Epidemiological Evidence for Adverse Birth Effects Associated with Prenatal Exposure to Air Pollution

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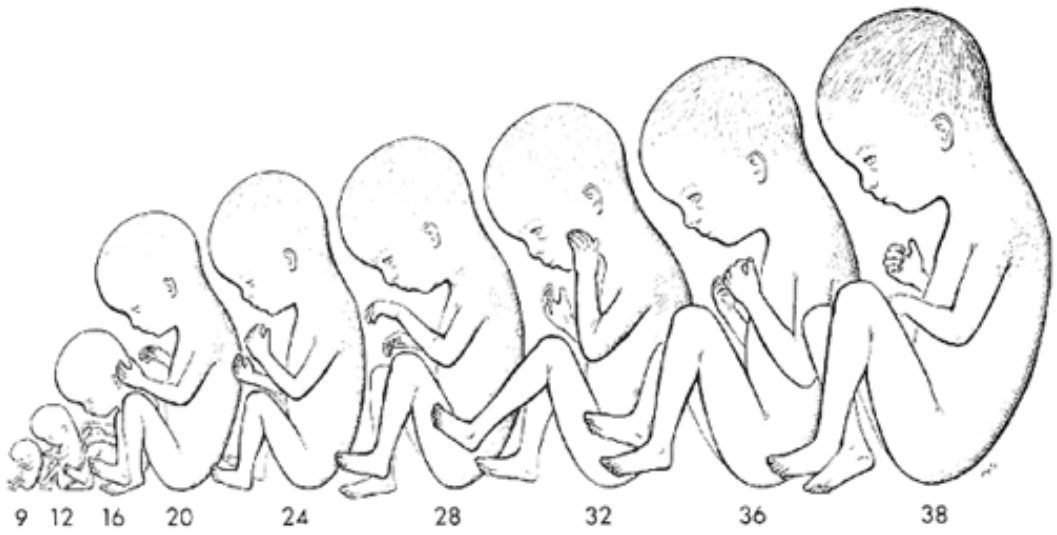
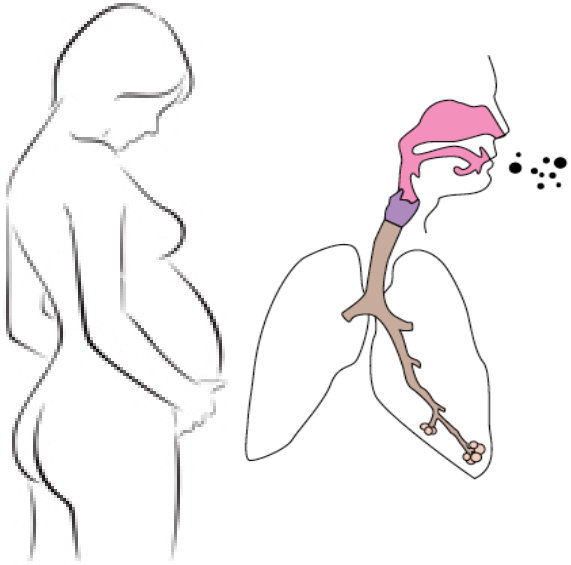
Why Study Effects of Exposure to Air Pollution During Prenatal Life?

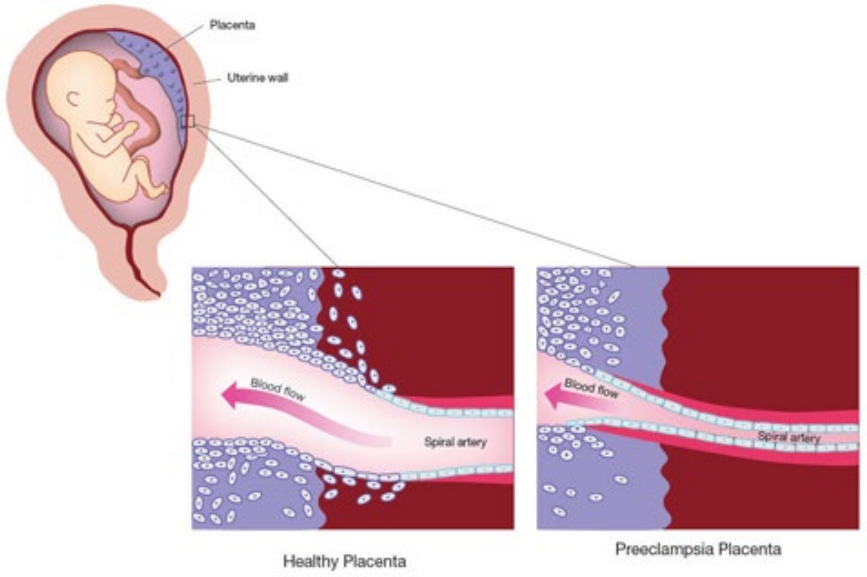
Because both the child and the mother are particularly vulnerable to exposure during these critical windows



During Pregnancy

- Women inhale more air (5 L versus 3 L per 8 hours during resting)
- Women are more vulnerable towards exposure to air pollution as they are already under physiological stress (Blackburn 2008)
- Exposures can affect maternal health, which may have adverse affects on the fetus due to suboptimal exchange of nutrients and gasses across the placenta (Pedersen et al. 2014; 2017)





Air pollution particles found in mothers' placentas

New research shows direct evidence that toxic air – already strongly linked to harm in unborn babies – travels through mothers' bodies

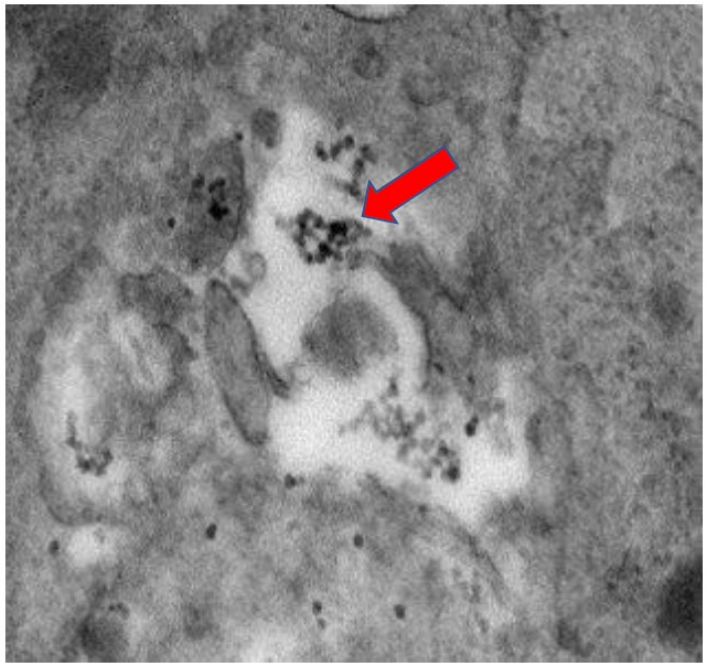
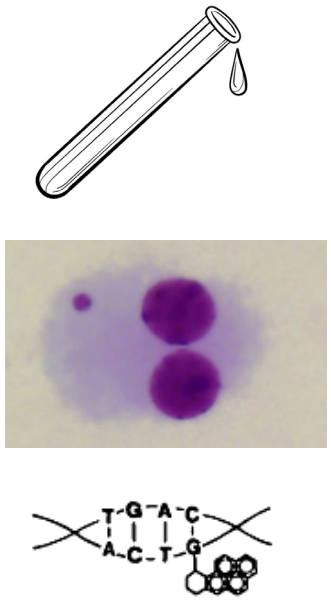
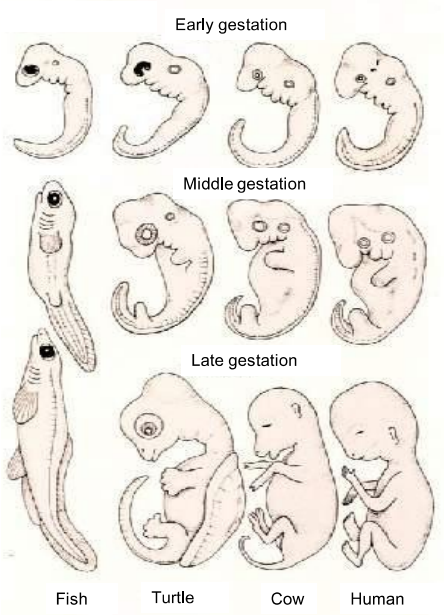


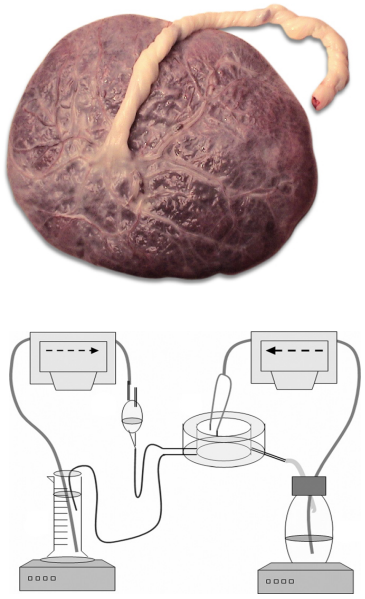
Photo kindly provided by Dr. Liu from Prof. Grigg's research group at Queen Mary's Blizard Institute, the UK.

