META-ANALYSIS OF EFFECT OF ATMOSPHERIC POLLUTION ON A BIRTH OUTCOMES: EVIDENCE FOR FUTURE RESEARCH

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ENVIRONMENTAL PUBLICH HEALTH CHALLENGES

PUBLIC HEALTH DETERMINANTS

- an average adult breathes daily from **10 to 20 m³ of air**
- different **lifetime exposure** – concentration, types

HEALTH EFFECTS

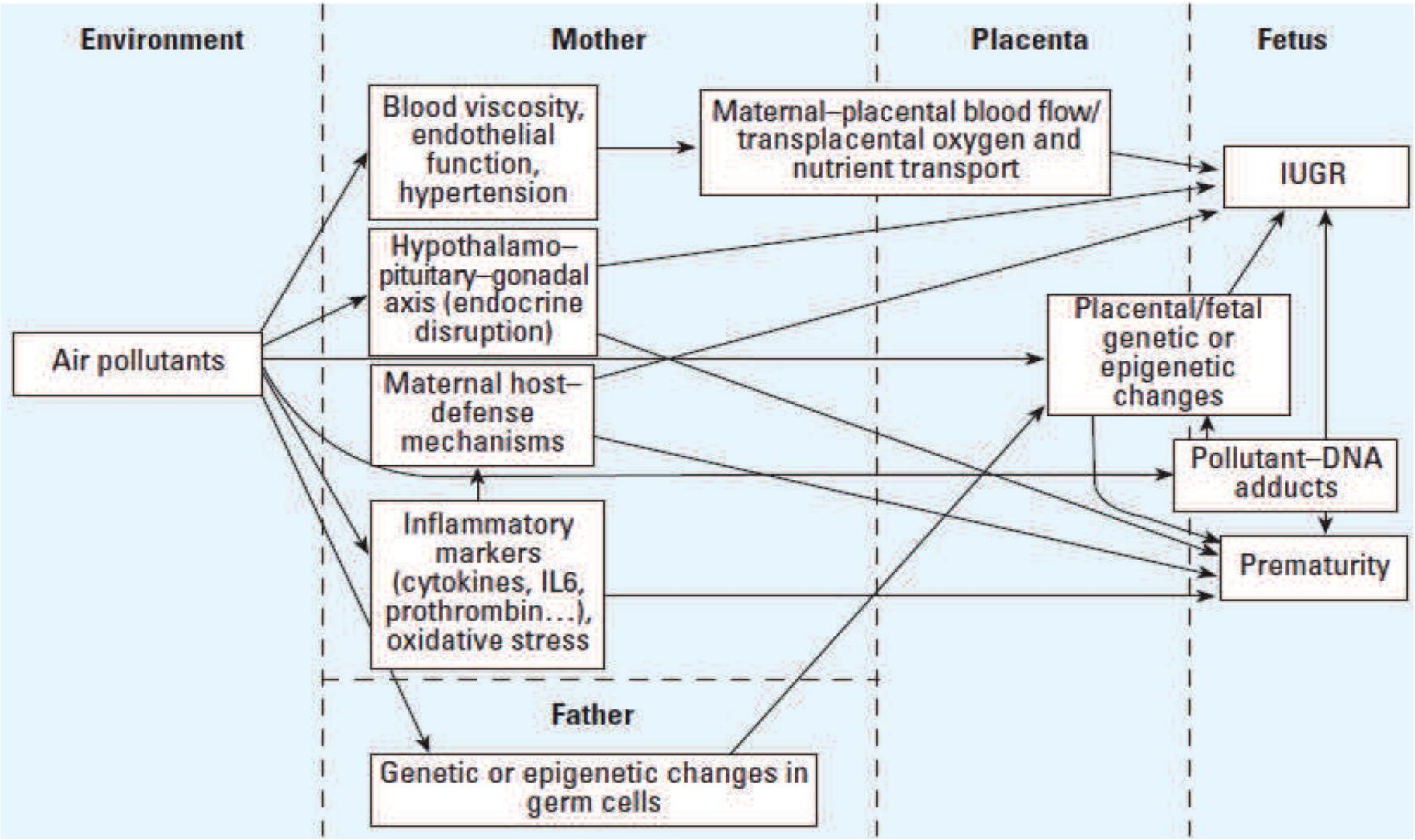
- strong association **respiratory and cardiovascular diseases**
- new **evidence** – exposure to AP during pregnancy with adverse pregnancy outcomes

↓

- the findings of epidemiological studies - inconsistent

Adverse pregnancy outcomes are associated with increased neonatal and childhood morbidity / mortality, as well as the risk of cardiovascular diseases, diabetes, liver disease and psychiatric conditions later in life

