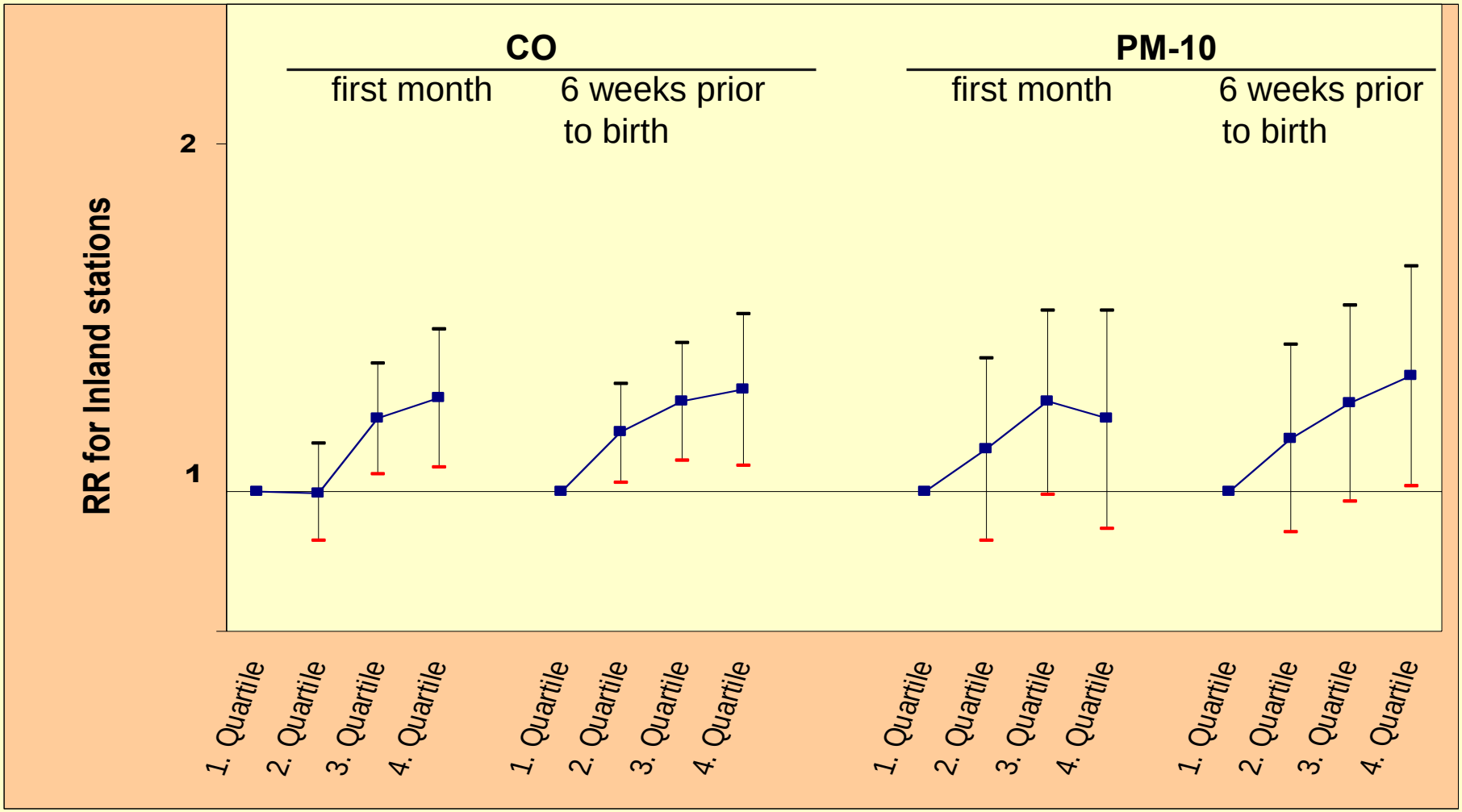
Ritz B, Yu F. The effect of ambient carbon monoxide on low birth weight among children born in southern California between 1989 and 1993. Environmental Health Perspectives 1999, 107(1):17-25.