Biological Mechanistic Evidence

Exposure to air pollution can induce adverse biological effects such as increased oxidative stress, inflammation, DNA adducts, DNA damage, immunological and epigenetic changes, altered endothelial and placental function, which may disturb the prenatal development and growth and cause adverse birth outcomes







Biomarker studies | Animal studies | *In vitro* studies | *Ex vivo* human placenta perfusions

(Maciel-Ruiz et al. 2019; Kannan et al. 2006; Pedersen et al. 2009; 2015; Topinka et al. 1997; Whyatt et al. 2001)

Intrauterine Growth Restriction (IUGR)

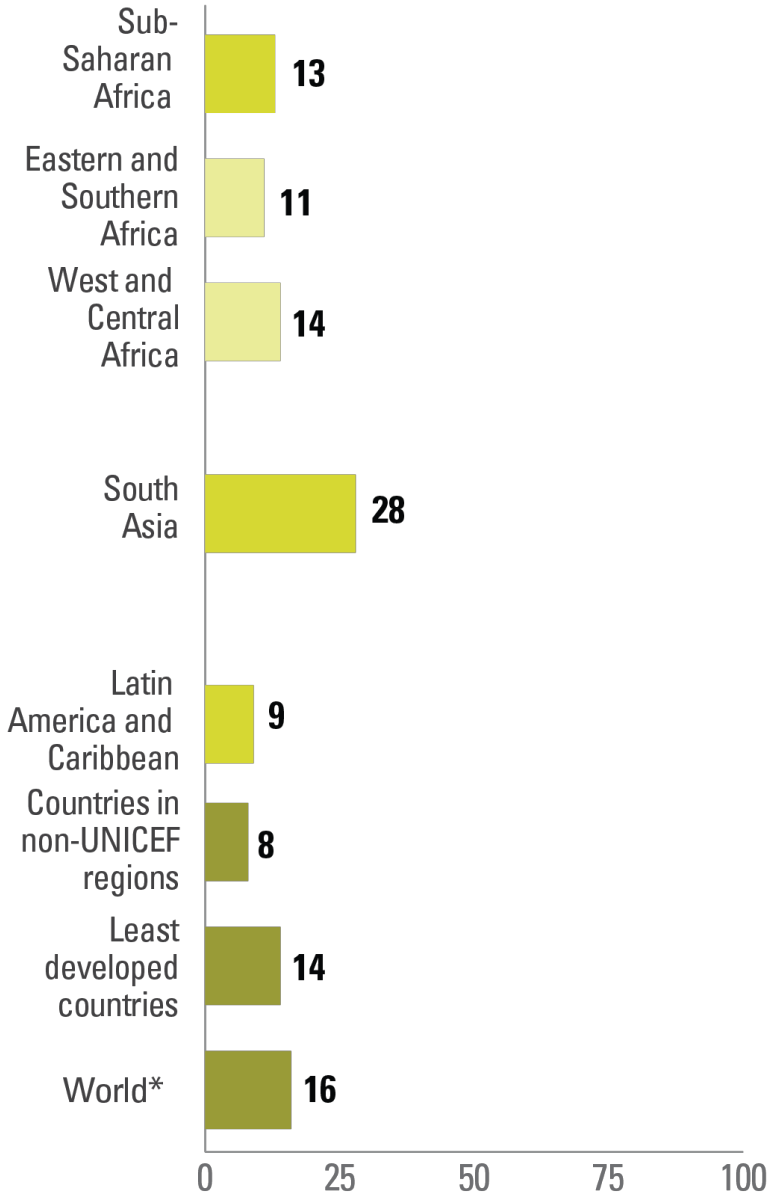
- Refers to a condition in which the fetus is smaller than expected

The most commonly studied indicators of IUGR are:

- Term low birth weight (LBW; <2,500 g born after 37 completed weeks of gestation)
- Small for gestational age (SGA; birth weight <10th percentile for the same gestational age (and sex), based on a reference population)
- Term birth weight (g)

Large Geographical Variation in LBW Prevalence

- Every year, about 20 million infants are born with low birth weight (LBW) worldwide
- 96% of them in low-income countries



(World Health Organization, 2004)

Fetal Origin of Adult Diseases

Low birth weight has been associated with increased risk of mortality and diseases such as cardiovascular diseases (Barker et al 1995), diabetes, obesity (Whincup et al. 2008), childhood cancer (Caughey & Michels, 2009)

Importance of Preterm Delivery

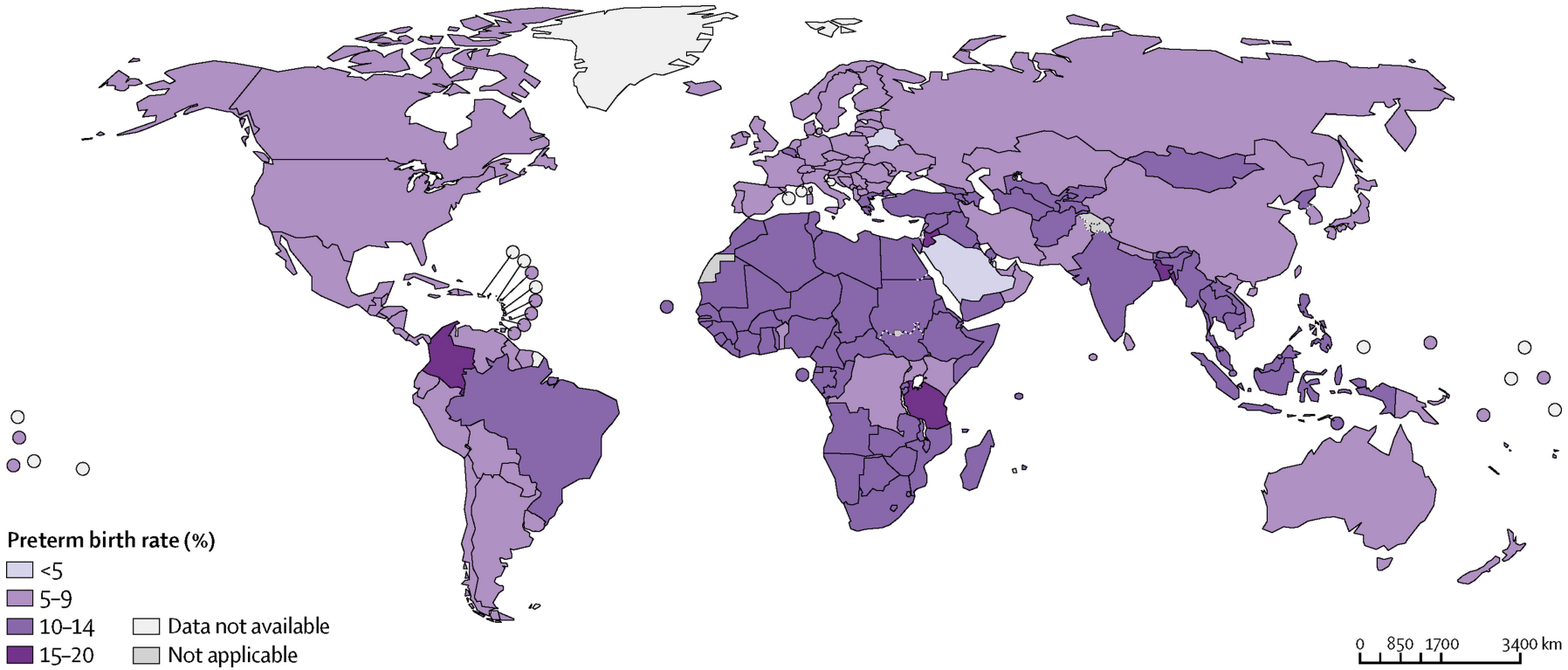
- Preterm delivery (PTD, born before 37 completed weeks) is the largest cause of newborn death and the second leading cause of all child deaths

- Infants with PTD often need intensive care, they are at greater risk of a range of short-term and long-term morbidities and disabilities such as intellectual, behavioral and respiratory problems

- Studies of PTD are challenged by the uncertainty of the date of conception

Large Geographical Variation in PTD Prevalence

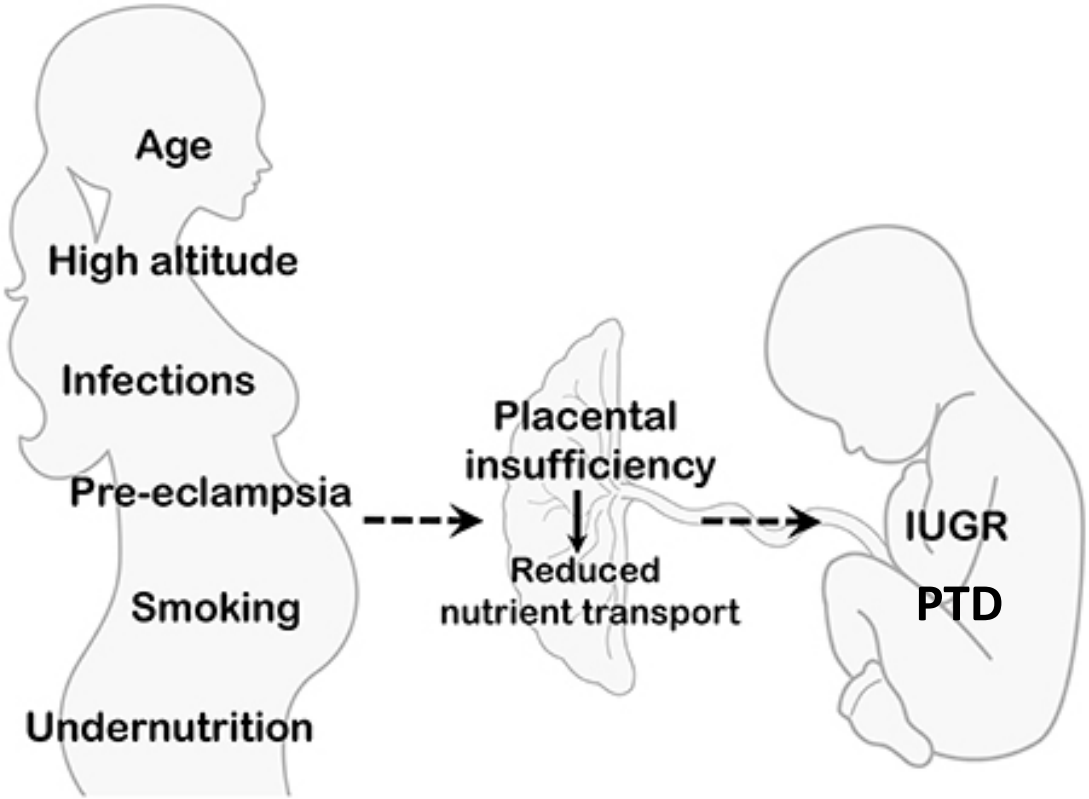
- Every year, about 15 million infants are born with preterm delivery (PTD) worldwide, with higher prevalence in low-income countries