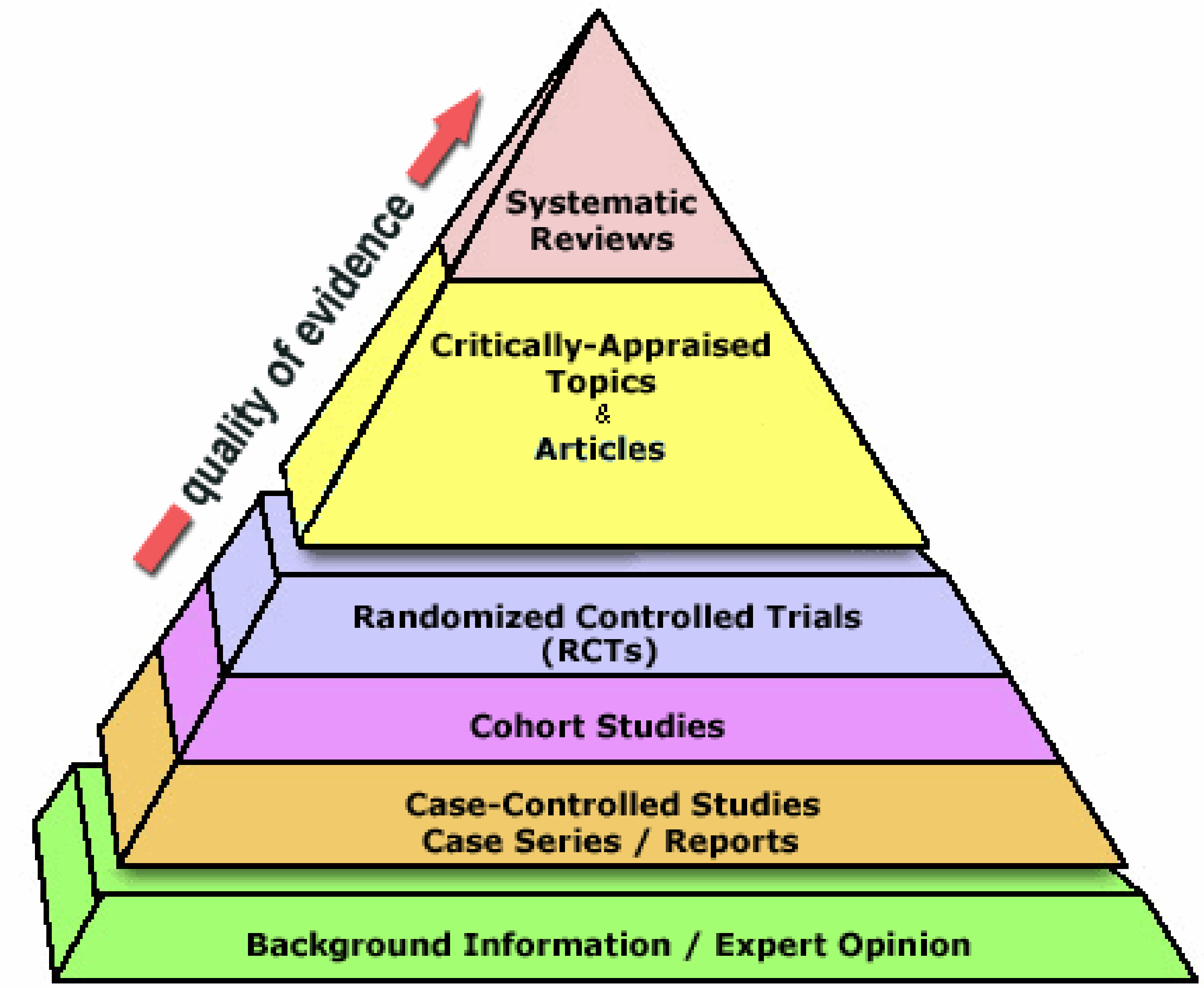
ENVIRONMENTAL PUBLICH HEALTH CHALLENGES



Source: Slama et al. Envrionmental Health Perspective, 2008, 116(6):795

Fig. 1. Possible biological mechanisms by which air pollutants may affect birth outcomes

EVIDENCE BASED PUBLIC HEALTH - APPROACHES



Not all evidence is judged to be of equal value, that is, there are hierarchies of research design that are evaluated to have different strengths, different levels of value in the decision making process.

PREVIOUS EVIDENCE BASED: AP and PREGNANCY OUTCOMES

Int. J. Environ. Res. Public Health **2014**, *11*, 7642-7668; doi:10.3390/ijerph110807642
OPEN ACCESS
International Journal of Environmental Research and Public Health
ISSN 1660-4601
www.mdpi.com/journal/ijerph

Review

Effects of Air Pollution on the Risk of Congenital Anomalies: A Systematic Review and Meta-Analysis

Esther Kai-Chieh Chen [1], Denis Zmirou-Navier [1,2,3], Cindy Padilla [1,2] and Séverine Deguen [1,2,]*

Research | Children's Health

Maternal Exposure to Particulate Air Pollution and Term Birth Weight: A Multi-Country Evaluation of Effect and Heterogeneity

Payam Dadvand,[1,2,3] Jennifer Parker,[4] Michelle L. Bell,[5] Matteo Bonzini,[6] Michael Brauer,[7] Lyndsey A. Darrow,[8] Ulrike Gehring,[9] Svetlana V. Glinianaia,[10] Nelson Gouveia,[11] Eun-hee Ha,[12] Jong Han Leem,[13] Edith H. van den Hooven,[14,15] Bin Jalaludin,[16,17,18] Bill M. Jesdale,[19] Johanna Lepeule,[20,21,22] Rachel Morello-Frosch,[19,23] Geoffrey G. Morgan,[24,25] Angela Cecilia Pesatori,[26] Frank H. Pierik,[15] Tanja Pless-Mulloli,[10] David Q. Rich,[27] Sheela Sathyanarayana,[28] Juhee Seo,[12] Rémy Slama,[21,22] Matthew Strickland,[8] Lillian Tamburic,[29] Daniel Wartenberg,[30] Mark J. Nieuwenhuijsen,[1,2,3] and Tracey J. Woodruff[31]

Review

Prenatal ambient air pollution exposure and the risk of stillbirth: systematic review and meta-analysis of the empirical evidence

Nazeeba Siddika,[1] Hamudat A Balogun,[1] Adeladza K Amegah,[1,2] Jouni J K Jaakkola[1,3]

EHT Environmental Health and Toxicology
CrossMark Open Access
Volume: 30, Article ID: e2015011, 19 pages
http://dx.doi.org/10.5620/eht.e2015011
eISSN: 2233-6567

• Review

A meta-analysis of exposure to particulate matter and adverse birth outcomes

Dirga Kumar Lamichhane[1], Jong-Han Leem[2], Ji-Young Lee[1], Hwan-Cheol Kim[2]

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ELSEVIER
Environmental Pollution
journal homepage: www.elsevier.com/locate/envpol

Association between ambient fine particulate matter and preterm birth or term low birth weight: An updated systematic review and meta-analysis☆

Xiangyu Li [a], Shuqiong Huang [b], Anqi Jiao [a], Xuhao Yang [a], Junfeng Yun [a], Yuxin Wang [a], Xiaowei Xue [a], Yuanyuan Chu [a], Feifei Liu [a], Yisi Liu [a], Meng Ren [a], Xi Chen [a], Na Li [a], Yuanan Lu [c], Zongfu Mao [a], Liqiao Tian [d], Hao Xiang [a,*]

Environmental Pollution 211 (2016) 38–47
Contents lists available at ScienceDirect
ELSEVIER
Environmental Pollution
journal homepage: www.elsevier.com/locate/envpol

The associations between birth weight and exposure to fine particulate matter ($PM_{2.5}$) and its chemical constituents during pregnancy: A meta-analysis

CrossMark

Xiaoli Sun [a], Xiping Luo [a,**], Chunmei Zhao [a], Bo Zhang [b], Jun Tao [c], Zuyao Yang [d], Wenjun Ma [e], Tao Liu [e,*]

There is a growing number of studies on the association between ambient air pollution and adverse pregnancy outcomes, but their results have been inconclusive

AIM

Systematically review the studies on the association of AP and pregnancy outcomes

- to outline the **pregnancy outcomes** according to AP, **exposure assessment methods**, **potential confounders** and **gestational windows of exposure**
- to summarize the effect estimates
- to indicate future environmental public health challenges

ID	Title	Status	Last edited
CRD42018081540	Association between prenatal exposures to ambient air pollution and birth weight, low birth weight and preterm birth: meta-analysis and identification of environmental public health challenges	Registered	11/02/2018

PROSPERO

International prospective register of systematic reviews

NHS

National Institute for Health Research

METHODS: meta-analysis approach

SEARCH STRATEGY CRITERIA

- electronic database **PubMed®** for the period up to June 2017
- **key words:** AP, birth or pregnancy outcomes, PB, LBW, spontaneous abortion, fetal death
- original studies, humans, English

ANALYSIS PROCESS

- **Phase 1-Qualitative synthesis**
- **Phase 2-Descriptive quantitative synthesis and meta-analysis**

METHODS: meta-analysis approach

ANALYSIS PROCESS

Qualitative synthesis

- **Pregnancy outcomes** and AP
- Potential **confounding factors** (mothers, newborns, SES, adequacy of prenatal care utilization, long-term trends, season, meteorological parameters)
- Assessment of **AP exposure**
  - **routine monitoring data** (MS)
  - **modelling approaches**
  - personal monitoring, biomonitoring, and exposure to traffic
- **Gestational windows** of exposure
  - definitions of gestational **months and weeks of exposure** (month 1: weeks 1-4,…month 9: weeks 36-40)