	All stations	South Central ONLY	
Third Trimester	**2-mile radius**	**2-mile radius**	**5-mile radius**
CO level:			
- 2.2 ppm	1.0	1.0	1.0
- 2.2-<5.5	1.04 (0.96-1.13)	1.06 (0.89-1.26)	1.07 (0.99-1.16)
- 5.5+	1.22 (1.03-1.44)	1.24 (0.87-1.77)	1.24 (1.06-1.45)

All Stations: 2 mile radius: case N=2,809; non-case N= 122,764;
South Central: 2 mile radius: case N= 572; non-case N= 23,533;
5 mile radius: case N=2,805; non-case N= 94,160;

Adjusted Rate Ratios (95% CI) for Preterm Birth by Quartile of Ambient CO and PM-10 (9 Inland Stations only)

Ritz B, Yu F, Chapa G, Fruin S. Effect of air pollution on preterm birth among children born in Southern California between 1989 and 1993. Epidemiology, 2000; 11:502-511



Pregnancy month	Odds Ratios (95% CI) adjusted for covariates *
CO (ppm)	Case N=234 Control N=7944
1st month	
<1.14	1 -
1.14-<1.60	1.05 0.66-1.68
1.60-<2.47	1.12 0.59-2.12
>=2.47	1.23 0.53-2.82
2nd month	
<1.14	1 -
1.14-<1.57	1.63 1.00-2.66
1.57-<2.39	1.97 1.00-3.91
>=2.39	2.84 1.15-6.99
3rd month	
<1.12	1 -
1.12-<1.51	0.77 0.49-1.22
1.51-<2.27	0.54 0.29-1.02
>=2.27	0.70 0.31-1.58

