

# Air Pollution During Pregnancy and Neonatal Outcome: A Review

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## Abstract

There is increasing evidence of the adverse impact of prenatal exposure to air pollution. This is of particular interest, as exposure during pregnancy—a crucial time span of important biological development—may have long-term implications. The aims of this review are to show current epidemiological evidence of known effects of prenatal exposure to air pollution and present possible mechanisms behind this process. Harmful effects of exposure to air pollution during pregnancy have been shown for different birth outcomes: higher infant mortality, lower birth weight, impaired lung development, increased later respiratory morbidity, and early alterations in immune development. Although results on lower birth weight are somewhat controversial, evidence for higher infant mortality is consistent in studies published worldwide. Possible mechanisms include direct toxicity of particles due to particle translocation across tissue barriers or particle penetration across cellular membranes. The induction of specific processes or interaction with immune cells in either the pregnant mother or the fetus may be possible consequences. Indirect effects could be oxidative stress and inflammation with consequent hemodynamic alterations resulting in decreased placental blood flow and reduced transfer of nutrients to the fetus. The early developmental phase of pregnancy is thought to be very important in determining long-term growth and overall health. So-called “tracking” of somatic growth and lung function is believed to have a huge impact on long-term morbidity, especially from a public health perspective. This is particularly important in areas with high levels of outdoor pollution, where it is practically impossible for an individual to avoid exposure. Especially in these areas, good evidence for the association between prenatal exposure to air pollution and infant mortality exists, clearly indicating the need for more stringent measures to reduce exposure to air pollution.

**Key words:** air pollution, pregnancy, neonatal outcome, placental barrier, birth weight, infant mortality, lung function, development

## Introduction

**E**XPOSURE TO AIR POLLUTION during pregnancy has potential long-term implications. Factors of little importance in later life can exhibit significant effects on development and maturation during that critical and vulnerable time span. The germ and fetal cells are especially susceptible compared with mature cells: they have faster rates of replication, faster differentiation, and higher sensitivity to surrounding signals, due to the developmental processes. External factors that interfere with this progress may result in impaired organ

function or increased susceptibility to disease in later life.<sup>(1)</sup> There is also evidence of a transgenerational effect of intra-uterine exposure. It has been shown that children whose grandmothers smoked during pregnancy have a higher risk of developing asthma, independent of the smoking activity of the mother.<sup>(2)</sup> Growing interest in the effects of prenatal exposure is also based on the increasing knowledge of epigenetics, *i.e.*, how the environment permanently affects gene expression.<sup>(3,4)</sup>

To assess the risk on a population-wide basis, two components must be considered: the exposure and the hazard.

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Compared with other harmful factors during pregnancy like infections or exposure to tobacco smoke, exposure to ambient air pollution cannot be avoided and affects large numbers of individuals. Although the individual hazard may be smaller than for other harmful factors, the ubiquitous distribution makes it of interest from a public health perspective. Good evidence exists on the effects of prenatal exposure to tobacco smoke and biological mechanisms. This is reviewed extensively<sup>(5-7)</sup> elsewhere and is, as such, not a topic of this article. We will only present studies that have assessed associations between exposure to outdoor air pollution during pregnancy and neonatal outcome.

The aim of this review is to summarize current epidemiological evidence of known effects of air pollution exposure during pregnancy on newborns and to report current knowledge of possible mechanisms behind this process. First, we present epidemiological data on neonatal outcomes that have been reported in recent studies worldwide.<sup>(8-10)</sup> Best data available concern possible effects on weight of the newborns, on neonatal mortality, on lung development, and on later respiratory morbidity, including potential effects on the immune system. In the second part, we give an overview of current understanding of possible underlying mechanisms.

## Epidemiological Evidence

### Birth weight

Most data regarding potential harmful effects of air pollution during pregnancy exist using birth weight as an outcome marker, as it is routinely measured and easily obtainable from hospital charts. Furthermore, it seems to be a good marker for intrauterine development and a good predictor of subsequent morbidity. The overall effect for a single subject (hazard) is rather small; however, on a population level, this may still have significant consequences. Table 1 gives an overview of recent publications, although the comparison of results is hampered by the heterogeneity between studies. As shown in Table 1 in detail, many studies found evidence for lower birth weight at term after higher exposure to air pollution, whereas other studies did not find any association. Apart from random variability, several factors may be responsible for this discrepancy: accuracy and method of exposure assessment, study size, absolute levels of pollutants, and land-use differences between studies. Moreover, how confounding is being addressed may also play a major role in determining possible effects. For example, social class as one of the most relevant confounding factors<sup>(11)</sup> may be differently distributed within polluted areas depending on countries or regions.<sup>(12)</sup>

To overcome this heterogeneity, international multicenter projects are trying to investigate the effect of air pollution on a large scale, with comparable exposure assessment and considering similar confounding factors in the analysis (ESCAPE,<sup>(13)</sup> ICAPPO,<sup>(12)</sup> GA<sup>2</sup>LEN,<sup>(14)</sup> ENRIECO<sup>(15)</sup>). Within Spain, four cohorts were merged together to investigate a possible effect of exposure to nitrogen dioxide (NO<sub>2</sub>) on anthropometric measures. The meta-analysis from these four cohorts, including 2,337 mothers, showed weak evidence for lower birth length: -0.9 (95% CI -0.27; -0.01) mm per increase in 10 μg/m<sup>3</sup> of NO<sub>2</sub>.<sup>(16)</sup> In a world-wide project, 13 groups of researchers, already involved in projects regarding

the effect of air pollution, formed the International Collaboration on Air Pollution and Pregnancy Outcomes (ICAPPO) and conducted a reanalysis of their data in a consistent manner. The first results, summarized quantitatively using a meta-analysis, provide an estimate of the relative risk of low birth weight (defined as lower than 2,500 g) associated with each 10 μg/m<sup>3</sup> increase in mean particulate matter (PM<sub>10</sub>) concentration. The results of the crude correlation show a weak but significant association: odds ratio (OR) 1.03 (95% CI 1.01; 1.05). Results remained stable after adjustment for confounding: OR 1.02 (95% CI 1.00; 1.03). However, there was significant heterogeneity between studies.<sup>(17)</sup>

### Neonatal prematurity

An analysis of the effect of air pollution on term birth weight without considering premature birth can bias the results. If fetuses more susceptible to air pollution encounter premature birth, they are not eligible for studies on the effect on birth weight in term-born babies. This may attenuate a possible effect. Table 2 gives an overview of current evidence of premature birth after prenatal exposure to air pollution. Most of the studies found a positive association between exposure to air pollution and premature birth; however, again comparison between studies is difficult due to heterogeneity.