Quantitative synthesis / meta-analysis

- **Effect estimates**
  - **fully adjusted single pollutant models**
  - linear regression coefficients, odds ratios (ORs) and relative risks (RRs)
- **Pooled effect estimates** (expressed as OR) for PTB)
  - Statistical package **Review Manager** (RevMan) version 5.3
  - **Heterogeneity of study results (I^2)** - the percentage of the variability in effect size that was due to heterogeneity rather than chance

SEARCH STRATEGY CRITERIA

RESULTS

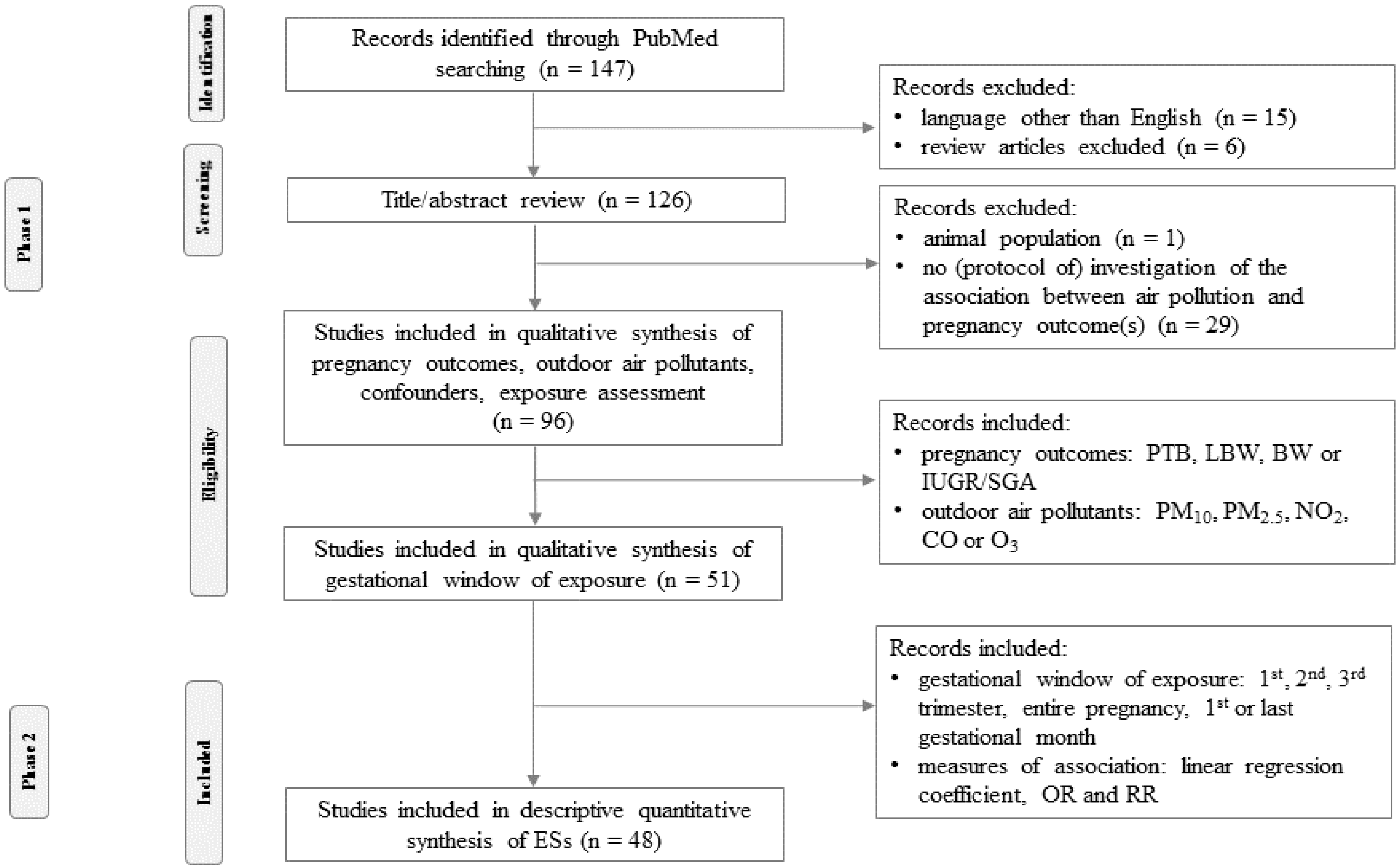


Figure 1. Flow chart of selection of studies.

- **retrospective cohort design (n=45)**
- routine **AP monitoring and birth records data**
- median sample size was 37.339 births
- North America (n=54), Europe (n=17), Asia (n=11), South America (n=9) and Australia (n=5)
- time period: less than a year to 31 years, most commonly 3-5 years (n=41)

Phase 1-QUALITATIVE SYNTHESIS

RESULTS

Pregnancy outcomes →

- PTB, LBW, congenital anomalies and small for gestational age/intrauterine growth restriction (SGA/IUGR)
- different definitions for the same outcome
  - **PTB was defined as birth <37 weeks of gestation**; PTB was categorized by different completed weeks of gestation: 20-23 (Padula et al., 2014a), 24-27 (Padula et al., 2014a), 20-27 (Padula et al., 2014b; Stieb et al., 2016),…
  - **LBW/VLBW** was defined as weight **<2500/<1500 g at birth**
  - **SGA/IUGR** were defined as **BW<10th percentile** for gestational age

Atmospheric pollutant →

- PM_{10}, $PM_{2.5}$, NO_2, CO, and O_3
- different definitions of the same exposure group
  - chemical constituents of the same particle group
  - $PM_{2.5}$ chemical constituents: chromium, copper, iron, manganese, nickel, vanadium…
  - measured exposure to mixtures of pollutants

Impacts of NO_2 and $PM_{2.5}$ on PTB were most commonly investigated in the included studies, followed by the effect of PM_{10} on PTB. PTB, LBW

Phase 1-QUALITATIVE SYNTHESIS

RESULTS

Potential confounding factors →

- **maternal covariates**
  - age, education, race/ethnicity, SES
  - smoking during pregnancy, exposure to environmental tobacco smoke, alcohol consumption during pregnancy,
  - BMI, history of adverse pregnancy outcomes, other maternal risk factors during pregnancy (gestational diabetes, hypertension, chronic heart,…)…
- **newborn**
  - sex,
  - gestational age…
- **long-term trends and seasonal fluctuations**
  - month/season/year of conception/last menstruation period/birth
- **meteorological parameters**
  - temperature, relative humidity

Phase 1-QUALITATIVE SYNTHESIS

RESULTS

Exposure assessment approaches

- **based on routine monitoring data**
  - Area-wide
  - Nearest MS
  - IDW -multivariate interpolation with a known scattered set of points

- **based on modelled data**
  - LUR modes
  - Dispersion models
  - Photochemical models
  - Chemical models
  - Spatio-temporal models