(World Health Organization, 2018)

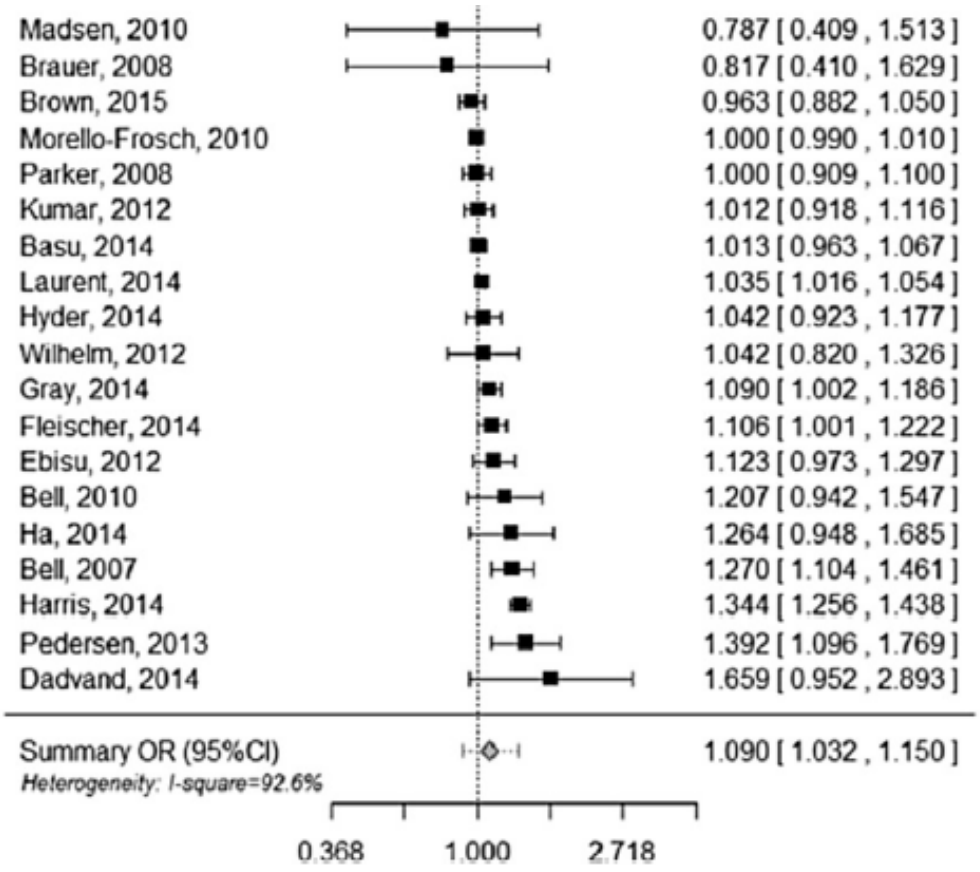
So what is the epidemiological evidence?

Can we add exposure to ambient air pollution as a risk factor of IUGR and PTD?



Exposure to Fine Particulate Matter ($PM_{2.5}$) Increases the Risk of LBW in Most, but Not in All Studies

Mean pregnancy exposure (per 10 μg/m^3)

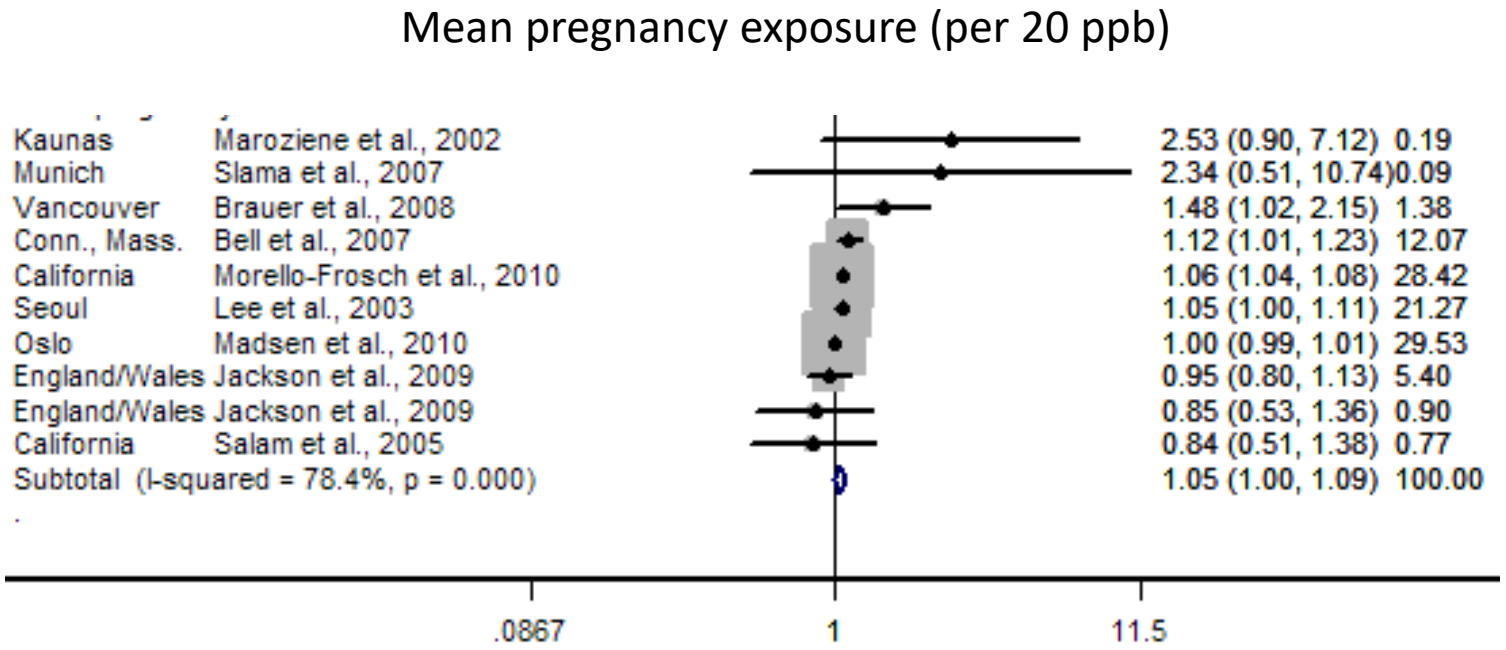


>300,000 LBW cases (Sun et al. 2016)

Additional supportive evidence from more recent studies (Balakrishnan et al. 2018; Coker et al. 2015; Smith et al. 2017; Stieb et al. 2016) but not from all studies (Hao et al. 2016; Laurent et al. 2016; Lavigne et al. 2016).

LBW = Low Birth Weight

Exposure to Nitrogen Dioxide (NO_2) Increases the Risk of LBW, but Not in All Studies



(Stieb et al. 2012)

Mixed findings in more recent studies (Chen et al. 2018; Hjortebjerg et al. 2016; Laurent et al. 2013; Pedersen et al. 2013; Smith et al. 2017; Stieb et al. 2016)

LBW = Low Birth Weight

Other Commonly Studied Pollutants and Their Associations With LBW

Summary results from a meta-analysis for mean pregnancy exposures

$PM_{2.5}$ per 10 µg/m³	PM_{10} per 10 µg/m³	NO_2 per 20 ppb	SO_2 per 5 ppb	CO per 1 ppm	O_3 per 20 ppb
1.09 (1.03, 1.15)	1.10 (1.05, 1.15)	1.05 (1.00, 1.09)	1.03 (1.03, 1.05)	1.07 (1.02, 1.12)	1.01 (0.82, 1.25)
93%	68%	78%	0%	38%	25%
n=19	n=14	n=10	n=7	n=6	n=3