One of the most recently published studies about the effect of NO<sub>2</sub>, PM<sub>10</sub>, and sulfur dioxide (SO<sub>2</sub>) on premature birth was conducted by Zhao *et al.* in Guagzhou China.<sup>(18)</sup> The study area shows a rather high pollution level with a NO<sub>2</sub> mean of 61 μg/m<sup>3</sup>, PM<sub>10</sub> mean of 82 μg/m<sup>3</sup>, and SO<sub>2</sub> mean of 51 μg/m<sup>3</sup>. They performed time-series analysis and found a consistent cumulative effect of the exposure to pollutants, resulting in a risk ratio (RR) for preterm birth for NO<sub>2</sub> of 1.054 (95% CI 1.008; 1.1), for PM<sub>10</sub> of 1.067 (95% CI 1.013; 1.124), and for SO<sub>2</sub> of 1.13 (95% CI 1.05; 1.21) per increased concentration of 100 μg/m<sup>3</sup> of pollutant.<sup>(18)</sup> Another time-series analysis performed in Atlanta (United States) did not confirm such a clear correlation: most of the results were not significant; however, NO<sub>2</sub> exposure in the last 6 months of pregnancy was associated with an increased rate of preterm deliveries: RR 1.06 (1.02; 1.09) per increase of 5 ppb NO<sub>2</sub>.<sup>(19)</sup> In a case-control survey nested in a birth cohort, Ritz *et al.* examined the effect of PM<sub>2.5</sub>, NO<sub>2</sub>, ozone (O<sub>3</sub>), and carbon monoxide (CO) exposure in the first trimester of pregnancy, as well as in the 6 weeks before birth.<sup>(20)</sup> They compared the odds for preterm birth within a subsample where detailed information about other relevant risk factors such as smoke and alcohol exposure was available. They found increased odds of preterm birth after higher exposure to all pollutants for both exposure time spans, *e.g.*, OR for preterm birth of 1.0, 1.15, and 1.29 for PM<sub>2.5</sub> tertile increase (<18.6; 18.6 to 21.4; >21.4 μg/m<sup>3</sup>).<sup>(20)</sup>

### Infant mortality

A World Health Organization review from 2005 concludes that good evidence exists for an association between air pollution exposure during pregnancy and infant mortality.<sup>(21)</sup> A review from Glinianaia *et al.* found best evidence for postneonatal mortality due to respiratory reasons.<sup>(22)</sup> Since then, two large studies have been published confirming these results. Woodruff *et al.* conducted a study with a population

TABLE 1. ASSOCIATION OF AIR POLLUTION EXPOSURE DURING PREGNANCY AND BIRTH WEIGHT IN TERM NEONATES

Reference	Area	Exposure assessment	Pollutant—mean (IQR)	Study size	Results (grams or OR for low weight)	Exposure unit
Aguilera 2009 [59]	Spain—Barcelona (Sabadell Study)	LUR	NO <sub>2</sub> µg/m <sup>3</sup> 30.77 (26.40 - 30.77 - 35.91)	570	-5.8 (-52.7; 41.0) <sup>2,a</sup>	Per increase of quartile
Ballester 2010 [64]	Spain—Valencia	LUR	36.9 (29.4 - 37.9 - 45.6)	785	NE <sup>b</sup>	>40 µg/m <sup>3</sup> versus <40 µg/m <sup>3</sup>
Bell 2007 [100]	USA—Connecticut	MS	17.4 (1.8) ppb	358,504	-8.9 (-10.8; -7.0) <sup>4</sup> AOR 1.027 (1.002;1.05) <sup>4</sup>	Per increase of quartile
Bobak 2000 [101]	Czech Republic	MS	37.7 (23.0 - 37.7 - 58.5)	69,935	AOR 1.06 (0.94;1.19) <sup>2</sup>	Per increase of 50 µg/m <sup>3</sup>
Brauer 2008 [102]	Canada—Vancouver	IDW	32.5 (11.3) IDW	70,249	AOR 1.11 (1.01;1.23) <sup>4</sup> IDW	Per increase of 10 µg/m <sup>3</sup>
Darrow 2011 [103]	USA—Atlanta	LUR	31.6 (9.3) LUR	406,627	AOR 0.97 (0.89;1.05) <sup>4</sup> LUR	Per increase of 10 µg/m <sup>3</sup>
Gehring 2011 [104]	The Netherlands (PIAMA study)	MS	23.8 (5.0) ppb	3,863	-4.5 (-8.5; -0.6) <sup>3</sup>	Per increase of quartile
Gehring 2011 [105]	The Netherlands—Amsterdam	LUR	30.4 (11.2)	7,762	5.6 (-14.1;25.3) <sup>4,c</sup> 21.3 (-11.1;53.6)	Per increase of quartile V versus I quintile
Gouveia 2004 [106]	Brazil—Sao Paulo (ABCDstudy)	MS	117.9 (51.2 SD)	179,460	-7.0 (-14.3;0.3) <sup>1,d</sup>	Per increase of 10 µg/m <sup>3</sup>
Ha 2001 [107]	Korea—Seoul	MS	33.6 (30.8 - 33.6 - 35.4) ppb	276,763	-8.41 (-6.07; -10.76) <sup>1</sup> ARR 1.07 (1.03;1.11) <sup>1</sup>	Per increase of quartile
Hansen 2007 [108]	Australia—Brisbane	MS	8.8 (5.5 - 7.8 - 11.4) ppb	26,617	NE	Per increase of 10 ppb
Liu 2003 [109]	Canada—Vancouver	MS	19.4 (15.1 - 19.4 - 22.3) ppb	229,085	AOR 0.98 (0.90;1.07) <sup>5,e</sup>	Per increase of 20 ppb
Liu 2007 [110]	Canada—Calgary, Edmonton, Montreal	MS	24.8 (17.5 - 22.6 - 29.1) ppb	386,202	AOR 1.16 (1.09;1.24) <sup>1,f,d</sup>	
Madsen 2010 [111]	Norway—Oslo	DM	29.8 (17.7)	25,229	NE	
Malmqvist 2011 [11]	Sweden—Scania	MS	35.6 (7.2)	81,110	-11 (-23;0)	IV versus I quartile
Mannes 2005 [112]	Australia—Sydney	MS	16.4 (9.0 - 16.4 - 22.7) <sup>1</sup>	138,056	AOR 0.93 (0.82;1.06) -1.48 (-2.70; -0.26) <sup>3,g</sup> -1.07 (-2.07; -0.07) <sup>1,g</sup>	Per increase of unit
Morello—Frosch 2010 [113]	USA—California	MS	23.2 (18.0 - 23.2 - 27.5) ppb	3,545,177	-9.0 g (-9.6; -8.4) <sup>4</sup>	Per increase of unit
Rich 2009 [114]	USA—New Jersey	MS	2.42 (1.69 - 2.42 - 3.12) pphm		AOR 1.03 (1.02;1.04) <sup>4</sup>	Per increase of quartile
Salam 2005 [115]	USA—California	MS	25.8 (10) ppb	114,411	PCR 7.0 (1.8;12.4) <sup>b,d</sup>	
Seo 2010 [116]	Korea	MS	36.1 (25) ppb	3,901	NE	
Slama 2007 [117]	Germany—Munich (LISA Study)	MS	0.03 (0.02 - 0.03 - 0.04) ppb	177,660	NE	
Bell 2007 [100]	USA—Connecticut	LUR	35.8 (32.7 - 35.8 - 39.0)	1,016	APR 1.16 (0.71;1.71) <sup>4,i</sup>	IV versus I quartile
Brauer 2008 [102]	Canada—Vancouver	MS	PM <sub>2.5</sub> µg/m <sup>3</sup> 11.9 (2.2)	358,504	-14.7 (-17.1; -12.3) <sup>4</sup> AOR 1.05 (1.02;1.09) <sup>4</sup>	Per increase of quartile
Darrow 2011 [103]	USA—Atlanta	MS	5.1 (1.1)	70,249	AOR 0.98 (0.92;1.05)	Per increase of unit
			4.0 (1.5)	406,627	AOR 1.03 (0.99;1.07)	Per increase of quartile
			16.4 (4.0)		-4.3 (-9.8;1.2) <sup>3</sup>	Per increase of quartile
			1.6 (0.5) PM <sub>2.5</sub> elemental carbon		-7.1 (-13.9; -0.3) <sup>3</sup>	Per increase of quartile