Exposure approach	Pollutants	Time resolution*	Spatial resolution	Address change**	n	References
Nearest MS (within 5, 10, 12, 16, 20, 36, 40 km)	SO_2, NO_2, CO, O_3, PM_{10}, $PM_{2.5}$, $PM_{2.5\_CC}$	Daily	Res. at birth	No	7	Darrow et al., 2009; Faiz et al., 2012; Gilboa, 2005; Gray et al., 2010; Marshall et al., 2010; Rich et al., 2009; Wilhelm and Ritz, 2005
	SO_2, NO_2, CO, O_3, PM_{10}	Daily	AU at birth	No	2	Hansen et al., 2009; Ritz et al., 2002
	PM_{10}	Daily	Res. during pregnancy	Yes[3]	1	Zhao et al., 2015
	NO_2, CO, $PM_{2.5}$	Daily	AU at birth	Yes[3]	1	Ritz et al., 2007
	SO_2, NO_2, CO, O_3, PM_{10}, $PM_{2.5}$, $PM_{2.5\text{-}10}$	Weekly	AU at birth	No	3	Chang et al., 2012; Green et al., 2015; Morello-Frosch et al., 2010
	O_3, $PM_{2.5}$	Weekly	Res. at birth	No	2	Pereira et al., 2014; Warren et al., 2013
	NO, NO_2, NO_X, CO, O_3, PM_{10}, $PM_{2.5}$	Monthly	Res. at birth	No	2	Laurent et al., 2013; Wu et al., 2011
	SO_2, NO, NO_2, CO, O_3, PM_{10}, $PM_{2.5}$	Monthly	AU at birth	Yes[2]	1	Brauer et al., 2008
IDW	NO, NO_2, CO, O_3, PM_{10}, $PM_{2.5}$	Daily	Res. during pregnancy	Yes[2]	5	Mobasher et al., 2013; Padula et al., 2013a, 2013b, 2013c, 2015
	PM_{10}	Daily	Res. during pregnancy	Yes[3]	1	Zhao et al., 2015
	NO_2, CO, PM_{10}, $PM_{2.5}$	Daily	Res. at birth	No	1	Padula et al., 2014a
	SO_2, O_3, PM_{10}	Daily	AU at birth	No	1	Dugandzic et al., 2006
	SO_2, NO_2, CO, O_3, PM_{10}	Monthly	AU at birth	No	3	Hwang et al., 2011, 2015; Lin et al., 2015
	$PM_{2.5}$, $PM_{2.5\_CC}$	Monthly	Res. at birth	No	1	Ebisu et al., 2014
	SO_2, NO_2, NO, CO, O_3, PM_{10}, $PM_{2.5}$	Monthly	AU at birth	Yes[2]	1	Brauer et al., 2008

Exposure estimate model	Pollutants	Time resolution	Final area of observation	Address change**	n	References
Dispersion models						
CALINE 4; Gaussian plume atmospheric transport model	NO_x, $PM_{2.5}$, SO_2, TSP	Daily, Annual	Res. at birth	No	2	Rogers et al., 2000; Wu et al., 2011
MHI-Airviro Gauss dispersion model and wind model	NO_x	Temp. adj. (MS)	100 m×100 m during pregnancy	Yes[1]	1	Olsson et al., 2015
CHRONOS	O_3	Temp. adj. (MS, IDW, monthly factor)	21 km×21 km during pregnancy	Yes[2]	1	(Lavigne et al., 2016)
ISCLT3	BTX, ethylbenzene	Annual	AU at birth	No	1	Lupo et al., 2011
Dispersion model, satellite images, kriging	NO_2	Hourly	Res. during pregnancy	Yes[2]	1	Clemente et al., 2015
Photochemical models						
CMAQ	$PM_{2.5\_CC}$	Weekly and daily	12 km×12 km at birth	No	2	Warren et al., 2012, 2013
Statistical fusion of MS data and CMAQ	SO_2, NO_2, CO, O_3, PM_{10}, $PM_{2.5}$, $PM_{2.5\_CC}$	Daily			3	Chang et al., 2013; Ha et al., 2014; Hao et al., 2015
	$PM_{2.5}$	Weekly			1	Chang et al., 2012
	O_3	Daily	AU at birth	No	1	Warren et al., 2013
Statistical fusion of MS data and CMAQ, kriging, stochastic simulator	$PM_{2.5}$	Daily	AU at birth	Yes[3]	1	Berrocal et al., 2011
Chemical models						
Chemistry CATT-BRAMS model	CO, $PM_{2.5}$	Daily	AU at birth	No	1	da Silva et al., 2014
Satellite data and simulations with the GEOS-Chem-global 3-D	$PM_{2.5}$	Temp. adj. (for seasonality, monthly factor)	Hospital of birth	No	1	Fleischer et al., 2014