Odds ratios (95% CIs), I^2 for heterogeneity; n: number of studies included

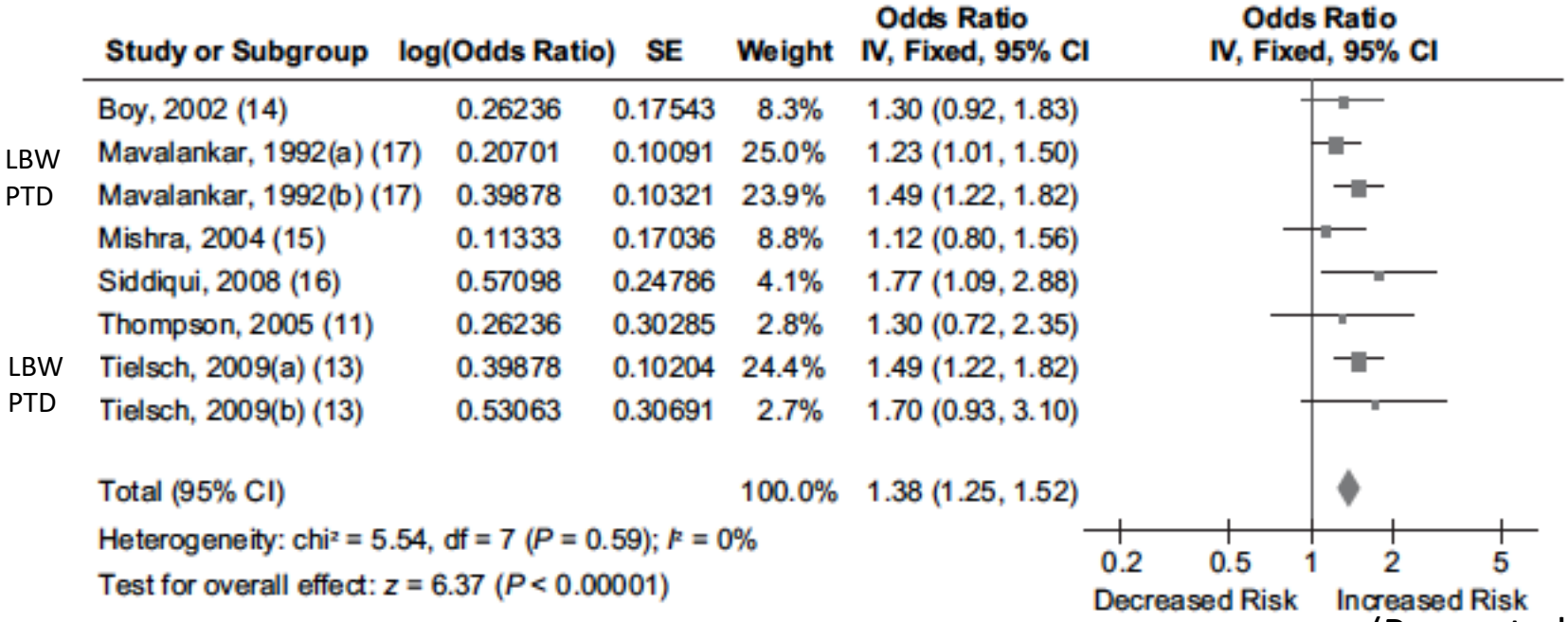
(Sun et al. 2016; Stieb et al. 2012)

NO_x, BC, PM components, traffic density and proximity to road traffic have also been linked with increased risk of LBW

(Shah et al. 2011, Stieb et al. 2012, Klepac et al. 2018)

LBW = Low Birth Weight

Supportive Evidence of Increased Risks of LBW from Studies on Solid Fuel Use Compared With Cleaner Fuels from Low-income Countries



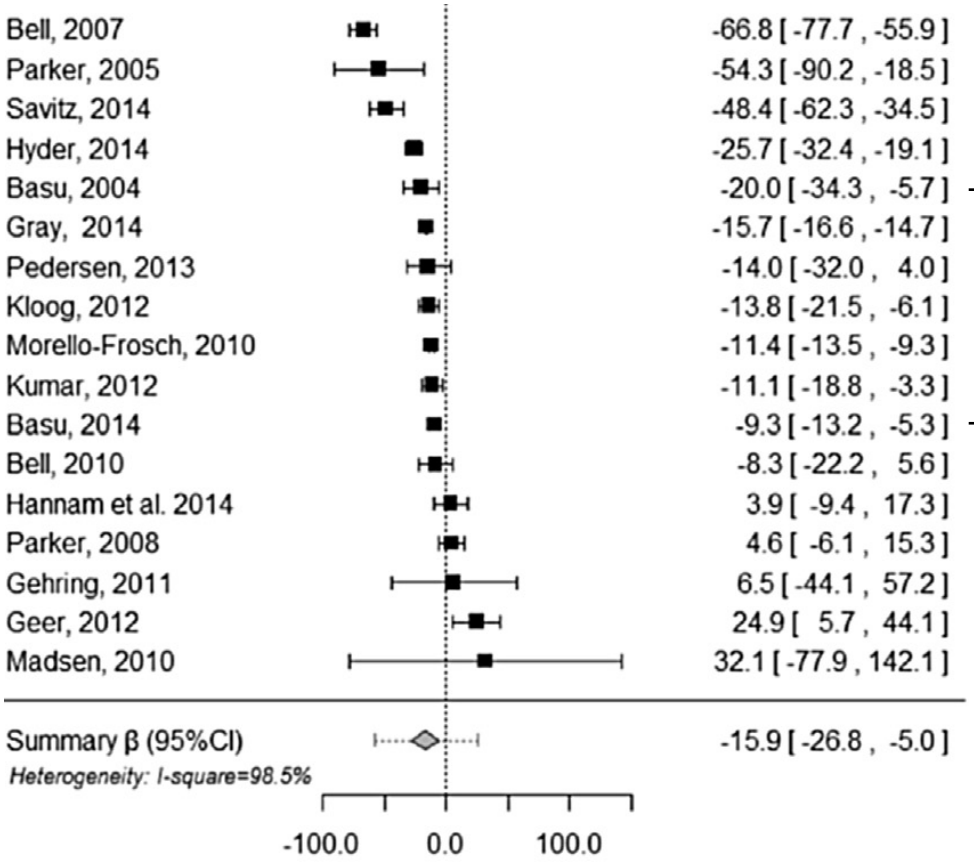
(Pope et al. 2010)

Real effect might be larger. Challenged by exposure assessment, study population size, suboptimal data on birth outcomes and residual confounding by poverty

LBW = Low Birth Weight

Exposure to $PM_{2.5}$ Has Also Been Associated With Significant Reduction in the Birth Weight (g) In Most, but Not in All Studies

Mean pregnancy exposure (per 10 μg/m^3) iated



Trimester of exposure	Birth weight (g) Mean change (95%CI)
1st	-8 (-17, 1)
2nd	-13 (-22, -3)
3rd	-10 (-17, -4)

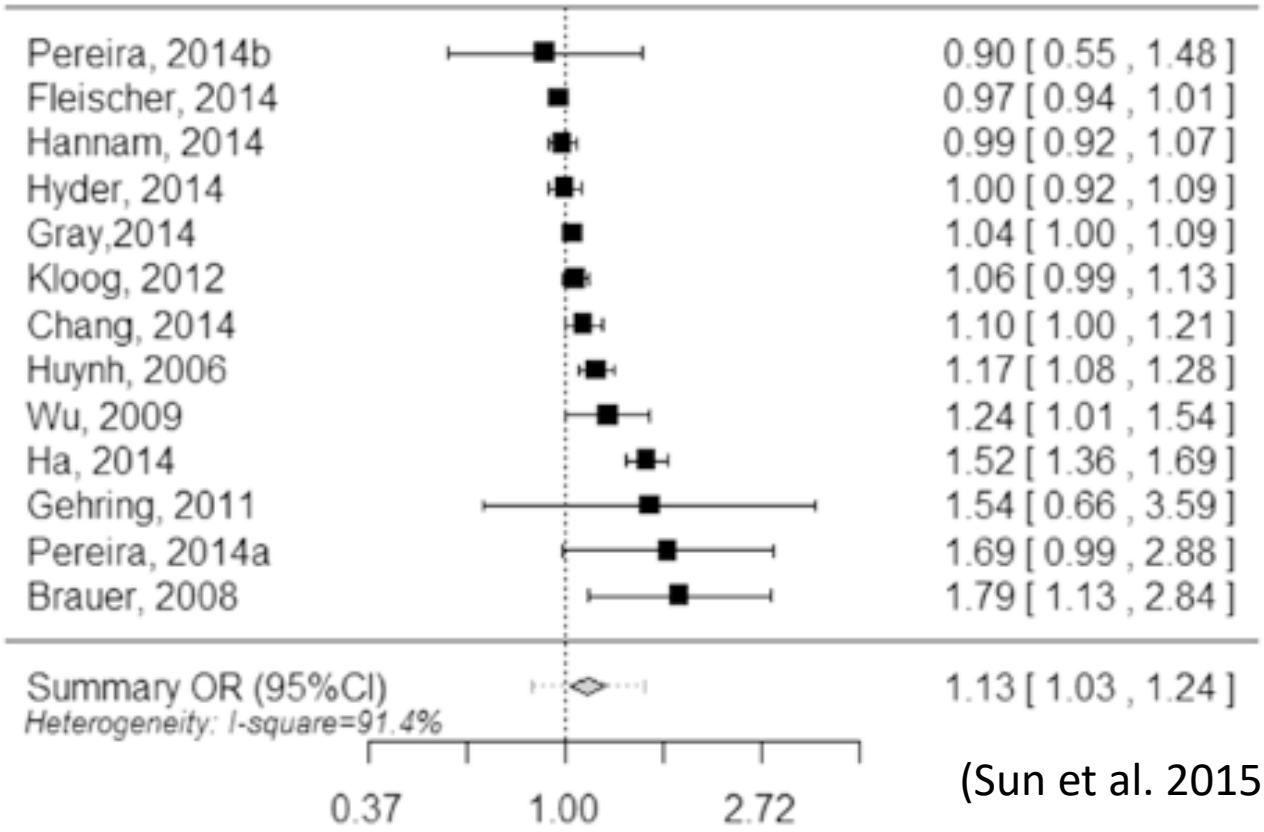
(Sun et al. 2016)

More supportive evidence for a significant reduction in birth weight

(Balakrishnan et al. 2018; Gehring et al. 2014; Kingsley et al. 2016; Stieb et al. 2016)