(continued)

TABLE 1. (CONTINUED)

Reference	Area	Exposure assessment	Pollutant—mean (IQR)	Study size	Results (grams or OR for low weight)	Exposure unit
Gehring 2011 [104]	The Netherlands (PIA-MA study)	LUR	20.1 (4.6)	7,762	3.0 (-20.3;26.3) <sup>4,j</sup>	Per increase of quartile
Jedrychowski 2009 [118]	Poland—Krakow	PM	35.3 (23.4 - 35.3 - 53.1)	481	-14.8 (-33.2;3.5) <sup>6,j</sup> -155.9 (-307;-4.7)	Per increase of quartile Per increase of quartile
Liu 2007 [110]	Canada—Calgary, Edmonton, Montreal	MS	12.2 (6.3 - 7.7 - 15)	386,202	AOR 1.07 (1.03;1.1) <sup>1,t,d</sup>	Per increase of 10 $\mu\text{g}/\text{m}^3$
Madsen 2010 [111]	Norway—Oslo	DM	12.0 (6.5) DM	25,229	NE	
Mannes 2005 [112]	Australia—Sydney	MS	12.6 (1.4) MS 9.4 (6.5 - 9.4 - 11.2)	138,056	-2.48 (-4.58;-0.38) <sup>6,k</sup> -4.10 (-6.79;-1.41) <sup>2,k</sup> -12.8 (-14.3;-11.3) <sup>4</sup>	Per increase of unit Per increase of 10 $\mu\text{g}/\text{m}^3$
Morello-Frosch 2010 [113]	USA—California	MS <sup>m</sup>	16.7 (12.0 - 16.7 - 21.0)	3,545,177	AOR 1.04 (1.02;1.07) <sup>4</sup> -35 (-58;-12) <sup>4</sup> AOR 1.23 (1.03;1.5) <sup>4,n</sup>	IV versus I quartile
Parker 2005 [119]	USA—California	MS	15.42 (5.08 SD)	107,731	PCR 4.5 (0.5;8.7) <sup>o</sup> APR 1.73 (1.15;2.69) <sup>4,i,dx</sup>	Per increase of quartile
Rich 2009 [114]	USA—New Jersey	MS	13.8 (4)	88,678		
Slama 2007 [117]	Germany—Munich (LISA Study)	LUR	14.4 (13.5 - 14.4 - 15.4)	1,016		
Beil 2007 [100]	USA—Connecticut	MS	$PM_{10}$ $\mu\text{g}/\text{m}^3$ 22.3 (7.4)	358,504	-8.2 (-11.1;-5.3) AOR 1.03 (0.99;1.06)	Per increase of quartile
Brauer 2008 [102]	Canada—Vancouver	IDW	12.5 (1.4)	70,249	AOR 1.01 (0.95;1.08)	Per increase of unit
Chen 2002 [120]	USA—Nevada	MS	31.5 (16.8 - 39.35)	39,338	-11 (-19.8;-2.3)	Per increase of 10 $\mu\text{g}/\text{m}^3$
Darrow 2011 [103]	USA—Atlanta	MS	23.4 (7.0)	406,627	-2.3 (-7.4;2.8) <sup>3</sup>	Per increase of quartile
Gouveia 2004 [106]	Brazil—Sao Paulo	MS	60.3 (25.2 SD)	179,460	-13.7 (-27.0;-0.4) <sup>1,p</sup> -4.4 (-18.9;10.1) <sup>2</sup> AOR 1.25 (1.03;1.53) <sup>2</sup>	Per increase of 10 $\mu\text{g}/\text{m}^3$ Per increase of 10 $\mu\text{g}/\text{m}^3$ IV versus I quartile
Hansen 2007 [108]	Australia—Brisbane	MS	19.6 (14.6 - 19.6 - 22.7)	26,617	NE	
Madsen 2010 [111]	Norway—Oslo	DM	13.5 (9.0) DM	25,229	NE	
Maisonet 2001 [10]	USA	MS	25.5 (6.6) MS	89,557	AOR 0.96 (0.88;1.06) <sup>3,d</sup>	Per increase of 10 $\mu\text{g}/\text{m}^3$
Mannes 2005 [112]	Australia—Sydney	MS	30.1 (24.7 - 30.1 - 35.6) <sup>3</sup> 16.8 (12.3 - 16.8 - 19.9)	138,056	-1.21 (-2.31;-0.11) <sup>6,q</sup> -2.05 (-3.36;-0.74) <sup>2,q</sup> -7.2 (-7.9;-6.6) <sup>4</sup>	Per increase of unit Per increase of 10 $\mu\text{g}/\text{m}^3$
Morello Frosch 2010 [113]	USA—California	MS <sup>m</sup>	31.4 (22.6 - 31.4 - 38.7)	3,545,177	AOR 1.00 (0.99;1.01) <sup>4</sup> -19.9 (-43.6;3.8)	Per increase of quartile Per increase of the city-specific $PM_{10}$ range
Salam 2005 [115]	USA—California	MS	45.8 (18)	3,901		
Seo 2010 [116]	Korea—Seoul	MS	Mean (min-max) city-specific range 65.40 (63.76 - 67.54) 8.30	177,660		
	Pusan		56.95 (53.18 - 60.92) 20.24	81,510	PAR 0.07 (-0.01;0.15)	
	Daegu		59.69 (56.10 - 63.78) 13.79	23,341	PAR 0.19 (0.02;0.34)	
	Incheon		62.80 (62.09 - 65.15) 13.05	18,874	PAR 0.16 (0.04;0.27)	
				20,516	PAR 0.11 (-0.02;0.22)	