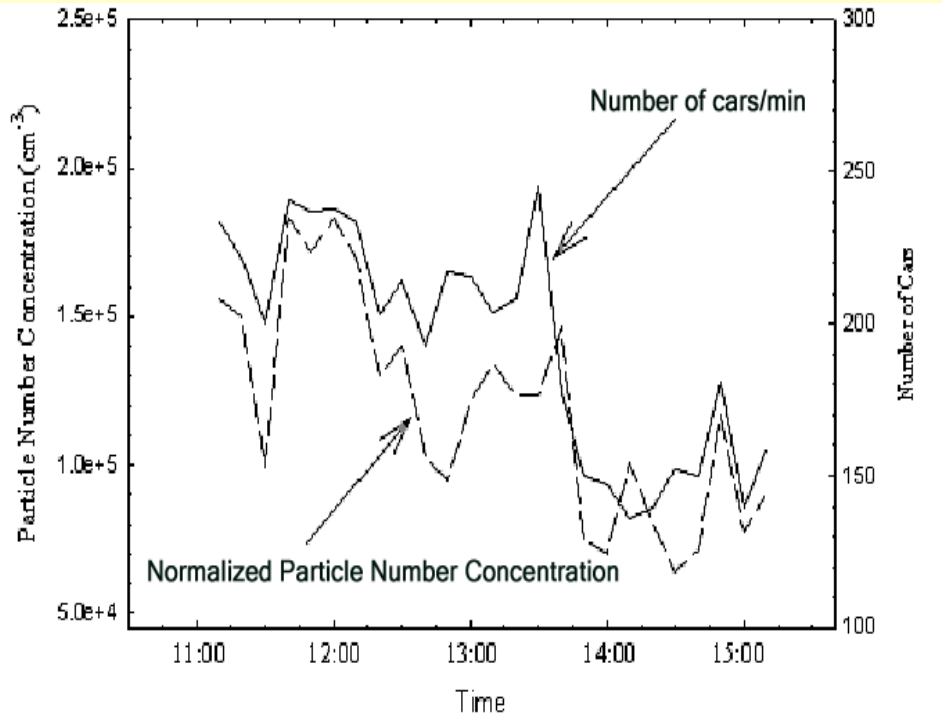
Cardiac Malformations

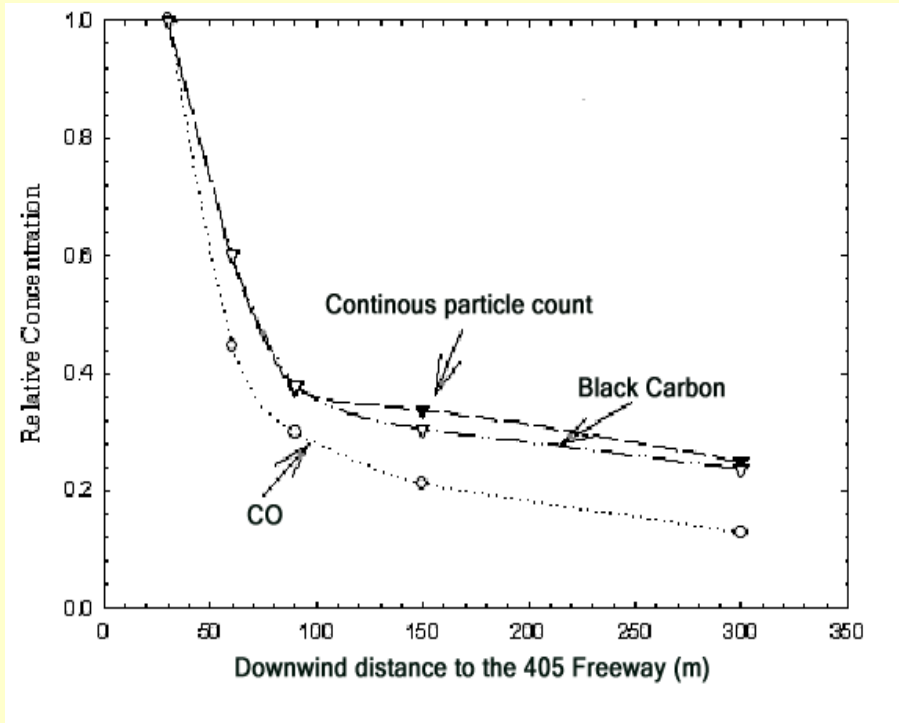
Ritz B, Yu F, Chapa G, Fruin S, Shaw G, Harris J. Ambient air pollution and birth defects. Am J Epidemiol 2002;155:17–25.

Data from CA Birth Defect Monitoring Program (1989-1993)

CO and (isolated) Ventricle Septum Defects in (multi-pollutant model)

Is CO a marker for traffic-related pollution?





Zhu Y.F., Hinds W.C., Kim S., and Sioutas C. 2002. Concentration and size distribution of ultrafine particles near a major highway. *J Air Waste Manag.Assoc* 52:1032-1042.

When using exposure data from ambient air monitoring stations, epidemiologic studies ignore potential spatial heterogeneity of vehicle-related air pollution

