Ambient pollution, in-utero exposures and childhood lung disease

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Introduction

- Ambient pollution has been associated with a range of adverse health outcomes in children.
- These effects range from birth outcomes such as low birth weight, prematurity and birth defects through to later childhood including respiratory outcomes such as asthma and neurological outcomes such as low IQ or learning disabilities (Glinianaia et al, 2004)
- Pollutant exposure during pregnancy could influence the organ development in the foetus, which subsequently impacts on the newborn's risk for acquiring diseases in childhood and later life (Bobak, 2000; Dejmek et al, 1999; Gauderman et al., 2002).

Pollutants associated with outcomes

- These adverse outcomes have been associated with a range of ambient pollutants, including particulate matter**,** oxides of nitrogen, sulphur dioxide, ozone, carbon monoxide and volatile organic compounds.

Multiple Opportunities for Organ Insult

- Pregnancy itself is considered an inflammatory state accompanied by elevated oxidative stress (Furness et al., 2011).
- Foetuses are a vulnerable sub-population, known to be highly susceptible to a variety of toxins, because of their physiologic immaturity
- The period in which the developing foetus is most susceptible to organ maldevelopment is the during organ formation in weeks 3-8 following fertilisation. (Sram et al, 2005; Perera et al, 1998)
- However, pollutant impacts, particularly for lung development continue in the neonatal period as well.

Pollutant impacts on foetal development

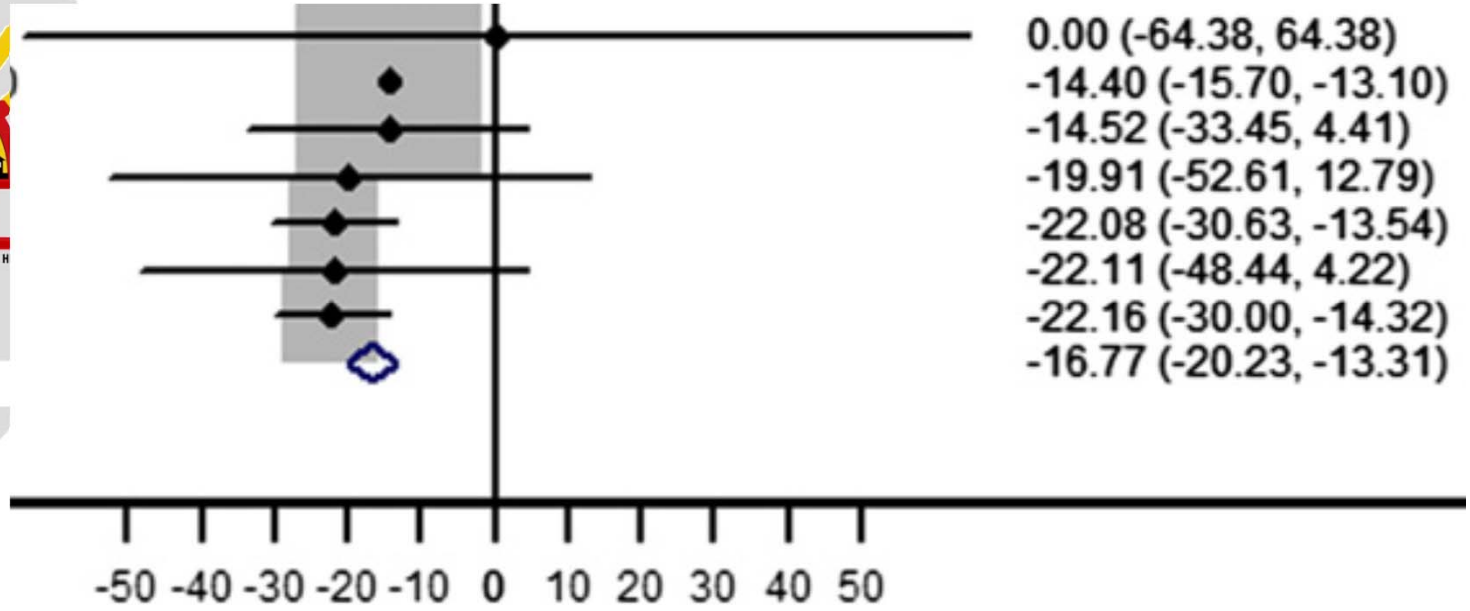
- PM exposure during pregnancy may contribute to inflammatory states in exposed mothers, resulting in the transplacental transfer of cytokines to the foetus.
- This triggers off cellular responses in the growing foetus
- In addition, placental vascular changes due to exposure may affect oxygen transfer, resulting in abnormal foetal growth
- Exposure to elevated levels of $PM_{2.5}$ during the early stages of pregnancy may cause negative foetal growth effects, including intrauterine growth restriction (IUGR)
- In one study, a 1.4 ppm and 12 ppb increase in exposure, respectively, to O_3 and CO resulted in a 20% increased risk of IUGR compared to normal exposure levels.