(continued)

TABLE 1. (CONTINUED)

Reference	Area	Exposure assessment	Pollutant—mean (IQR)	Study size	Results (grams or OR for low weight)	Exposure unit
Xu 2011 [121]	Kwangju Daejeon Ulsan USA—Allegheny County	IDW MS	40.39 (34.93 - 42.08) 14.86 47.87 (46.35 - 48.73) 4.01 42.98 (42.58 - 45.84) 9.82 28.7 (7) <sup>1</sup>	11,878 12,341 9,200 92,447	PAR 0.18 (-0.02;0.34) PAR 0.05 (0.00;0.10) PAR 0.16 (0.03;0.28) AOR 1.13 (1.02;1.25) <sup>1</sup>	Per increase of quartile
Bobak 2000 [101] Choi 2008 [122]	Czech Republic USA—New York City	MS Personal air monitoring	28.2 (7) <sup>2</sup> <b>Other pollutants</b> 71.5 (54.8 - 86.9) TSP $\mu\text{g}/\text{m}^3$ 3.212 (1.545 - 2.299 - 3.663) PAHs $\text{ng}/\text{m}^3$	78,148 535	AOR 1.10 (1.00;1.22) <sup>2,r</sup> AOR 1.15 (1.07;1.24) <sup>1,d</sup> AOR 2.15 (1.09;4.25) <sup>s</sup>	Per increase of 50 $\mu\text{g}/\text{m}^3$ Per natural-log-unit increase
Ha 2001 [107]	Korea—Seoul	MS	82.3 (76.7 - 91.0) <sup>1</sup> TSP $\mu\text{g}/\text{m}^3$	276,763	-6.06 (-3.85;-8.27) <sup>1</sup> ARR1.04 (1.00;1.08) <sup>1</sup>	Per increase of quartile
Salam 2005 [115] Van Den Hooven 2009 [123]	USA—California The Netherlands—Rotterdam	MS DWTD	50.6 (26) ozone ppb 546,770 (158,503 - 1,235,384) vehicles/24 hr <sup>4</sup> m	3,901 7,339	-49.9 (-72;-27.8) -20 (-47;8); -9 (-37;18); 6 (-21;34)	Per increase of quartile Each quartile or quintile compared with the I quartile
Wang 1997 [124]	(Generation R Study) China—Beijing	Proximity to a major road MS	50 m - 100 m - 150 m - 200 m quintiles 211 - 280 - 361 - 437 - 498 - 618 TSP $\mu\text{g}/\text{m}^3$ quintiles	74,671	-21 (-52;9); -41 (-69;-12); 8 (-20; 37); -6 (-36;24) -19.3 (SE 4.8; $p < 0.01$ ) AOR 1.24 (1.08;1.42) <sup>t</sup>	V versus I quintile

Associations are given for odds ratios of having birth weight <2,000 g at term.

MS, monitoring stations; DM, dispersion model; LUR, land-use regression model; IDW, inverse-distance weighting; DWTD, distance-weighted traffic density; PM, personal monitoring; IQR, interquartile range; OR, odds ratio; AOR, adjusted odds ratio; APR, adjusted prevalence ratio; ARR, adjusted risk ratio; PAR, population attributable risk; PCR, percentage change in risk; NE, no effect or little evidence for an effect.

<sup>1</sup>First trimester exposure; <sup>2</sup>Second trimester exposure; <sup>3</sup>Third trimester exposure; <sup>4</sup>Whole pregnancy exposure; <sup>5</sup>First month exposure; <sup>6</sup>Last month exposure.

<sup>a</sup>Adjusted analysis for the pollution level during the other two trimesters. In a subgroup of women who spent <2 hr in the nonresidential outdoor environment, -74.7g (-140.4;-9.0).

<sup>b</sup>NE for birth weight, but for birth length -0.271 cm (-0.514;-0.028) for exposure during first trimester, and birth head circumference -0.171 cm (-0.339;-0.003) for exposure during entire pregnancy.

<sup>c</sup>NE also for exposure during the first trimester 17.5 g (-2.4;37.5) and the last month -5.2 g (-23.3;12.9).

<sup>d</sup>Similar effect for exposure during the other two trimesters.

<sup>e</sup>Similar results for exposure during the last month AOR 0.94 (0.85;1.04).

<sup>f</sup>Risk for term birth weight <10 percentile.

<sup>g</sup>NE for exposure during the last month -0.76g (-1.72;0.20) and the second trimester -0.95g (-2.07;0.17).

<sup>h</sup>Percentage change in risk of very low for gestational age (VSGA) for the first trimester. NE for small for gestational age (SGA) for the whole pregnancy.

<sup>i</sup>APR for birth weight <3,000 g.

<sup>j</sup>Also NE for exposure during the first trimester 10.9g (-11.5;33.2).

<sup>k</sup>NE for exposure during the third trimester -0.98g (-3.74;1.78) and the first trimester 0.36g (-2.29;3.01).

<sup>l</sup>Monitoring stations within 10 km from residential address.

<sup>m</sup>Odds ratios for SGA in newborns delivered at 40 weeks.

<sup>n</sup>Percentage change in risk of low for gestational age (SGA) for the first trimester. Similar results for the second trimester. NE for VSGA for the whole pregnancy.

<sup>o</sup>NE for exposure during the third trimester -0.95 (-2.30;0.40).

<sup>p</sup>NE for exposure during third trimester AOR 1.05 (0.96-1.16) and entire pregnancy AOR 1.07 (0.99-1.14)

<sup>q</sup>Odds ratio for SGA among African-American ethnicity. NE for Dominican ethnicity.

<sup>r</sup>Odds ratio for birth weight <2,500 g.