Distance **W**eighted **T**raffic **D**ensity

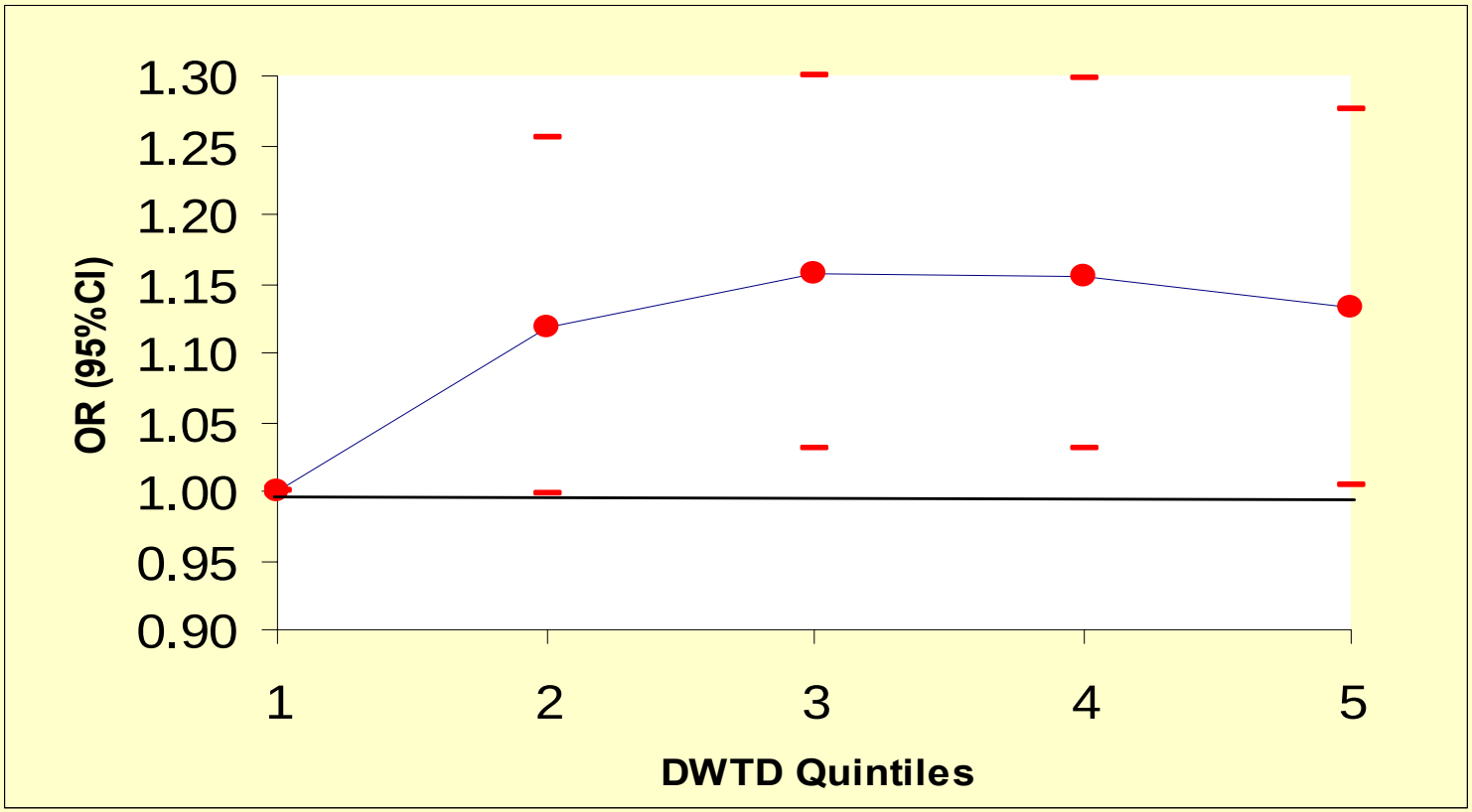
calculated for each subject

- for all streets within 750 ft. buffer of home
- Weighted traffic counts on each street by distance of home to street (using a Gaussian distribution)
- summed over weighted counts for all streets in buffer

Results Distance Weighted Traffic Density and Term Low Birth Weight, 1994-2000

Wilhelm M, Ritz B. Residential proximity to traffic and adverse birth outcomes in Los Angeles County, California, 1994-1996. Environ Health Perspect. 2003 Feb; 111(2):207-16