Phase 1-QUALITATIVE SYNTHESIS

RESULTS

Gestational windows of exposure

1st, 2nd, 3rd trimester

Entire pregnancy

First and last month of pregnancy

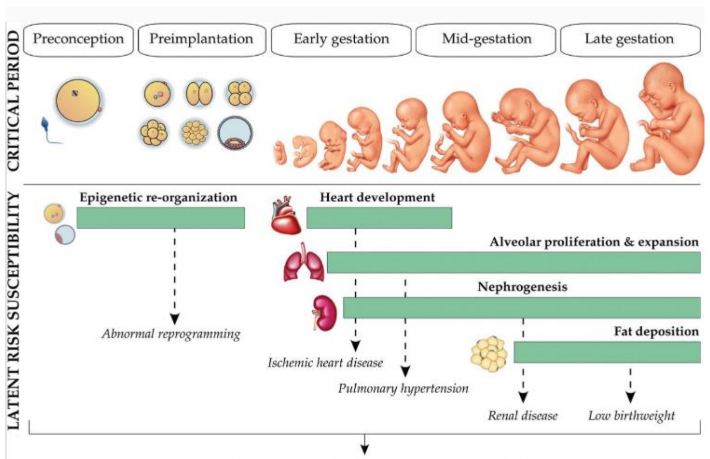


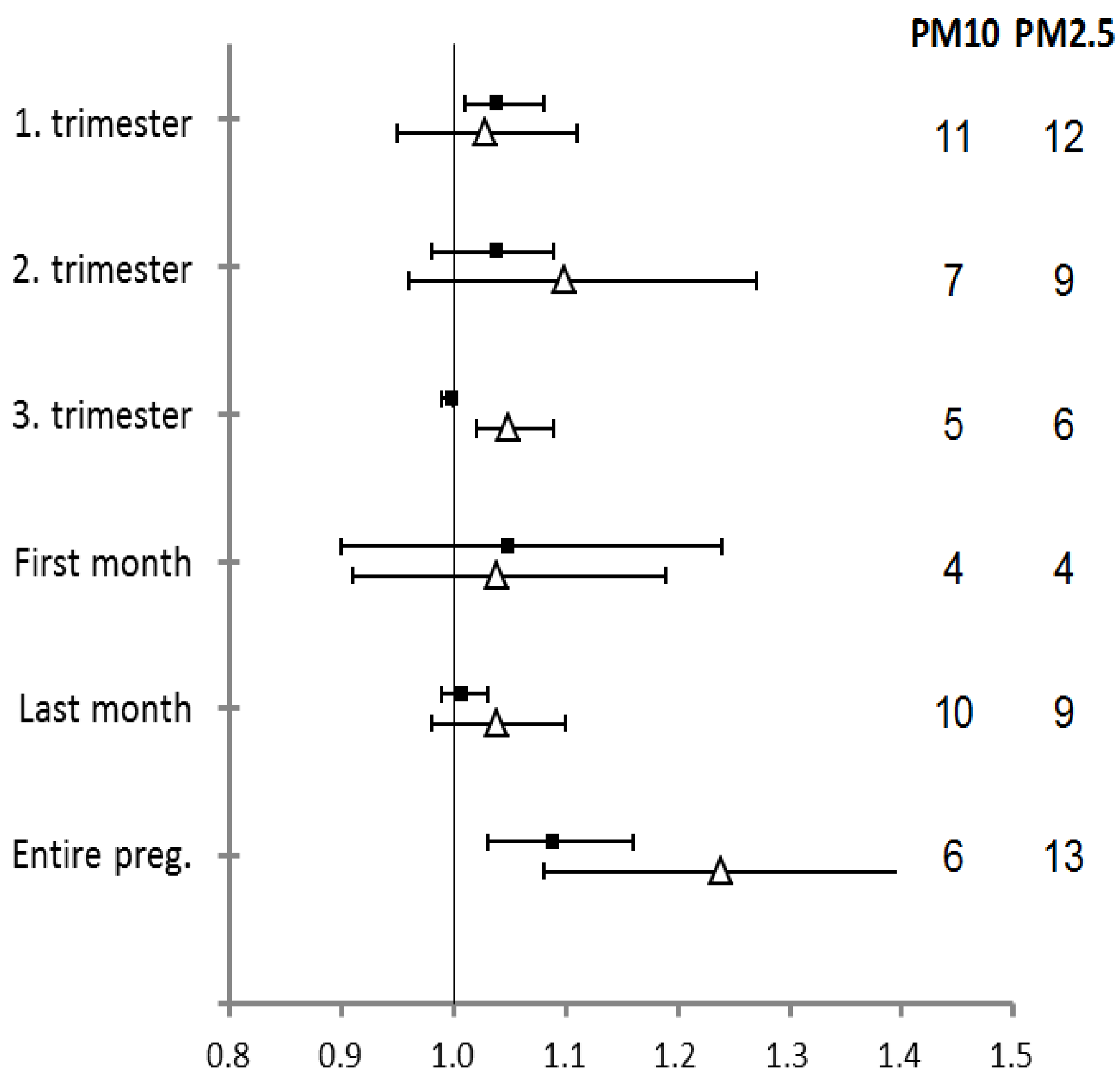
Table 2: Distribution of included studies by defined gestational windows of exposure for selected pregnancy outcomes and selected ambient air pollutants.

	PM_{10}	$PM_{2.5}$	NO_2	CO	O_3
PTB					
1. trimester	11	12	12	8	9
2. trimester	7	9	10	5	6
3. trimester	5	6	7	3	4
Entire pregnancy	6	13	8	5	5
Last 3 months	2	2	2	1	2
LBW (<2.500 g)					
1. trimester	4	3	5	4	5
2. trimester	4	4	6	4	6
3. trimester	5	4	6	5	6
Entire pregnancy	6	11	9	5	4
1.-4. week+1. month+1.-6. week	1	/	2	2	1
Last 6 weeks+last mont +last 4 weeks	1	/	2	2	1
BW					
1. trimester	7	6	10	4	4
2. trimester	7	7	10	4	4
3. trimester	7	5	10	4	4
Entire pregnancy	7	10	10	4	3
1.-4. week+1. month+1.-6. week	/	1	/	/	/
2 months	/	1	/	/	/
Last 3 months	/	1	/	/	/
Last 2 months+last 8 weeks	/	1	/	/	/
Last 6 weeks+last month+last 4 weeks	1	3	1	1	1
SGA/IUGR (BW<10th percentile for gestational age)					
1. trimester	2	1	4	2	3
2. trimester	1	1	5	2	3
3. trimester	1	1	5	2	3
Entire pregnancy	1	3	4	1	1
8. month	1	/	/	/	/
9. month	1	/	/	/	/
Last 6 weeks+last month+last 4 weeks	1	/	2	2	2

Phase 2
META-ANALYSIS

RESULTS

Summary of pooled effects estimates, expressed as odds ratios for preterm birth (PTB) for increased exposure of ambient air pollutants;
10 µg/m³ increment in PM_{10} (closed square) or $PM_{2.5}$ (open triangle)



PM and PTB (entire preg.)
the polled EEs per 10 µg/m³ increase in pollutant concentration were 1.09 [95% confidence interval (CI), 1.03-1.16] for PM_{10} and 1.24 (1.08-1.41) for $PM_{2.5}$.

Phase 2
META-ANALYSIS

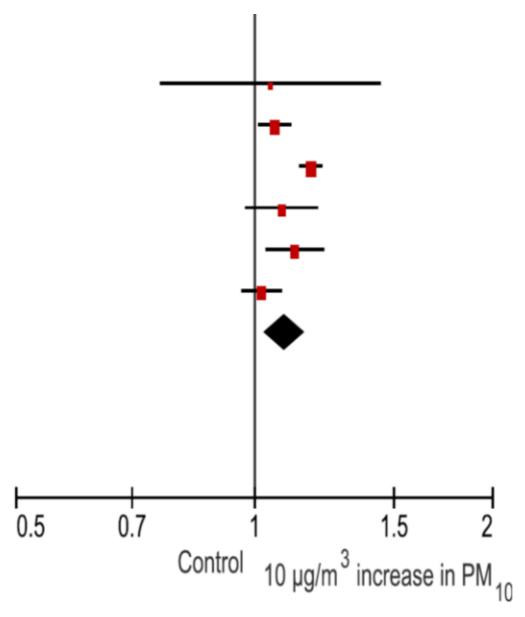
RESULTS

Forest plots of odds ratios for preterm birth (**PTB**) for increased exposure 10 μg/m^3 increment in PM_{10}

1.1.6 Entire pregnancy

Dibben 2015	3.2%	1.05 [0.76, 1.44]
Hao 2016	21.8%	1.06 [1.01, 1.11]
Padula 2014 Dec	23.3%	1.18 [1.14, 1.22]
Wu(a) 2011	14.4%	1.08 [0.97, 1.20]
Wu(b) 2011	16.9%	1.12 [1.03, 1.22]
Zhao 2015	20.4%	1.02 [0.96, 1.08]
Subtotal (95% CI)	**100.0%**	**1.09 [1.03, 1.16]**

Heterogeneity: Tau² = 0.00; Chi² = 24.01, df = 5 (P = 0.0002); I² = 79%
Test for overall effect: Z = 2.80 (P = 0.005)