TABLE 2. ASSOCIATION OF AIR POLLUTION EXPOSURE DURING PREGNANCY AND PRETERM DELIVERY

Author [Reference]	Area	Exposure assessment	Pollutant—mean (IQR)	Study size	Results (OR for preterm delivery)	Exposure unit
Bobak 2000 [101]	Czech Republic	MS	NO <sub>2</sub> $\mu\text{g}/\text{m}^3$ 37.7 (23.0 - 58.5)	69,935	AOR 1.10 (1.00;1.21) <sup>1</sup> AOR 1.08 (0.98;1.19) <sup>2</sup> AOR 1.11 (1.00;1.23) <sup>3</sup> AOR 0.93 (0.68;1.27) <sup>4</sup>	Per increase of 50 $\mu\text{g}/\text{m}^3$  V versus I quintile
Gehring 2011 [105]	Netherlands—Amsterdam (ABCD study)	LUR	38.7 (34.6; 37.4; 40.2; 44.8)	7,762	NE	
Gehring 2011 [104]	Netherlands (PIAMA study)	LUR	30.4 (11.2)	3,863	AOR 1.01 (0.94;1.07) <sup>5</sup>	Per increase of 10 $\mu\text{g}/\text{m}^3$
Liu 2003 [109]	Canada—Vancouver	MS	19.4 (15.1 - 22.3) ppb	229,085	AOR 1.08 (0.99;1.17) <sup>6</sup>	IV versus I quartile
Malmqvist 2011 [11]	Sweden—Scania	DM	16.4 (9.0 - 22.7) NO <sub>x</sub> <i>PM<sub>2.5</sub> <math>\mu\text{g}/\text{m}^3</math></i>	81,110	AOR 0.90 (0.82;0.98)	
Brauer 2008 [102]	Canada - Vancouver	IDW	5.1 (1.1)	70,249	AOR 1.06 (1.01;1.11)	Per increase of quartile
Chang 2012 [125]	USA—North Carolina	MS	14 (1.73)	161,078	ARR 6.8% (0.5;13.6)	Per increase of quartile
Gehring 2011 [104]	Netherlands (PIAMA study)	LUR	20.1 (4.6)	3,863	NE	
Huynh 2006 [126]	USA—California	MS	17.75 (5.2 SD) <i>Other pollutants</i>	42,692	AOR 1.15 (1.15;1.16)	Per increase of 10 $\mu\text{g}/\text{m}^3$
Bobak 2000 [101]	Czech Republic	MS	71.5 (54.8 - 86.9) TSP $\mu\text{g}/\text{m}^3$	78,148	AOR 1.27 (1.16;1.39) <sup>1</sup> AOR 1.25 (1.14;1.38) <sup>2</sup> AOR 1.24 (1.13;1.36) <sup>3</sup> AOR 1.09 (1.03;1.15) <sup>3</sup> NE <sup>1,2</sup>	Per increase of 50 $\mu\text{g}/\text{m}^3$
Suh 2009 [127]	South Korea	MS	65 (16.5) PM <sub>10</sub> $\mu\text{g}/\text{m}^3$	374,167		Per increase of quartile
van den Hooven 2009 [123]	Netherlands—Rotterdam (Generation R Study)	DWTD	546,770 (158,503 - 1,235,384) vehicles/24 hr*m	7,339	AOR 1.37 (1.02;1.84); 1.33 (0.98;1.79); 1.18 (0.87;1.59) AOR 1.15 (0.84;1.58)	Each quartile or quintile compared with the I quartile or baseline V versus I quintile

MS, monitoring stations; DM, dispersion model; LUR, land-use regression model; IDW, inverse-distance weighting; DWTD, distance-weighted traffic density; IQR, interquartile range; OR, odds ratio; AOR, adjusted odds ratio; ARR, adjusted risk ratio; NE, no effect, data not reported.

<sup>1</sup>First trimester exposure; <sup>2</sup>second trimester exposure; <sup>3</sup>third trimester exposure; <sup>4</sup>whole pregnancy exposure; <sup>5</sup>first month exposure; <sup>6</sup>last month exposure.

of 3,583,495 births including 6,639 postneonatal deaths in 96 counties throughout the United States.<sup>(23)</sup> They considered the monitoring data of pollutants in the first 2 months after birth as a proxy for chronic exposure, as these data were highly correlated with annual averages, after adjusting for season. Linking the data with birth and death records, they showed that infants exposed to the highest quartile of pollution ( $>34 \mu\text{g}/\text{m}^3$   $\text{PM}_{10}$  and  $>18.7 \mu\text{g}/\text{m}^3$   $\text{PM}_{2.5}$ ) had elevated odds especially for respiratory mortality compared with the lowest quartile ( $<23.3 \mu\text{g}/\text{m}^3$   $\text{PM}_{10}$  and  $<11.7 \mu\text{g}/\text{m}^3$   $\text{PM}_{2.5}$ ): for  $\text{PM}_{10}$  OR 1.31 (95% CI 1.00; 1.71) and for  $\text{PM}_{2.5}$  OR 1.39 (95% CI 1.04; 1.85).<sup>(23)</sup> The second study was conducted in South Korea. Son *et al.* assessed  $\text{PM}_{10}$ ,  $\text{PM}_{2.5}$ , and total suspended particles (TSP) during pregnancy and found a hazard ratio for all causes of mortality of 1.44 (95% CI 1.06; 1.97) for  $8.9 \mu\text{g}/\text{m}^3$  TSP increase, 1.65 (95% CI 1.18; 2.31) for  $6.9 \mu\text{g}/\text{m}^3$   $\text{PM}_{10}$  increase, and 1.53 (95% CI 1.22; 1.9) for  $3.15 \mu\text{g}/\text{m}^3$   $\text{PM}_{2.5}$  increase.<sup>(24)</sup> When they analyzed respiratory causes of mortality, the hazard ratios increased to 3.78 (95% CI 1.18; 12.13) for  $8.9 \mu\text{g}/\text{m}^3$  TSP increase, 6.2 (95% CI 1.5; 25.6) for  $6.9 \mu\text{g}/\text{m}^3$   $\text{PM}_{10}$  increase, and 3.15 (95% CI 1.26; 7.85) for  $3.15 \mu\text{g}/\text{m}^3$   $\text{PM}_{2.5}$  increase.<sup>(24)</sup>