Pollutant impacts on birth outcomes

- Various studies have reported dose-responses to pollutant exposure:
  - For each 50 g/m^3 increase in ambient PM_{10} concentration, there was a 20% increase in preterm birth among 97 000 births in California (Ritz et al, 2000)
  - A 6-15% increase in preterm births was reported for each 10g/m^3 in PM_{10}. (Huyhn et al., 2006)
- A 128% increased risk in preterm birth was reported among pregnant women subjected to the highest NOx exposure quartiles
- Increased incidence of stillbirth was associated with
  - a 1-ppb increase in SO_2 exposure during the first trimester;
  - A 10-g/m3 increase in PM_{10} exposure during both the first and second gestational months

Change in birth weight

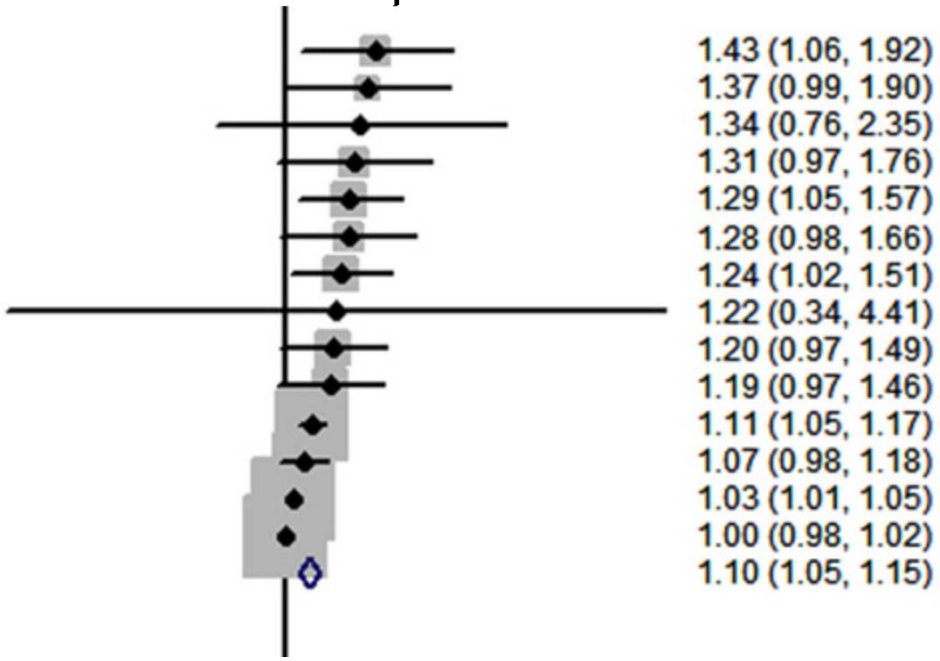
- Particulates are associated with changes in birth weight.