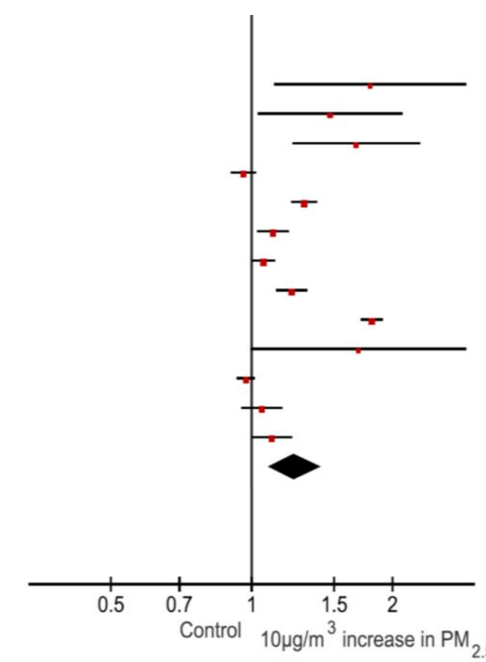


Forest plots of odds ratios for preterm birth (**PTB**) for increased exposure 10 μg/m^3 increment in $PM_{2.5}$

2.1.6 Entire pregnancy

Brauer 2008	4.3%	1.79 [1.12, 2.87]
Chang 2012	5.6%	1.47 [1.03, 2.10]
Chang 2013	6.1%	1.67 [1.22, 2.29]
Fleischer 2014	9.0%	0.96 [0.90, 1.02]
Ha 2014	9.0%	1.30 [1.21, 1.38]
Hao 2016	8.9%	1.11 [1.03, 1.20]
Kloog 2012	9.0%	1.06 [1.00, 1.12]
Lavigne 2016	8.9%	1.22 [1.13, 1.31]
Padula 2014 Dec	9.0%	1.81 [1.71, 1.91]
Pereira 2014	3.8%	1.69 [0.99, 2.87]
Stieb 2016	9.1%	0.97 [0.93, 1.02]
Wu(a) 2011	8.7%	1.05 [0.95, 1.16]
Wu(b) 2011	8.7%	1.10 [1.00, 1.22]
Subtotal (95% CI)	**100.0%**	**1.24 [1.08, 1.41]**

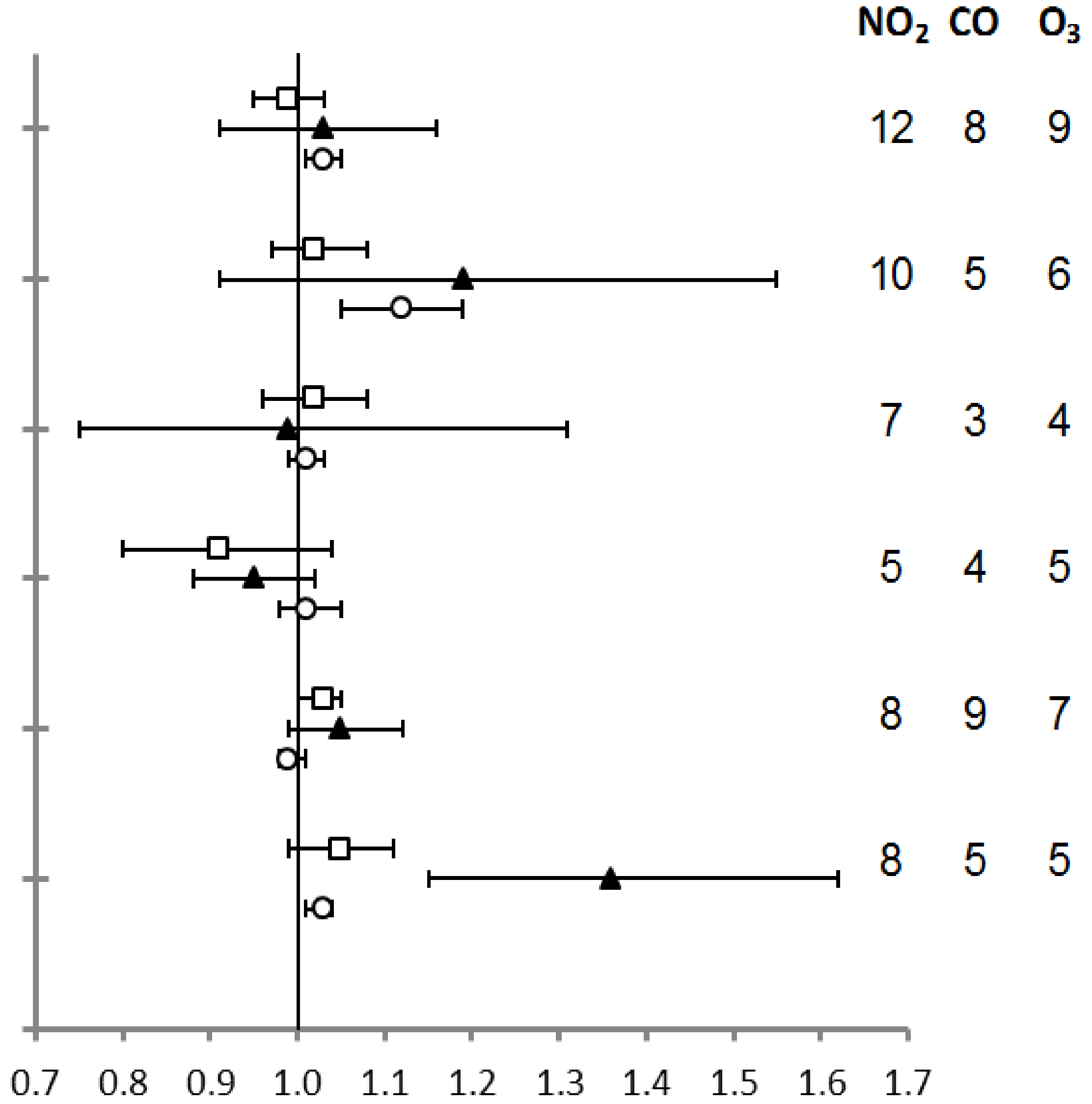
Heterogeneity: Tau² = 0.05; Chi² = 391.00, df = 12 (P < 0.00001); I² = 97%
Test for overall effect: Z = 3.12 (P = 0.002)



Phase 2
META-ANALYSIS

RESULTS

Summary of pooled effects estimates, expressed as odds ratios for preterm birth (**PTB**) for increased exposure of ambient air pollutants; 10 ppb increment in NO_2 (open square) or O_3 (circle), 1 ppb increment in CO (closed triangle)