In the framework of an estimation of years of life lost attributable to air pollution, Rösli *et al.*<sup>(25)</sup> conducted a meta-analysis of five studies on infant mortality.<sup>(23,26–29)</sup> They found an overall relative risk of 1.056 (95% CI 1.026; 1.088) per increase of  $10 \mu\text{g}/\text{m}^3$   $\text{PM}_{10}$ . Applying this risk estimate to the Swiss situation in the year 2000 (77,800 infants aged below 1 year and an average  $\text{PM}_{10}$  level of  $19.6 \mu\text{g}/\text{m}^3$ ) resulted in 1,705 (95% CI 915; 2,482) estimated years of life lost due to ambient air pollution.<sup>(25)</sup>

#### Lung development and respiratory effects

Development of airways and the lung begins with the embryonic phase at 4–7 weeks of gestational age, reaches the alveolar phase at around 36 weeks of gestational age, and continues until adolescence. This maturational process takes place over a relatively long time period compared with that of other organs, so potentially harmful factors have a greater opportunity to interfere with the developmental process. Moreover, the repair mechanisms of the developing lung tissue are not as efficient as those of the mature lung.<sup>(1)</sup> Considering all these aspects, it seems quite plausible that—analogue to tobacco smoke<sup>(6)</sup> or postnatal exposure to air pollution<sup>(30)</sup>—prenatal exposure to air pollution may also affect lung development.

In the BILD study, a healthy birth cohort in Switzerland,<sup>(31)</sup> where air pollution is relatively low (mean  $\text{PM}_{10}$   $22 \mu\text{g}/\text{m}^3$ ), we performed lung function measurements at 5 weeks of postnatal age.<sup>(32,33)</sup> 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  $1 \mu\text{g}/\text{m}^3$  increased exposure to  $\text{PM}_{10}$  during pregnancy.<sup>(34)</sup> This suggests that prenatal exposure to air pollution may affect lung development. This finding may be one explanation for the above-mentioned increased risk for infant mortality due to respiratory causes. Exposure to air pollution during pregnancy seems to affect lung function not only in infants, but also in older children. In Poland, measurements performed at 5 years of age showed reduced forced vital capacity (FVC)

and forced expiratory volume in the first second ( $\text{FEV}_1$ ) if higher prenatal  $\text{PM}_{2.5}$  exposure occurred.<sup>(35)</sup> Another study conducted in California on asthmatic children aimed to investigate the influence of prenatal and early childhood exposure to air pollution on lung function at 6–11 years of age. The results showed consistent evidence for an association between prenatal exposure and FVC, peak expiratory flow (PEF), and  $\text{FEV}_1$ .<sup>(36)</sup> Impaired lung function should correspond to susceptibility to airway infection and increased respiratory symptoms. Studies on prenatal exposure to  $\text{NO}_2$  and respiratory symptoms during the first year of life,<sup>(37)</sup> prenatal exposure to  $\text{O}_3$  and  $\text{NO}_2$  and occurrence of apnea,<sup>(38)</sup> prenatal polycyclic aromatic hydrocarbon exposure and frequency and duration of respiratory symptoms over the first year of life,<sup>(39)</sup> and prenatal exposure to fine particle matter and severity of respiratory symptoms within different wheezing phenotypes<sup>(40)</sup> support this hypothesis. Air pollution affects not only lung function and respiratory symptoms, but also the development of asthma. In a case-control study including 37,401 subjects in Canada, Clark *et al.* investigated the incidence of asthma up to the age of 3–4 years in relation to individual exposure to air pollution during gestational time and the first year of life.<sup>(41)</sup> They found a positive association: a  $10 \mu\text{g}/\text{m}^3$  increase in  $\text{NO}_2$  was associated with an OR of 1.12 (95% CI 1.07; 1.17) for asthma incidence.<sup>(41)</sup>

#### Immune system

Environmental exposure occurring in early life influences the pattern of immune maturation and resulting immune response.<sup>(42)</sup> Exposure to air pollution may influence immune programming and, together with a genetic predisposition, may cause immunological diseases such as asthma.<sup>(43)</sup> Although knowledge of changes in the immune system of neonates after maternal smoke exposure during pregnancy has existed for some time,<sup>(44–46)</sup> data on systemic inflammation in the mother and alteration in the neonatal immune system upon maternal exposure to outdoor air pollution have only recently been published. In one study from Pennsylvania, authors measured blood concentration of C-reactive protein (CRP) in 1,696 women before the 22<sup>nd</sup> week of gestation and estimated exposure during the previous 20 days to air pollution from maternal ZIP codes. Among the nonsmokers, the odds ratio to have an increased CRP ( $>8 \text{ ng/ml}$ ) was 1.47 (95% CI 1.06; 2.02) for  $10 \mu\text{g}/\text{m}^3$   $\text{PM}_{10}$  increase and 1.55 (1.15; 2.11) for  $5.2 \mu\text{g}/\text{m}^3$   $\text{PM}_{2.5}$  increase.<sup>(47)</sup> In the BILD study, healthy term-born infants exposed to moderate levels of  $\text{PM}_{10}$  showed an attenuated expression of the cytokines interleukin (IL)-10 and IL-1 $\beta$  in cord blood after higher prenatal exposure with different peak effects, depending on stages of pregnancy and cytokines measured.<sup>(48)</sup> Lymphocyte proportions were investigated in three studies of one larger project assessing the effect of air pollution on fetal and childhood development in the Czech Republic. The first study found an association between exposure to polycyclic aromatic hydrocarbons (PAH) and  $\text{PM}_{2.5}$  and higher natural killer (NK) cell fractions in cord blood.<sup>(49)</sup> Furthermore, they found a decreased percentage of T lymphocytes and an increase of B lymphocytes in cord blood when the exposure occurred during the 14 days before birth.<sup>(50)</sup> Finally, they investigated the effect on lymphocyte distribution

in cord blood for each month of exposure during pregnancy separately. Using this time period-based approach, they were able to show that exposure during early gestation was associated with increased percentages of T lymphocytes (CD3<sup>+</sup> and CD4<sup>+</sup> cells) and reduced percentages of B lymphocytes (CD19<sup>+</sup>) and NK cells, whereas exposure during late gestation was associated with reduced percentages of T lymphocytes and increased percentages of B lymphocytes and NK cells.<sup>(51)</sup> Using a comparable approach, this group was also able to show an association of PAH exposure during gestational months 4–7 with elevated concentrations of cord-blood IgE, with robust results after adjusting for several confounders.<sup>(52)</sup>