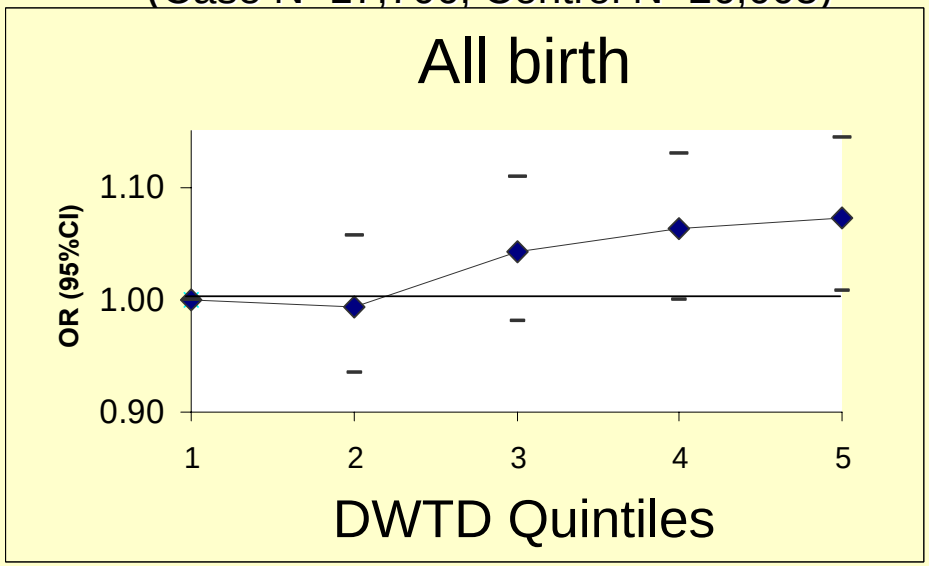
Case N=3,736; Control N=26,196

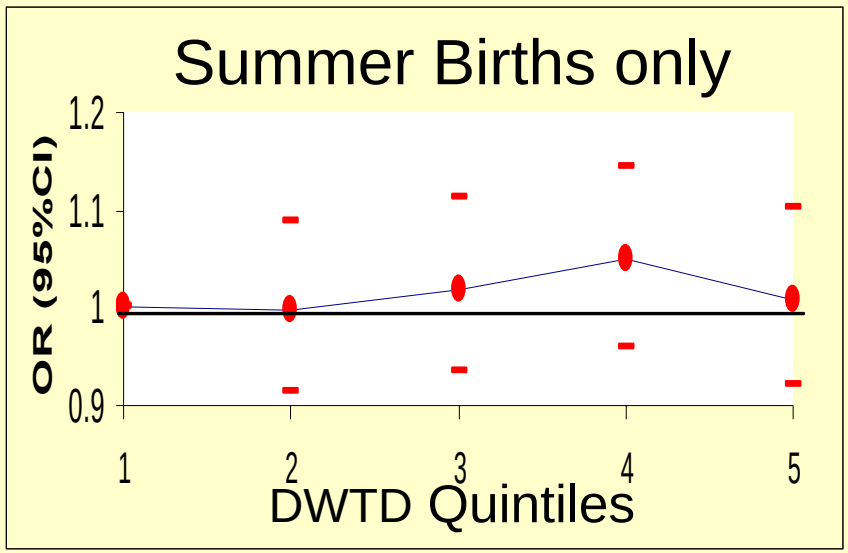


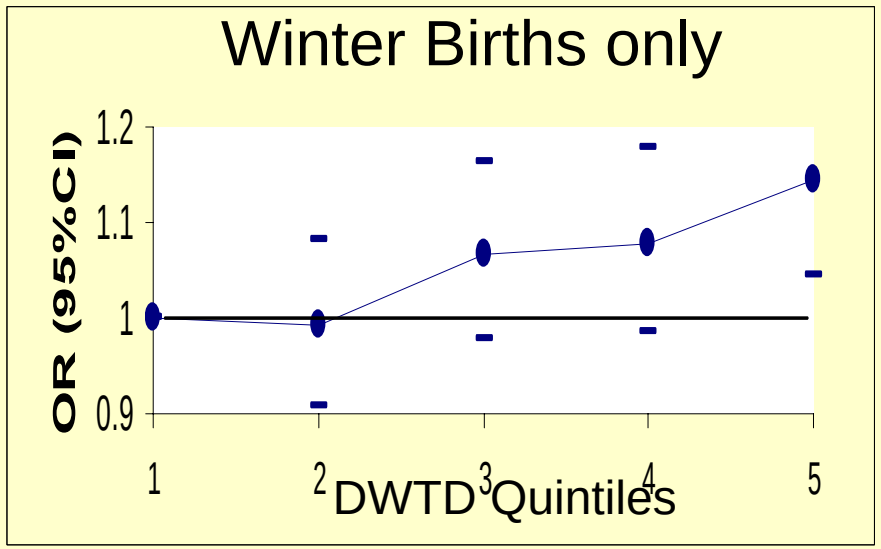
DWTD and Preterm Birth 1994-2000

Wilhelm M, Ritz B. Residential proximity to traffic and adverse birth outcomes in Los Angeles County, California, 1994-1996. Environ Health Perspect. 2003 Feb; 111(2):207-16