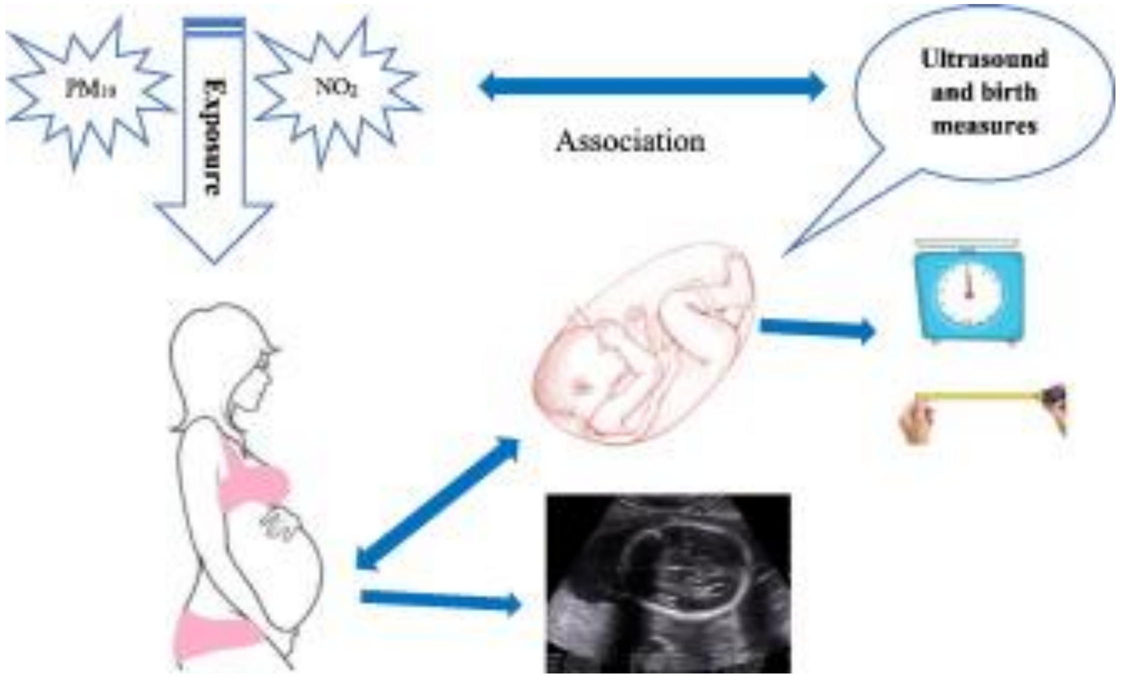
O_3 showed significant association with PTB: the polled EEs per 10 ppb increase in O_3 concentration were 1.03 (1.01-1.04) for entire pregnancy.
CO also showed possible association with PTB in entire pregnancy exposure: the polled EEs per 1 ppb increase in CO concentration were 1.36 (1.15-1.62).

FUTURE EPH CHALLENGES

In this systematic review, we have revealed many methodological problems related to investigation of effect of AP on pregnancy outcomes

- updated current scientific evidence
  - pregnancy outcomes
  - atmospheric pollution
  - AP exposure assessment
  - potential confounders
  - gestational window of exposure

- improvement of scientific evidence



Pregnancy outcomes

FUTURE EPH CHALLENGES

- PTB and LBW were most frequently investigated outcomes
  - different subcategories of PTB might have different etiology
  - cut-off value of 2.500 g for LBW may not be appropriate for all settings (VLBW and extremely LBW: BW less than 1.500 and less than 1.000 g)
- birth records as a source of pregnancy outcome
  - monitoring programs/registries/perinatal information systems
  - Limitation
    - gestational age misclassification (first day of the last menstrual period)
    - exposure misclassification (occupational exposure, changes of maternal residence address)

Pregnancy outcomes overlap either in terms of definitions or one outcome may be a risk factor for another

Atmospheric pollution

FUTURE EPH CHALLENGES

- NO_2 and $PM_{2.5}$ were most commonly observed pollutants
  - routinely monitored at MS
  - marker for traffic-related AP
- Size and chemical composition of PM influence its health effects
  - marker for traffic-related AP
  - UFP effects on health outcomes (not routinely monitored pollutants)
  - the effect of mixtures of pollutants

Different range of approaches in included studies from simple (e.g. calculating indexes of AAP) to complex ones (e.g. building multi-pollutant statistical models)

Exposure assessment

FUTURE EPH CHALLENGES

- Routine monitoring at MS
  - easily accessible and available for a relatively long period of time
  - not optimal for exposure assessment (predetermined set of pollutants, methods, missing data)
- Modelling approaches
  - spatially more precise exposure estimates
  - different models (input data, modelling technique,..)
- Future approaches
  - maternal time-activity patterns, address changes and indoor exposures
  - MS, modelling approaches

Comprehensively reviewing exposure assessment approaches according to observed ambient air pollutants, time and spatial resolution, modelling tools/techniques and maternal time-activity patterns

Confounding factors

FUTURE EPH CHALLENGES

- many factors influencing pregnancy outcomes that vary in space and time simultaneously with AP
- accurate data on all potential confounders are usually not available
  - maternal smoking
  - alcohol consumption
  - pre-pregnancy BMI
- that different measures of SES probably need to be constructed in each country