Change in birth weight (g) and 95% confidence intervals per 20 mg/m^3 PM_{10} over the entire pregnancy from various studies. Diamond shape represents pooled estimate. (from Steib et al, 2012)

Low Birth Weight

- Similarly, a strong increased risk for low birth weight is associated with PM exposure



Odds ratios for low birth weight (g) and 95% confidence intervals per 20 mg/m^3 PM_{10} over the entire pregnancy from various studies. Diamond shape represents pooled estimate. (from Steib et al, 2012)

Pollutant and adverse birth outcomes

Air pollution exposure	*n*	Preterm birth (< 37 weeks) (*n* = 7,045)	*n*	Low birth weight (< 2,500 g) (*n* = 7,003)	*n*	SGA at birth (< 5%)* (*n* = 6,997)
PM_{10}						
First quartile	78	Reference	74	Reference	73	Reference
Second quartile	75	0.96 (0.70, 1.33)	66	0.76 (0.49, 1.20)	78	1.05 (0.75, 1.47)
Third quartile	106	1.40 (1.03, 1.89)*	93	0.89 (0.58, 1.34)	98	1.38 (1.00, 1.90)*
Fourth quartile	105	1.32 (0.96, 1.79)#	90	0.91 (0.60, 1.40)	97	1.23 (0.89, 1.70)
Trend test (per 1-μg/m^3 increase)		1.03 (1.00, 1.07)		1.00 (0.95, 1.05)		1.03 (0.99, 1.07)
p-Value for trend		0.07		0.93		0.13
NO_2						
First quartile	79	Reference	75	Reference	70	Reference
Second quartile	92	1.10 (0.81, 1.51)	71	0.84 (0.54, 1.31)	73	0.93 (0.66, 1.31)
Third quartile	95	1.09 (0.79, 1.49)	88	0.86 (0.55, 1.33)	101	1.25 (0.90, 1.73)
Fourth quartile	99	1.10 (0.77, 1.57)	89	0.95 (0.58, 1.55)	102	1.35 (0.94, 1.94)
Trend test (per 1-μg/m^3 increase)		1.01 (0.98, 1.04)		1.00 (0.95, 1.04)		1.03 (0.99, 1.06)
p-Value for trend		0.43		0.87		0.11

Values are ORs (95% CI) and reflect the risk for adverse birth outcomes for each quartile of air pollution exposure during pregnancy (from conception until delivery) compared with the reference group (lowest quartile). Cutoff values for cat-

* SGA = small for gestational age. Van der Hooven et al., 2012

Effects of adverse birth weights

- Thus, the evidence supporting adverse birth outcomes associated with pollution is increasing. However, these adverse birth outcomes in themselves compromise infant development.
- A low birth weight (less than 2500g), from either premature birth or intrauterine growth retardation (IUGR) is strongly associated with increased infant mortality and morbidity.
- These neonates are more likely to have hypertension and coronary heart disease (Sram et al, 2005).
- As well as being a marker of early child health, low birth weight is associated with increased risk of developing various diseases in later life including heart disease and type 2 diabetes (Spinillo et al, 1995; Osmond and Barker, 2000).

Lung Development

- During the early post neonatal period the developing lung is highly susceptible to damage after exposure to environmental toxins. (American Academy of Pediatrics, 2004)
- Eighty percent of the alveoli are formed in the post natal period and changes in the lung continue until adolescence.
- Most babies and preschool children spend a very high fraction of their time indoors – if this is a critical window of exposure to allergens and the subsequent development of asthma, greater emphasis on the investigation of the indoor environment is necessary.
- Although numerous studies have shown that exposure to outdoor air pollution exacerbates asthma, the effect on lung development has been less clear (American Academy of Pediatrics, 2004)

Lung development and pollution

- Evidence from the Swiss Birth Cohort study supports the hypothesis that prenatal exposure affects lung development in the postnatal period (Fuchs et al., 2012).
- Lung function measurements were conducted at 5 weeks of postnatal age. Air pollution exposure was assessed during pregnancy and stratified per trimester.
- Adjusted results showed an increase of minute ventilation in newborns of 24.9 mL/min (95% CI 9.3; 40.5) per 1 g/m^3 increased exposure to PM_{10} during pregnancy.
- Children are more vulnerable to the effects of air pollution than adults; they have increased exposure levels due to higher minute ventilation and higher levels of physical activity