For Preterm delivery: Some, but More Mixed Evidence of An Increased Risk

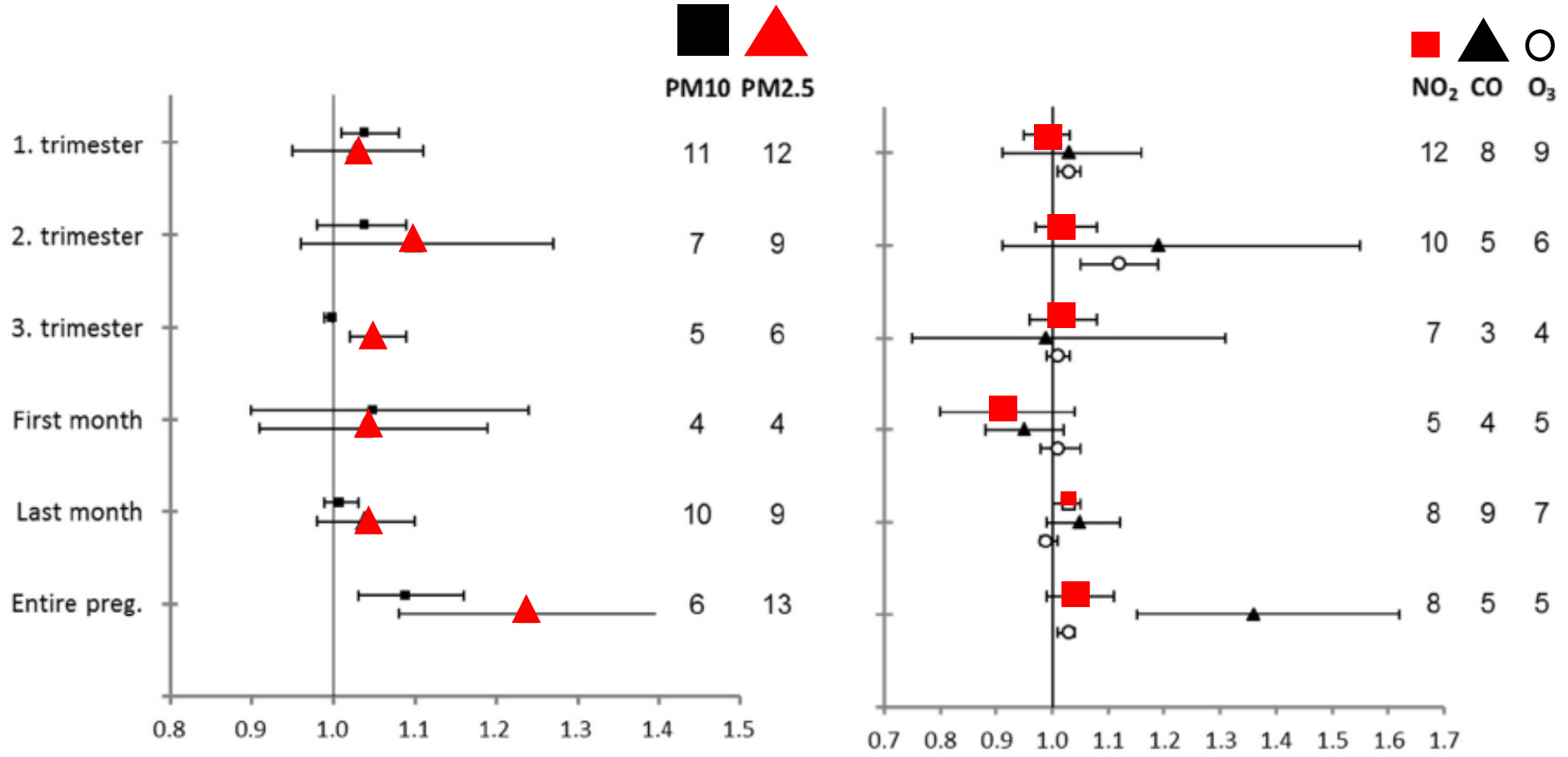
Mean pregnancy exposure to $PM_{2.5}$ (per 10 µg/m^3)



(Sun et al. 2015)

No evidence of increased risk in some of the more recent large studies (Balakrishnan et al. 2018; Giorgis-Allemand et al. 2016; Kingsley et al. 2016; Johnson et al. 2016; Stieb et al. 2016;) and supportive evidence in others (Chen et al. 2018; Hao et al. 2016; Laurent et al. 2016; Lavigne et al. 2016; Li et al. 2018; Qian et al. 2016).

Particulate Matter (PM) is Most Consistently Associated With Significant Increased Risk of Preterm Delivery (PTD) As Compared With the Results of Meta-Analysis of Studies With NO_2, CO and O_3

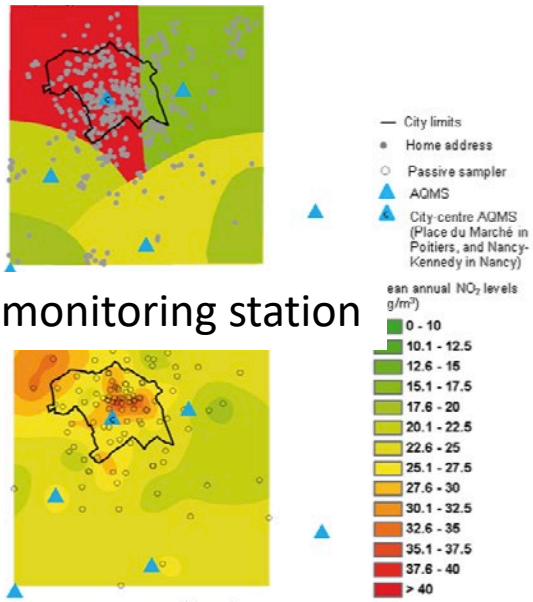


Summary effects from random-effect meta-analysis per 10 µg/m^3 increment in particulate matter less than 10 (PM_{10}) or 2.5 ($PM_{2.5}$) micrometers in diameter, 10 ppb increment in nitrogen dioxide (NO_2) or ozone (O_3), and 1 ppb increment in carbon monoxide (CO). Numbers indicate numbers of studies included for each pollutant.

(Klepac et al. 2018)

Possible Explanations For Variation in the Findings

- These mixed results could reflect real differences in the study areas and populations
- Differences in the designs and methods of exposure assessment and ability to control for confounding



Nearest monitoring station

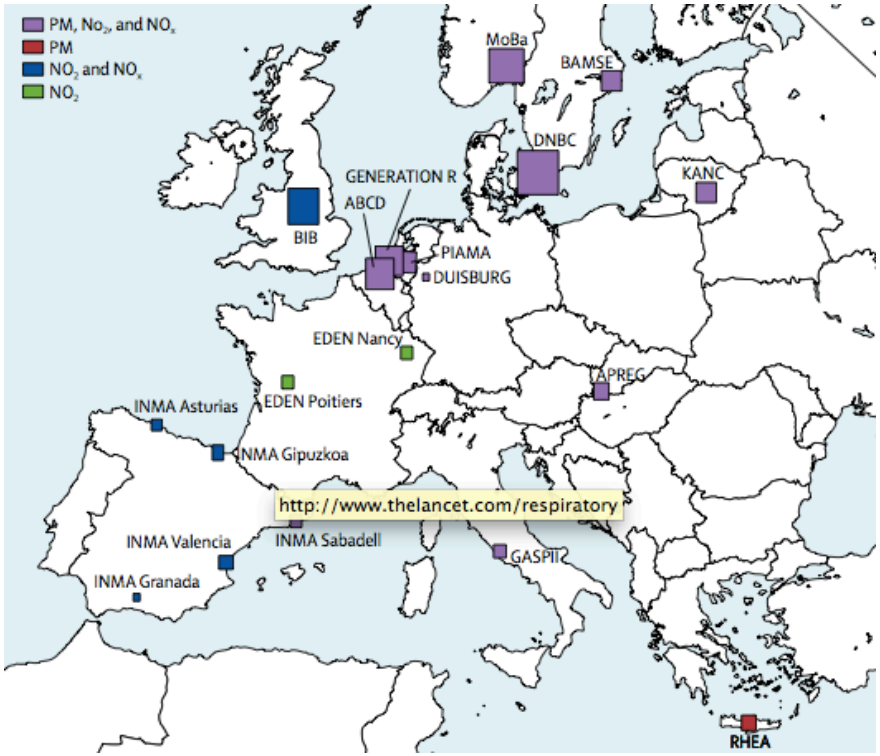
LUR model

Maps. from Slama

The European Study of Cohorts for Air Pollution Effects (ESCAPE) Low Birth Weight Study

- Pooled analyses of individual data from 74,000 singletons obtained from 14 European birth cohorts (Pedersen et al. 2013)

- Harmonized (fine-scale) exposure assessment (Eeftens et al 2012; Beelen et al. 2013)



Adjusted Odds Ratios for Term Low Birthweight Associated with Pregnancy Mean Exposure

	OR	(95%CIs)
$PM_{2.5}$ (per 5 $\mu g/m^3$)*	1.18	(1.06, 1.33)
$PM_{2.5-10}$(per 5 $\mu g/m^3$)*	1.01	(0.88, 1.15)
PM_{10} (per 10 $\mu g/m^3$)*	1.16	(1.00, 1.35)
Soot (per 1 10^{-5}/m)*	1.17	(0.95, 1.39)
NO_2 (per 10 $\mu g/m^3$)**	1.09	(1.00, 1.19)
NO_X (per 20 $\mu g/m^3$)***	1.04	(0.97, 1.11)
Traffic density (per 5000 mv/d)****	1.05	(1.00, 1.10)
Traffic load (per 400000mv/d*m) *****	1.01	(0.96, 1.07)

Effect estimates are from the pooled sample using logistic regression models with random effect of center adjusted for gestational age (weeks and weeks^2), sex, parity (0, 1, 2+), maternal height (cm), pre-pregnancy weight (broken stick model with a knot at 60 kg), maternal active smoking during pregnancy (cigarettes/day), maternal age (years), maternal education (low, middle, high) and season of conception (Jan.-March, April-June, July-Sep., Oct.-Dec.). Traffic density on nearest street and traffic load is further adjusted for background levels of NO_2 ($\mu g/m^3$).