(Case N=17,706; Control N=26,005)







CO –Term LBW (Singleton births only)

Wilhelm M, Ritz, B. Local variations in CO and particulate air pollution and adverse birth outcomes in Los Angeles County, California. Environ Health Perspect; 2005 Sep;113(9):1212-21

CO – Third Trimester	
	Odds Ratio (95% CI)
Zip Code Level (LA County stations) ≥75th quartile (≥1.94 ppm)	(n=2,001; 81,892) **1.28 (1.10-1.50)**
Address Level	
Homes within <1 mile radius ≥75th quartile (≥1.8 ppm)	(n=653; 28,144) **1.36 (1.04-1.76)**
Homes within 1-2 mile radius ≥75th quartile (≥1.8 ppm)	(n=2,077; 87,049) **1.10 (0.95-1.28)**
Homes within 2-4 mile radius ≥75th quartile (≥1.8 ppm)	(n=6,888; 293,904) **1.08 (1.00-1.18)**

1994-2000: Differences in effect estimates by distance to station (<1, 1-<2, 2-4 mile)

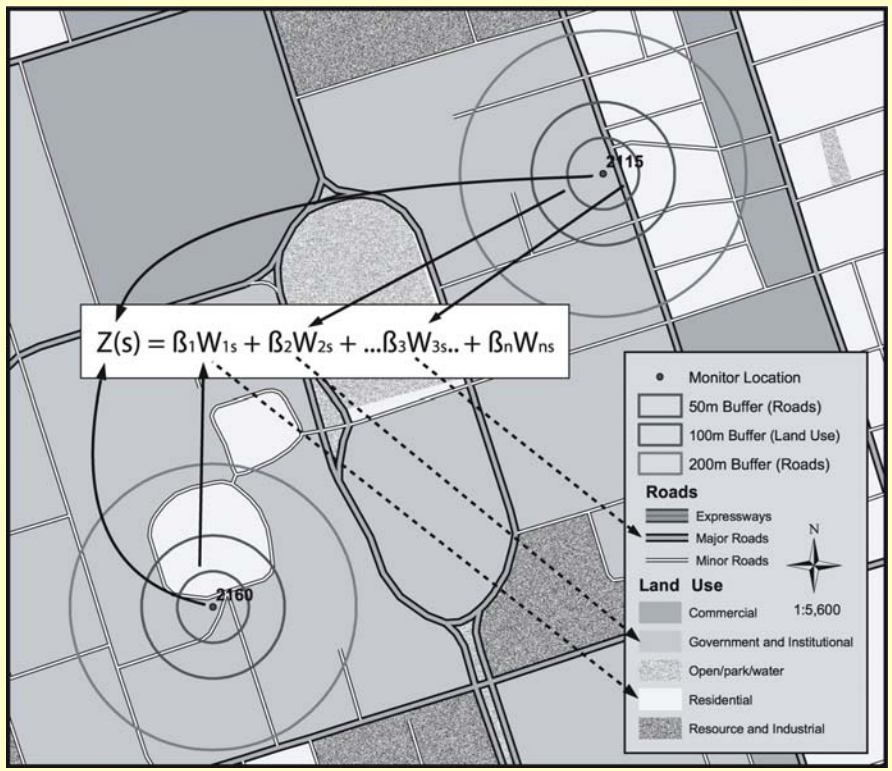
PM 2.5 - Preterm Birth (Singleton Vaginal)