### Miscellaneous outcomes

The harmful effect of air pollution on the fetus may potentially involve not only lung or immune development, but any organ or system. Evidence of effects on congenital anomalies is limited and controversial. Data from North England did not show any association of black smoke and SO<sub>2</sub> with any congenital malformation,<sup>(53)</sup> whereas a later study from the same area investigated the exposure to CO and NO<sub>2</sub> and found an association with ventricular septal defects and cardiac septal malformations, but no consistent results after exposure to O<sub>3</sub> and PM<sub>10</sub>.<sup>(54)</sup> Another study from the United States found just one significant correlation out of 60 investigated: PM<sub>10</sub> and patent ductus arteriosus.<sup>(55)</sup> A recent meta-analysis of 10 studies (including two of the above) shows clear evidence of an increased relative risk (between 3% and 20% per unit of exposure) for coarctation of the aorta and tetralogy of Fallot after NO<sub>2</sub> and SO<sub>2</sub> exposure, for atrial septal defects after PM<sub>10</sub> exposure, and for cleft lip with or without cleft palate after O<sub>3</sub> exposure.<sup>(56)</sup>

Evidence of an effect on neurodevelopment and behavior is sparse, but seems quite consistent. Data from a case-control study in California (United States) suggests an association between residential proximity to freeways (<300 m) and cases of autism.<sup>(57)</sup> The INMA (Infancia y Medio Ambiente) project from Spain found an association between prenatal exposure to NO<sub>2</sub> and benzene, and cognitive development in the second year of life, strongest in infants who were not breast-fed and whose mothers had a lower fruit and vegetable intake.<sup>(58)</sup> This finding supports the hypothesis that the adverse effects of air pollution act through oxidative pathways.

### Methodological considerations

To fully appreciate possible associations between air pollution during pregnancy and health outcomes, some important issues regarding exposure assessment need to be considered.

The precision of estimating individual exposure affects the power of the study and, therefore, the detected effect of air pollution on health. The most common approach is to assess the residential exposure at the mother's address, with a lower or higher resolution: district, postal code, or street number. This approach assumes that in the considered area the pollution level is homogeneous, that the subject did not move during pregnancy, and that the mothers stay most of the time at home, or that the exposure at the work place is comparable to that at home. Aguilera *et al.* collected data on

time-activity patterns of pregnant women and analyzed the correlation between air pollution exposure during pregnancy and birth weight.<sup>(59)</sup> Limiting the analysis to a subgroup of women, who spent less than 2 hr per day outside home, the association between aromatic hydrocarbons [benzene, toluene, ethylbenzene, xylene (BTEX)] and birth weight changed from -7.6 g (95% CI -54.9; 39.8) to -76.6 g (95% CI -146.3; -7.0) per increase of 4 µg/m<sup>3</sup> BTEX, indicating that effects are underestimated due to nondifferential exposure misclassification, and the true, stronger association may only be seen in studies with more exact exposure assessment.<sup>(59)</sup>

The exposure to coarse particles (PM<sub>10-2.5</sub>) and the consequent effect are not necessarily comparable between different areas. Particulate matter is measured as total mass, but despite similar gravimetric values dramatically different particle composition may arise, depending on the source. Particles measured, *e.g.*, at the seaside, are derived mostly from natural sources (sand and ocean droplets), whereas urban airborne particulates derive mainly from vehicle re-suspension from the road and abrasion processes from wheels and brakes. These last highly correlate with combustion-derived ultrafine particles that share the same source. Biological effects could also be exhibited through redox activity and content of organic and elemental carbon and PAH, which are all higher in ultrafine particles.<sup>(60)</sup> Beside the composition, the surface of all particles also needs to be considered. The smaller the particles, the smaller the mass and the larger the relative surface, which may be relevant for the biological activity. Most of the available epidemiological studies on air pollution measured PM<sub>10</sub> or PM<sub>2.5</sub> (*e.g.*, Table 1). Thus, depending on the design of a study or the source of particulate matter in the study area, PM<sub>10</sub> levels are or are not a surrogate measure for exposure to ultrafine particles.<sup>(60-62)</sup> However, this is difficult to judge just from the publication without additional information.

Another open question is the shape of the association between exposure and effect. Most studies found or assumed a linear correlation between air pollution and birth outcome, although many biological processes are under feedback control and, when related to continuous predictors, may not behave linearly.<sup>(63)</sup> For the INMA study, Ballester *et al.* performed cubic smoothing splines to describe nonlinear correlations for birth weight and length.<sup>(64)</sup> Reduction in birth weight in that study was evident between 35 and 55 µg/m<sup>3</sup> NO<sub>2</sub>, and in birth length above 40 µg/m<sup>3</sup> NO<sub>2</sub>.<sup>(64)</sup> This kind of analysis can be useful for policy makers in order to evaluate the merit of setting their limits of pollutants. In the above example, reducing NO<sub>2</sub> levels from 60 to 45 µg/m<sup>3</sup> would lead to small effects, whereas benefit would derive from reducing NO<sub>2</sub> down to 35 µg/m<sup>3</sup>. These cutoff levels may, of course, vary between different locations and for different outcomes.

As the development of the fetus is a very dynamic process, the effect of exposure can differ in the different periods, suggesting changing windows of vulnerability. These timing effects are not surprising and have been shown in several of the studies cited above.<sup>(48,50,51,65)</sup> The susceptibility to air pollution and the effect from increased exposure depend on both the stage of pregnancy and the developmental process assessed. The pathophysiological basis of these timing effects relates to the mechanisms by which air pollutants impact upon the developing fetus. The first period of pregnancy is

crucial for the correct establishment of a fully functional vascularity of the placenta. Factors acting during this time period may alter the implantation of trophoblasts and lead to subsequent chronic placental insufficiency.<sup>(66)</sup> The last trimester, on the other hand, is characterized by the fastest somatic growth. At the last workshop on “methodologies in epidemiological studies of air pollution and birth outcome,” the identification of these windows of vulnerability was regarded as one of the main challenges for future research.<sup>(67)</sup> The high intercorrelation of exposures during those time windows and throughout the whole period of pregnancy, however, makes those timing effects difficult to disentangle.

## Possible Mechanisms

### General considerations

As shown above, effects of different pollutants have been largely investigated in recent years in epidemiological studies. However, the ways by which particles actually are transported beyond the lungs in humans and the exact mechanisms of their effects on fetuses are still unclear to a large extent. Although animal and *in vitro* studies suggest it is very likely that small amounts of ultrafine particles can be transported to other organs, it is not clear if this translocation of particles, or rather the larger fraction, which deposits in the upper respiratory tract,<sup>(68)</sup> is responsible for health effects in humans. Despite this uncertainty, we review current knowledge on toxicokinetics and toxicodynamics of pollutants in the following paragraphs and try to relate it to possible mechanisms in health effects. We give higher weight to ultrafine compound rather than coarse particles, as better data for ultrafine particles are available despite the fact that most epidemiological studies mentioned further above use coarse particles to estimate pollution exposure.