* All cohorts, but not BIB, INMA, Asturias, INMA, Giouzkoa, INMA, Valencia, INMA, Granada and EDEN, ** All cohorts, but not RHEA, ***All cohorts, but not RHEA and EDEN, ****All cohorts, but not APREG, INMA, Asturias, INMA, Giouzkoa, INMA, Valencia, INMA, Granada and RHEA, *****All cohorts, but not APREG, INMA, Asturias, INMA, Giouzkoa and RHEA, ***** All cohorts, but INMA, Granada and MOBA

(Pedersen et al. 2013)

No association with Preterm delivery (PTD) (Giorgis-Allemand et al. 2016)

Comparison of the Population-Attributable Risk (PAR) of $PM_{2.5}$ with the PAR of Maternal Active Smoking for Term Low Birthweight

Exposure	Exposed (N)	PAR, % (95% CI)
Pregnancy mean $PM_{2.5}$ *	45,430	22 (8-33)%
Maternal active smoking	6,237	15 (11-20)%

* Exposure to >10 µg/m^3 (WHO target value)

(Pedersen et al. 2013)

The New York Times

The New York Times

theguardian

L'air pollué diminue le poids des bébés à la naissance

LE MONDE | 15.10.2013 à 16h26 • Mis à jour le 15.10.2013 à 16h56 |

EL PAIS

SOCIEDAD

Hasta la contaminación 'legal' aumenta el riesgo de bajo peso al nacer

Según el mayor estudio europeo realizado hasta ahora en la materia, incluso con escaso nivel de polución el crecimiento fetal se ve afectado

Air pollution linked to low birthweight in Europe

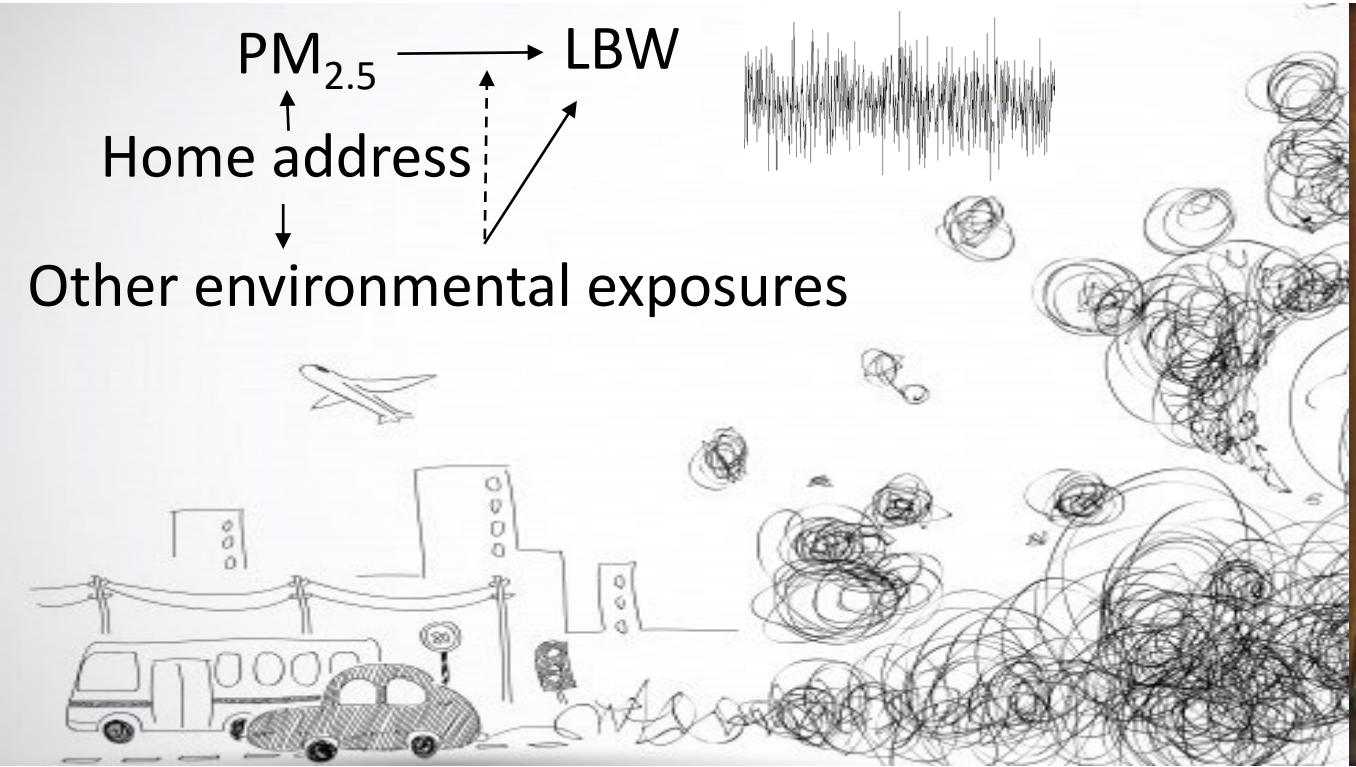
La pollution de l'air augmente le risque d'avoir des bébés de faible poids – Santé – LeVif.be

Ganske små mængder luftforurening skader fostre

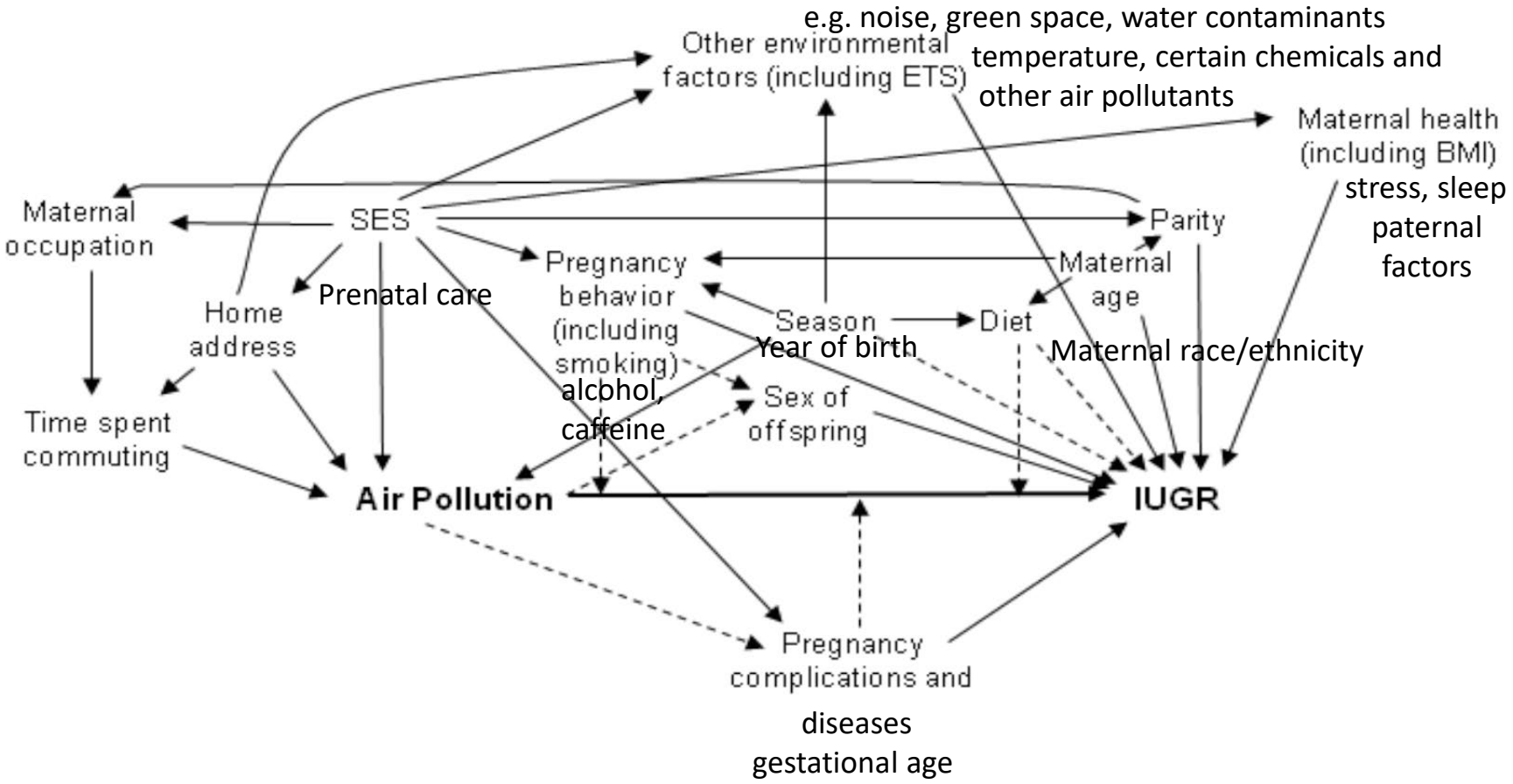
Föroreningar ökar risk för låg vikt hos nyfödda