Wilhelm M, Ritz, B. Local variations in CO and particulate air pollution and adverse birth outcomes in Los Angeles County, California. Environ Health Perspect; 2005 Sep;113(9):1212-21

$PM_{2.5}$ – 6 weeks prior to birth	
	Odds Ratio (95% CI)
Zip Code Level (SoCAB stations) $\geq 75^{th}$ quartile (≥ 25 ug/m^3)	(n=1,381; 14,047) **1.19 (1.02-1.40)**
Address Level	
Homes within 1 mile radius $\geq 75^{th}$ quartile (≥ 24 ug/m^3)	(n=378; 3,778) **1.25 (0.93-1.68)**
Homes within 2 mile radius $\geq 75^{th}$ quartile (≥ 25 ug/m^3)	(n=1,185; 12,170) **1.04 (0.87-1.24)**
Homes within 4 mile radius $\geq 75^{th}$ quartile (≥ 25 ug/m^3)	(n=5,229, 48,855) **1.08 (0.99-1.17)**

Improving Exposure Assessment: Land Use Regression Modeling

- Land Use Regression (LUR) modeling
  - Campaign of NO_x measurement throughout LA County (n=200 locations)
  - Relate measured concentrations to data contained in a GIS
    - Land use, traffic flow, population density



Jerrett et al., 2005 J Expo Anal Environ Epidemiol 15:185-204

Improving Exposure Assessment: Land Use Regression Modeling

Personal air monitoring during pregnancy using backpacks

- Sioutas impactor to measure particles <0.25 μm, PAHs, EC/OC, hopanes and steranes, NO, NO_2

Biosamples

- Maternal and/or cord blood
  - Cotinine, PAH DNA-adducts,
- Urine – hydroxylated PAH metabolites

Exposure Assessment: Biomarkers

Specific **air toxics** or **mixtures**

- PAH-DNA adduct concentrations in umbilical cord blood and placenta (higher in areas with polluted air)
  - Sram et al in Czech Rep (22% increase in SGA per 10 ng/m3 PAHs sorbed to particles)
  - Perera et al in NY city no effect on birth size for B(a)P-DNA adducts measured in cord blood at delivery

- 48-hour personal PAH measurements or ambient PAH
  - Perera et al in NY city 8 PAHs reduced birth weight in African Americans but not Dominicans
  - Perera et al in Poland PAHs reduced birth weight (exposures were 10-fold higher in Poland than in NYC)

Small samples….

Confounding?

- Typical air pollution times series methods not applicable
  - only time-varying factors possible confounders
- Vulnerable periods for specific adverse events are of medium length (trimesters, months) - spatial and temporal contrasts
  - Residual confounding (e.g. SES related) is a larger concern

Risk Factors for Preterm Birth and/or Low Birth Weight (LBW)

Controlled for in the analysis

- birth type (single or other)
- parity
- sex of the infant
- maternal age
- maternal ethnicity
- maternal educational attainment
- delivery interval <12 months
- prenatal care
- transportation time to work (from census data)

Risk Factors Not Reported on Birth Certificates

Not controlled for in the analysis:

- pre-pregnancy weight, weight gain, and height of mother
- history of loss of the most recent pregnancy
- social factors (marital status?, occupational exposures to toxins?)
- **behavioral factors** (e.g. **smoking**, caffeine use, marijuana smoking, alcohol drinking during pregnancy)

UCLA-**E**nvironment and **P**regnancy **O**utcome **S**tudy

NIEHS funded study 1R01ES013717

Survey of a sample of mothers who gave birth to LBW/Preterm or normal weight/term children in 2003 in LA County

- Collect information on
  - Individual-level risk factors during pregnancy: smoking, alcohol, diet, occupation, psychosocial stress
  - Indoor pollution sources
  - In-transit exposures
  - Time-activity

- Primary Goal:
  - Use this information to evaluate and adjust for confounding employing a two-stage design
  - Secondary goals – assess the following:
    - Additional air pollution exposures sources (passive smoking, gas heating and cooking, in transit traffic-related exposures)
    - Potential influence of selection bias due to response in population-based case control study with records for all cohort members