Early life impact on adult health

- The evidence for poor respiratory health in early life subsequently affecting adult respiratory outcomes is increasing.
  - 30-40% of the patients hospitalized for wheezing at less than 24 months of age have had asthma at 17-20 years of age.
  - In the Tucson birth cohort study, 30% of those wheezing at <36 months of age was still symptomatic at 22 years of age.
  - Transient and persistent wheezers had reduced lung function by spirometry, compared with never wheezers at 16 years of age.
  - Reduced lung function after birth in Australian cohorts was associated with wheezing at less than 3 years of age and remained reduced until at least 11 years of age.
- Parental asthma, repeated early-life wheezing and early passive smoking have been the most important early-life predictors of both adulthood asthma and lung function (Piippo-Savolainen et al., 2009)

Oxidative Stress and the Foetus

- A key biochemical process that is likely to be associated with the various adverse outcomes in-utero is oxidative stress in pregnant females.
- As indicated previously, these biochemical processes release a range of cytokines, which when crossing the transplacental barrier, is likely to impact on the growing foetus.
- The lung in the foetus and newborn is subject to these oxidative stressors. This effect is exacerbated in the premature infant
- Oxidative stress adversely impacts on the regulation of the T-helper cytokines. IgE and Th2 cytokines are present in the amniotic fluid, and ingested and aspirated by the foetus, exposing the respiratory tract to these immunoglobulins and cytokines. This creates the environment for the development of allergic sensitisation (Vance and Halloway, 2002).

Oxidative stress, pollution and dietary interventions

- Exposure to ambient and indoor pollutants, particularly cigarette smoking, ozone and particulates are postulated to impact on oxidative pathways, increasing oxidative stress.
- Studies have examined whether the impact of such exposures could be modified by antioxidant supplementation (Romieu 2002).
- The latter was able to show that there were protective effects against ozone associated with vitamin C and E supplementation amongst asthmatic children.

Genetic Polymorphisms

- Studies have shown that asthma has a strong genetic component and research has shown that the genetic and environmental factors may interact to exacerbate the disease.
- Variants of GSTM1, GSTP1 and TNF-308 genes affect susceptibility to disease and have been implicated in possible gene-environment interactions in the context of respiratory diseases.
- GSTM1 and GSTP1 have been linked to oxidative stress responses, while TNF-308 has been associated with inflammatory responses.
- The clearest examples of genetic interactions for inhaled pollutants exist for ozone, environmental tobacco smoke and endotoxins (London, 2007).

Epigenetics

- Emerging science supports the epigenetic theory of adverse health outcomes. These are intragenerational changes in gene patterns (as compared to across generations)
- These epigenetic changes can result in impacts on the airway epithelial barrier which predisposes to asthma risk and severity in later life (Ho, 2010).
- Early studies are beginning to suggest that environmental pollutants may be implicated in these epigenetic changes.
- Pollutants such as ozone have been linked to epigenetic changes in the lung. Pollution decreases methylation across the genome which is associated with oxidative stress (Miller and Ho, 2008).
- Methylation of the ACSL3 59-CGI gene was associated with maternal airborne PAH exposure > 2.41 ng/m^3 (OR = 13.8; p =0.001) and with a parental report of asthma symptoms in children prior to age 5 (OR = 3.9; p,0.05).

Concluding remarks

- The burden of respiratory disease is increasing globally across the age spectrum
- Adults with poor respiratory health may have acquired an increased risk as a result of early childhood respiratory illness.
- These early childhood illnesses, in turn could be a consequence of poor birth outcomes, affected by in-utero factors
- At all stages of this life cycle (in-utero > infancy > childhood > adulthood), environmental pollutants have shown to have a significant association with adverse respiratory outcomes, modifying the impact of the insult in the preceding life stage
- A comprehensive strategy for exposure reduction commencing from the time of pregnancy is essential
- Additional risk factors need to be identified and interventions implemented

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