Study Design Challenges

- Multiple exposures



Large Studies With Assessment of Multiple Exposures and Personal Characteristics at Individual Level Are Needed



(Modified Slama et al. 2008)

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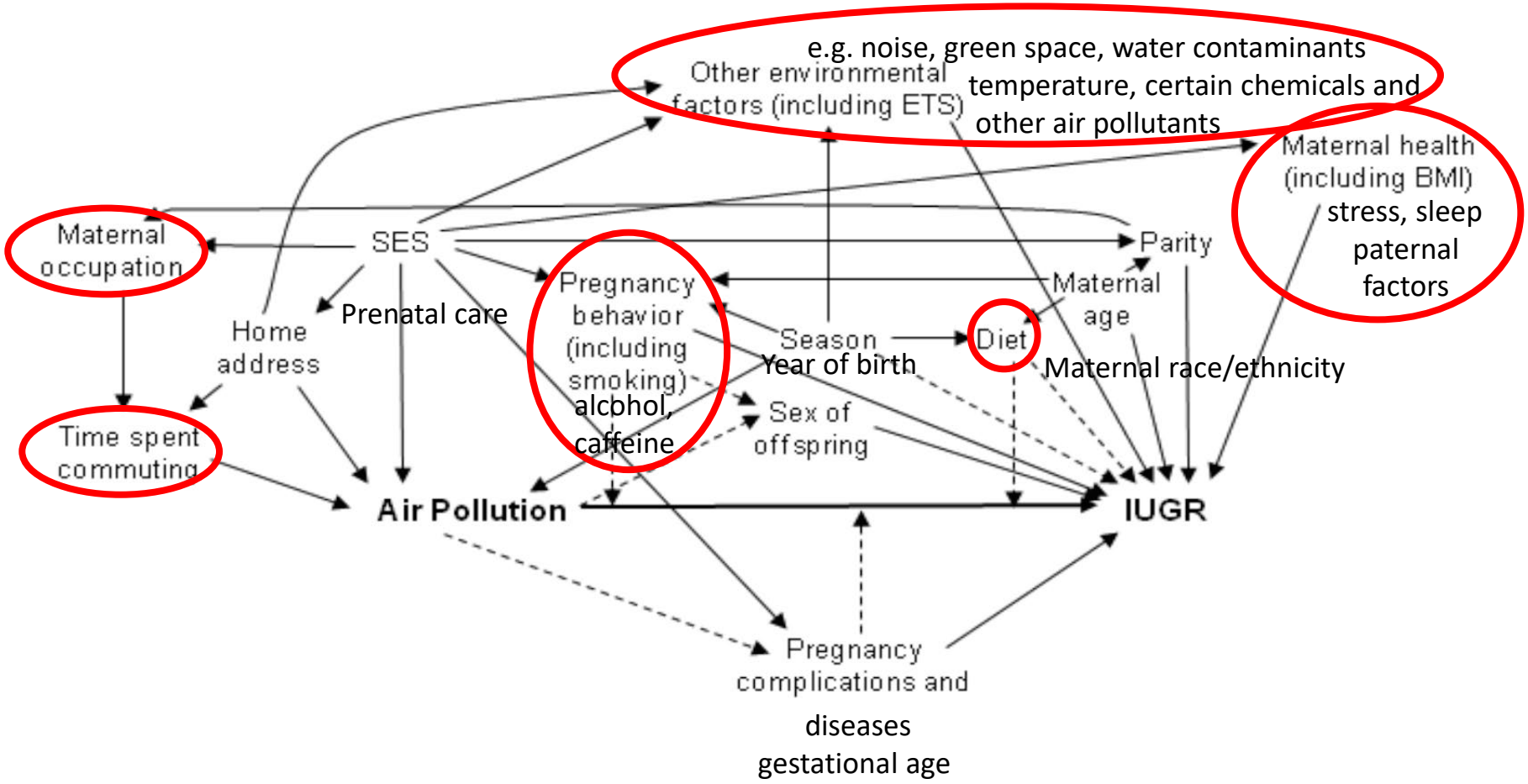
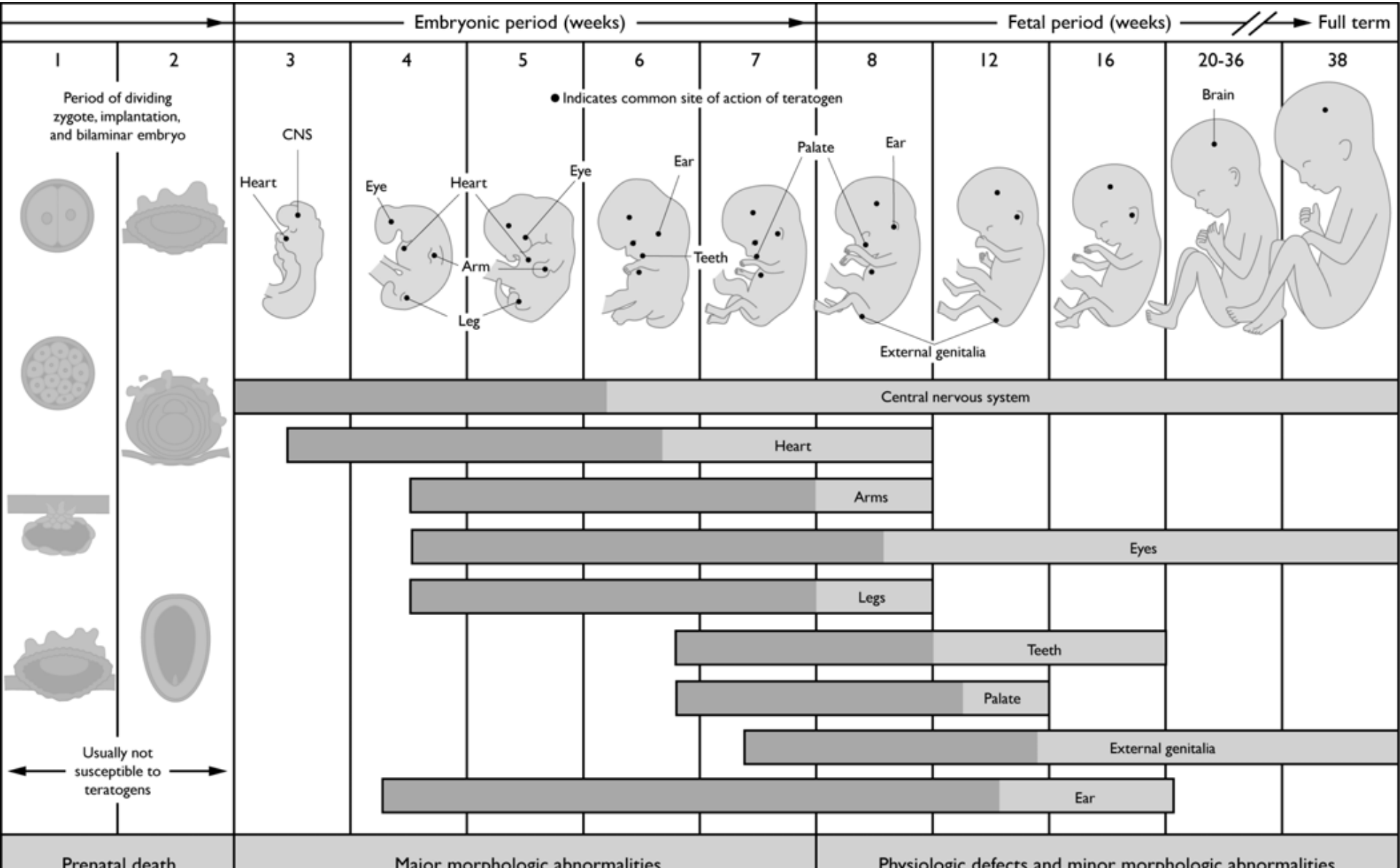


(Modified Slama et al. 2008)

Critical Windows of Heightened Vulnerability – Does the Timing of Exposure Matter?



Critical Windows of Heightened Vulnerability – Does the Timing of Exposure Matter?

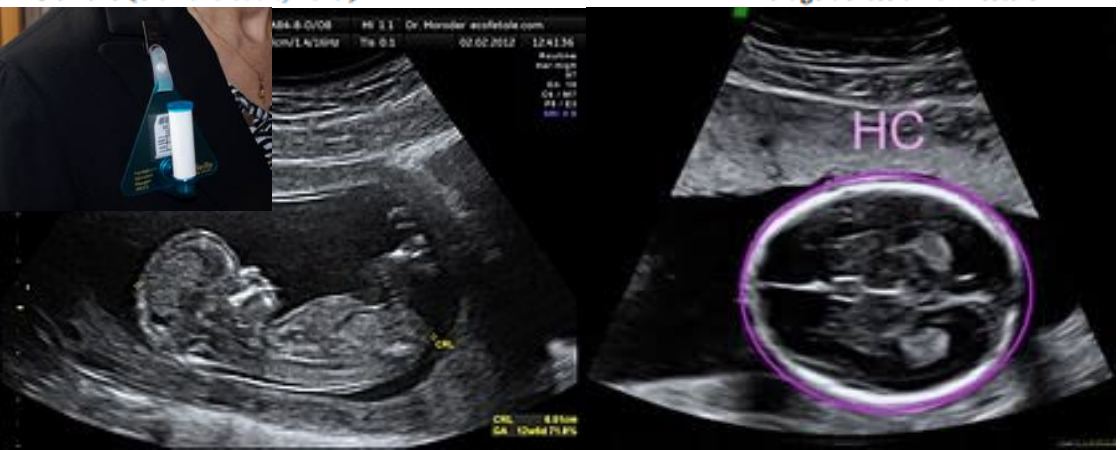
- It is still being debated, but the 1st and 3rd trimester have been proposed as being the most biologically relevant (Stieb et al. 2012, Klepac et al. 2018)