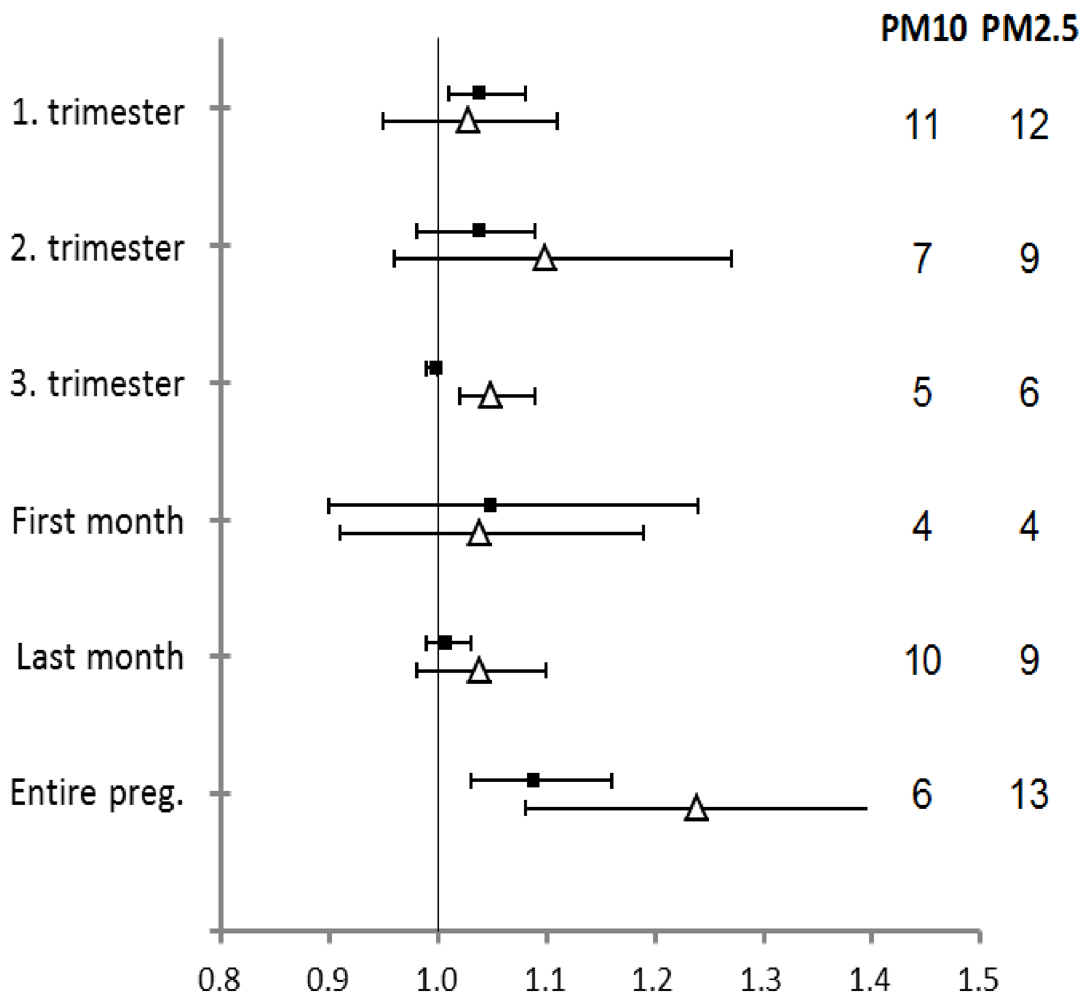
Gestational windows of exposure

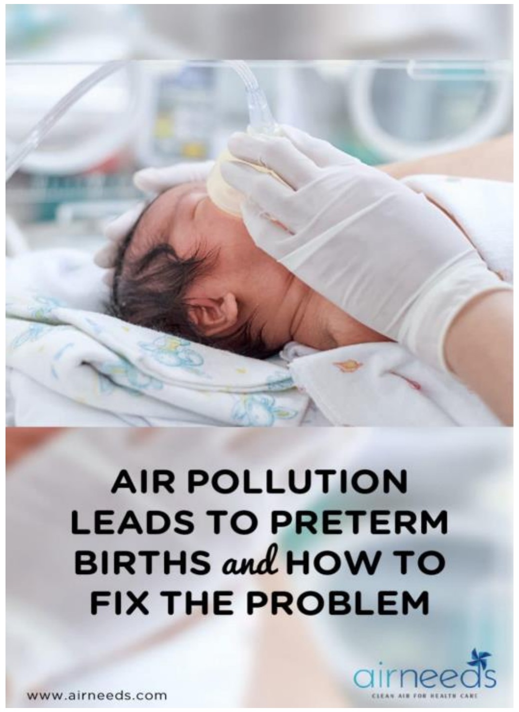
FUTURE EPH CHALLENGES

- Pregnancy trimesters and entire pregnancy were most frequently defined gestational windows of exposure
- New approaches to account for time-varying exposures
    - time series
    - survival models

Summary of pooled effects estimates

FUTURE EPH CHALLENGES





- variability in observed EEs
  - different input data
  - methodological approaches

- significantly increased risks of PTB for higher entire pregnancy exposures to particulate matter

FUTURE EPH CHALLENGES – REPRUDUCTIVE HEALTH

NEW STUDIES

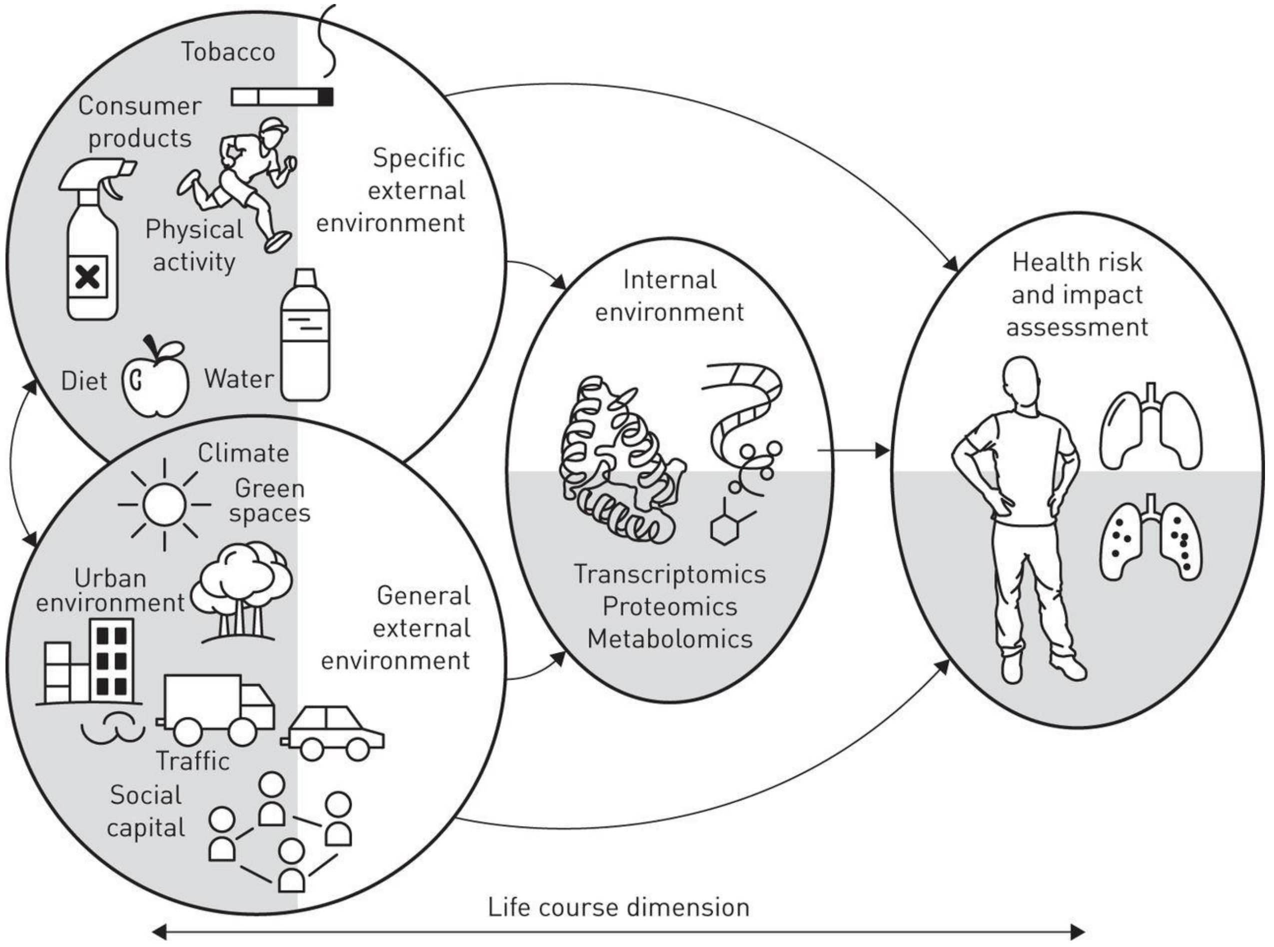
adjusting for spatially and temporally varying risk factors

DETERMINE POTENTIAL CRITICAL WINDOW OF EXPOSURE

shorter gestational windows and biological mechanisms

STATISTICAL METHODS

using and developing appropriate statistical methods - effects of multi-pollutant environmental exposures



Important that appropriate policies are adopted on a global scale to diminish AP emissions and to raise awareness of pregnant women

GLOBAL QUALITY OF LIFE

HOLISTIC APPROACH

- **exposome concept** - describe human environmental (i.e. non-genetic)
- **pregnancy** may be the key starting point of describing exposome (sensitivity and potential lifetime impact)