UCLA-**E**nvironment and **P**regnancy **O**utcome **S**tudy

- Cohort of infants born 1/1/03-12/31/03 to residents of 111 Los Angeles County zip codes (n=58,316)
  - Located near a monitoring station (n=24 zip codes, 100% of cases) or a major roadway (n=87 zip codes, sampled randomly 30% of cases); randomly sampled 1 control for each case from same zip code set
  - Interviewed selected mothers 3-6 months after birth
    - n = 6,374 eligible individuals, n = 2,544 responders (40%)
- Outcome: term and preterm low birth weight = infant weighed <2500g at delivery or <37 weeks of gestation

Phase 1 and Phase 2 variables-- Compare case-control and two-phase CO and LBW results

Covariates included in the models:

Phase 1: maternal age, race, parity, education, quarter of birth

1. Birth cohort: 1.15 (1.06 – 1.25)
2. Case-control: 1.32 (1.05 – 1.66)

Phase 2: maternal smoking during pregnancy, alcohol consumption, residence in house with a smoker, marital/partner status (and income)

Case-control: 1.30 (1.0 – 1.6) (adj for all covariates simultaneously)

Using two-phase estimators to account for sampling from birth cohort

PL: 1.14 (1.01 – 1.29)

WL: 1.13 (1.03 – 1.25)

UCLA-EPOS Results Preterm Births

Ritz B, Wilhelm M, Hoggatt KJ, Ghosh JKC. Ambient air pollution and preterm birth in the UCLA Environment and Pregnancy Outcomes Study. In Press: Am J Epidemiol 2007

	Birth Cohort (N=59,025)		EPOS Responders (N=2,546)			
	Crude OR (95% CI)	Adj. OR (95% CI)*	Crude OR (95% CI)	Adj. OR (95% CI)*	Adj. OR (95% CI)**	2-Phase model OR (95% CI)**
1st Trimester CO						
≤0.58	1.0	1.0	1.0	1.0	1.0	1.0
≥1.25	1.14 (1.05-1.23)	1.25 (1.12-1.38)	1.18 (0.94-1.50)	1.24 (0.91-1.68)	1.21 (0.86-1.71)	1.25 (0.96-1.63)
Entire Pregnancy CO						
≤0.58	1.0	1.0	1.0	1.0	1.0	1.0
≥1.25	1.22 (1.09-1.37)	1.03 (0.92-1.17)	1.13 (0.82-1.56)	0.86 (0.60-1.23)	0.88 (0.59-1.31)	0.90 (0.74-1.10)

* Adjusted for state covariates: birth season, parity, and mother's age, race, and education.
** Adjusted for both state covariates (birth season, parity, and mother's age, race, and education and EPOS survey covariates (active and passive smoking, marital status, and alcohol use during pregnancy).

Biologic Mechanism?

- What is affected: mother, fetus or placenta?
- Can we take cues from smoking?

- Animal data suggests fetus may be vulnerable to **hypoxia** (but at ambient CO levels?)

- Ultrafine particles, adsorbed toxins (PAHs, hydroquinones etc), or vehicle exhaust gases
  - Damage fetal tissues?
  - Cause infections or inflammation in mother?
  - Disrupt trophoblast formation and placental function (impair mitochondrial function in giant cells of trophoblast)?
  - Interfere with hypothalamic-pituitary-placental axis (epigenetic or endocrine disruption)?

Summary

- New field
- Few of the problems/limitations are unique to perinatal epidemiology
- Many plague all of air pollution epidemiology
- When is accumulated evidence enough to inform standard setting and policy as done for other endpoints like mortality and respiratory and cardiovascular diseases?

Fetuses are

- Susceptible
- Disruption of fetal development may have impact on child and adult health
- Millions of women throughout the world are exposed to air pollution levels similar to or greater than these levels

A more pre-cautionary viewpoint may be a prudent approach

Many Thanks To….

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J. Chan Ghosh (Epidemiology)

UC Berkeley

M. Jerrett

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