- Depends on the pollutants and their sources, fine particulate matter ($PM_{2.5}$) from winter heating may have more temporal variation than traffic-related pollutants such as nitrogen dioxide (NO_2) in areas where traffic is similar across seasons

- Challenged by high correlation between trimesters, the uncertainty of the date of conception and that most studies rely on address at birth. It is likely that 1st trimester exposures are less accurate than 3rd trimester exposures

Ultrasound Scan Studies of Fetal Size Can Give Us More Insight In the Importance of Timing

	Exposure	Trimester when exposure was measured[a]	Second trimester fetal measurement				Third trimester fetal measurement			
			HC/ BPD	FL	AC/ MAD	EFW	HC/ BPD	FL	AC/ MAD	EFW
Hansen (Hansen et al., 2008)	Ambient air pollution[e]	1 (first 120 days)	↓	↓	↓					
Slama (Slama et al., 2009)		2 (week 27)	↓				↓			
Aguilera (Aguilera et al., 2010)		1 (weeks 1–12) 2 (weeks 12–20) 3 (weeks 20–32)	↓[f]	x	x	x	↓[f]	x	↓[f]	↓[f]
Iniguez (Iniguez et al., 2012)		1 (weeks 1–12) 2 (weeks 12–20) 3 (weeks 20–32, 32-term)	x	x	x	x	↓[f]	x	↓[f]	↓[f]
van den Hooven (van den Hooven et al., 2012)		1, 2 and 3	x	↓		↑	↓	↓		↓
Ritz (Ritz et al., 2014)		1 (weeks 0–19) 2 (weeks 19–29) 3 (weeks 29–37)					↓	x	x	
Iniguez (Iniguez et al., 2016)		1 (weeks 1–12) 2 (weeks 12–20) 3 (weeks 20–34 and 34-term)	x	x	↓[f]	↓[f]	↓[f]	x	↓[f]	↓[f]
Carvalho (Carvalho et al., 2016)		1 (week 12) 2 (week 22) 3 (week 32)								x
Malmqvist (Malmqvist et al., 2017)		1, 2 and 3					x	↓	↓	↓
Clemens (Clemens et al., 2017)		Average across all trimesters	x	x	x		↓	x	x	

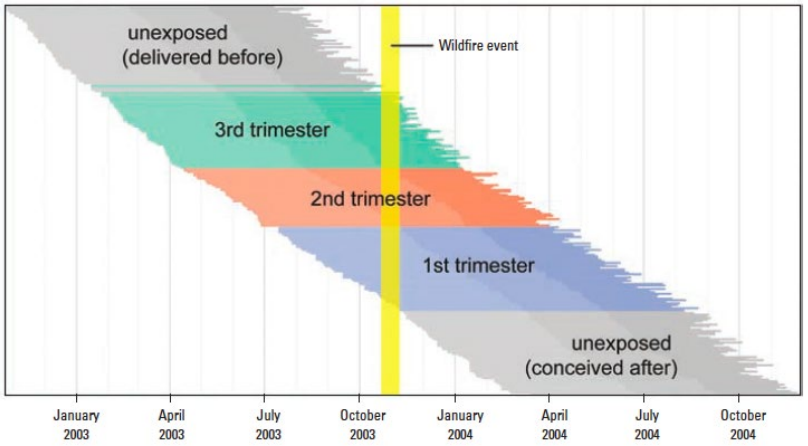


HC: head circumference,
BPD: biparietal diameter,
AC: abdominal circumference,
MAD: mean abdominal circumference,
EFW: estimated fetal weight
X: no association present,
↑: exposure associated with increased fetal size
↓: exposure associated with reduced fetal size

(Reviewed by Huang et al 2019)

Wildfire and Other Natural Experiment Studies Provide Evidence of Effects of Temporal Variation

Southern Californian Wildfire Oct to Nov 2003



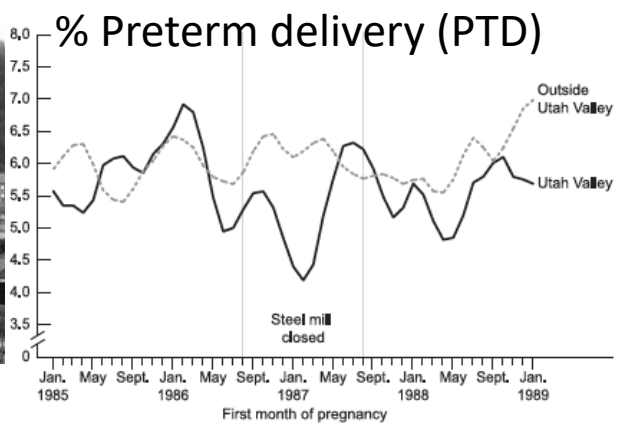
Trimester of exposure	Birth weight (g) Mean change (95% CI)
1st	-3 (-7, 1)
2nd	-10 (-15, -5)
3rd	-7 (-12, -2)

Adjusted for sex, gestational age, parity, age, education, race, secular trend and season

(Holstius et al. 2012)

Almost 900,000 births

Temporary closure of a steel mill in Utah Aug 1986 to Sep 1987



Birth during closure vs. not closure
RR (95% CI) for PTD

Tri.	Utah Valley	Outside Utah V.
1st	0.94 (0.81, 1.08)	1.03 (0.97, 1.10)
2nd	0.86 (0.75, 0.98)	1.01 (0.95, 1.07)
3rd	1.02 (0.89, 1.16)	1.03 (0.97, 1.10)

No effect on LBW and BW

(Parker et al. 2008)

Limited by its ecological study design, few low birth weight cases, lack of data on maternal economic hardship & stress and uncertainty of gestational age

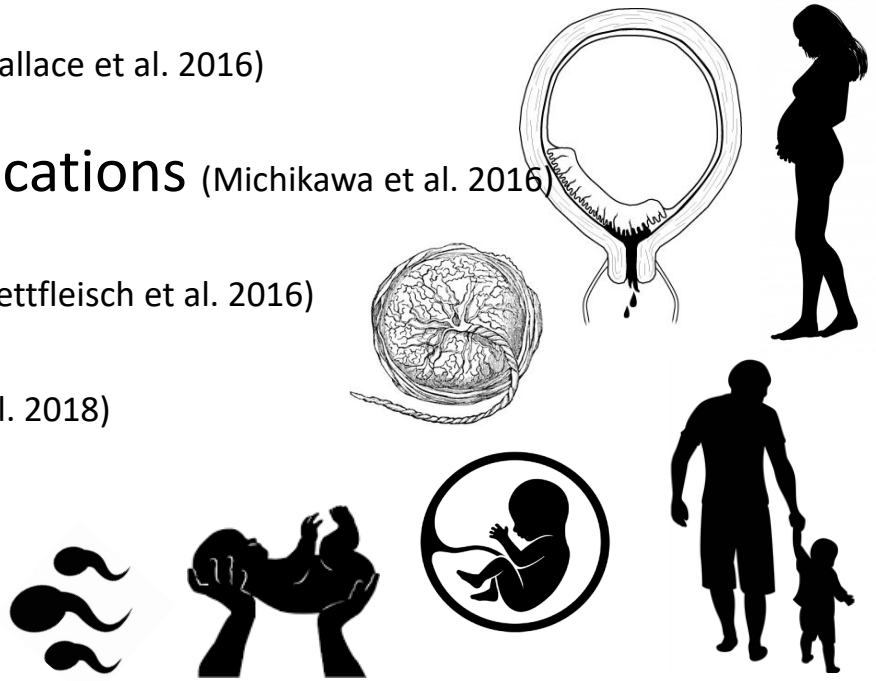
For more examples e.g. air improvement due to Beijing Olympics see Melody et al. 2019

Further Studies Needed

- Source-specific, multiple exposures including diet
- Additional reproductive outcomes

Additional Reproductive Outcomes For Which the Level of Proof Is Lower

- Reduced fertility e.g. sperm quality (Lafuente et al. 2016)
- Miscarriage and stillbirth (Checa Vizcaino et al. 2016; Siddika et al. 2016; Kioumourtzoglou et al. 2019)
- Pregnancy complications e.g. GDM (Pedersen et al. 2014, 2017)
- Premature rupture of membranes (Wallace et al. 2016)
- Placental praevia and related complications (Michikawa et al. 2016)
- Placenta function (van den Hooven et al. 2012; Hettfleisch et al. 2016)
- Uterine vascular resistance (Contreras et al. 2018)
- Birth defects (Chen et al. 2014, Pedersen et al. 2017)



GDM = Gestational diabetes mellitus

Further Studies Needed

- Source-specific, multiple exposures including diet
- Additional reproductive outcomes
- Residential mobility
- Differential vulnerability among women (Westergaard et al. 2018)
- Populations from rural settings and low-income countries
- Biomarkers and personal monitors

Take Home Message

- Strong evidence that ambient air pollution increases the risk of low birth weight (LBW), more suggestive evidence for preterm delivery (PTD)
- Substantial variation in the findings across studies which may reflect differences in study populations and designs, differences in the air composition and levels of air pollution and degree of residual confounding
- We need contemporary studies as air quality, settings and population constantly change (e.g. winter episodes in France, forest fires)
- We have little knowledge of the importance of timing, and interactions between multiple exposures including diet
- We know less about other reproductive outcomes

Air Pollution During Prenatal Life – Much More to Discover, but There is Sufficient Evidence to Act Now

Thank You

To you, all my collaborators, study participants and funding bodies

Questions: mp@sund.ku.dk