### Toxicokinetics of pollutants

The first step to consider is the route of the pollutant from the environment into the body. Possible points of entry are the skin, the gastrointestinal tract, and the respiratory tract. From the anatomical point of view, the small intestine and the lungs have a wider surface (200 m<sup>2</sup> and 140 m<sup>2</sup>, respectively) than the skin (2 m<sup>2</sup>), and the lungs have the thinnest barrier (<1 μm at the alveolar segments compared with 20–25 μm of the small intestine and 30–50 μm of the skin).<sup>(69)</sup> In the lung, surfactant plays a major role for the clearance of particles and their interaction with airway epithelial cells.<sup>(70)</sup> Particles with a diameter >1 μm are usually cleared by mucociliary clearance procedures and do not pass the air–blood barrier.<sup>(71)</sup> Smaller particles are, however, able to pass through the airway epithelium.<sup>(72)</sup> Those processes depend on the size and the properties of the surface and involve passive diffusion, if the ultrafine particle is uncharged, or caveolae-mediated pinocytosis.<sup>(73)</sup> This endocytosis pathway depends not only on the characteristics of the particles, but also on the cell types and their state of differentiation.<sup>(74)</sup> *In vivo* and *in vitro* studies have shown that another pathway exists by which particles pass the epithelial barrier, which is mediated by cells of the immune system. Macrophages and dendritic cells are able to take up particulates at the apical side of the epithelium<sup>(75,76)</sup> and transport them via the epithelial barrier to the interstitial tissue.<sup>(77)</sup> Macrophages and

dendritic cells express tight junction proteins and interact with each other by a transepithelial cellular network, allowing the particle to translocate through the epithelium.<sup>(78)</sup> Dendritic cells containing the particles are then activated to migrate to the draining lymph nodes and into the bloodstream, where they activate further processes by cellular mediators such as cytokines.<sup>(75,79,80)</sup>

The passage of ultrafine particles from the bloodstream through the placenta may depend primarily on the stage of pregnancy. In the first months, the thickness of the placental barrier reaches up to 20 μm, there is no perfusion from maternal blood, and nutrients reach the embryo only by passive diffusion. Subsequently, the fetal capillaries increase along with maternal blood supply in the maternal–fetal interface until the 10<sup>th</sup> week of gestation, when the full fetomaternal circulation is completed. As pregnancy progresses, the placental barrier gets thinner, the blood perfusion improves from both sides, and the exchange of nutrients and other elements increases.<sup>(81)</sup> The membrane of the syncytiotrophoblast has similar properties and selective transporters as the blood–brain barrier, the blood–testis barrier, and the blood–retina barrier.<sup>(82)</sup> Efficacy of those barriers is strongly influenced by inflammatory processes and—best known for the blood–brain barrier—efficacy of the barrier decreases if inflammation occurs. The same mechanism may partly explain enhanced effects of air pollution in diseased subjects, and this could happen at the placental barrier as well.

Very small particles, such as nanoparticles, are well known to cross the placental barrier easily. Wick *et al.* investigated the placental passage of nanoparticles using an *ex vivo* human placental perfusion model and fluorescently labeled polystyrene (PS) beads with diameters of 50, 80, 240, and 500 nm.<sup>(83)</sup> They showed that PS beads up to a diameter of 240 nm were able to cross the placental barrier with likely transport routes of passive diffusion and clathrin- or caveolin-mediated endocytosis.<sup>(83)</sup>

### Toxicodynamics of pollutants

In this section, hypothetical ways of action and interaction of the particle matters within the organism, including the compound’s effect on processes at the organ, cellular, and molecular levels, are reviewed. An understanding of the biophysico-chemical interactions at the air–blood barrier in the mother and the placental barrier helps to explain the heterogeneous effects in different subjects exposed to similar pollutants. The nano–bio interaction depends on (1) the particle surface, (2) the suspending medium or biological fluid, and (3) the solid–liquid interface’s contact zone with biological substrate. These three components dynamically interact with each other, *i.e.*, they change their characteristics as they come into contact. In a given medium, some of the main characteristics of a particle relevant for the surface properties include the chemical composition, the shape, the surface crystallinity and roughness, and the lipo- or hydrophilicity. Other characteristics, such as charge, state of aggregation, dispersion, dissolution, biodegradability, hydration, and valence, may change depending on the properties of the suspending media.<sup>(61)</sup> In biological fluids or interstitium, pH, ionic strength, salts, and the type and concentration of large organic molecules such as proteins depend also on cell secretion, local or systemic inflammation, and microbiological

flora. The particles are cleared from macrophages, depending on the type and amount of proteins on the coat, as well as processes such as opsonization, attachment of immunoglobulins and Fc $\gamma$ , and complement receptor-mediated phagocytosis.<sup>(74)</sup> The particles that resist degradation may lead further to inflammation, or stimulate fibroblast-mediated collagen production resulting in fibrosis. The ultrafine matters that escape phagocytosis may interact with other cells not specialized to recognize and process foreign substances.<sup>(61)</sup>

For example, in chronic atopic lung inflammation, the cells secrete cytokines, immunoglobulins, and degradation products that modify the pH of the suspending medium and protein and glycidic contents. The physiological and pathological flora of the lung may both be influenced by and influence the local environment.<sup>(84)</sup> The nanoparticles reaching the bronchial wall and alveolar segments experience coating and charge modification according to the surrounding medium, which determines whether they are bioavailable and may participate in biocompatible or bioadverse interactions.

Considering a nonchanging local environment, what are the effects caused by the particles on the biological target? The most common result is the production of reactive oxygen species (ROS) with subsequent oxidant injury and proinflammatory effects. Evidence on mitochondrial damage with impaired ATP production is also quite consistent.<sup>(60)</sup> The combustion-derived ultrafine matters contain a particle component that carries the chemical compounds, many of which are semivolatile organic substances, through which the combined toxic effect is enhanced. The particle transports the organic component through the lung epithelium, the particle surface triggers the oxidative reaction, and the chemical compound enhances subcellular damage. Other cytotoxic mechanisms involve disruption of membrane integrity and transport processes, lysosomal damage, protein unfolding, disruption of the conformation, aggregation, and fibrillation (amyloid fiber) as well as DNA damage.<sup>(61,85,86)</sup> Epigenetics play a central role in the hypothesis of permanent phenotypical changes due to prenatal environment exposure. The previously described mechanisms may also result in histone modifications, ATP-dependent chromatin remodeling complexes, noncoding RNA, and DNA methylation, all of which affect protein transcription. During the embryonic and fetal period, an enhanced or reduced protein expression may permanently affect the development of immature cells, organs, and systems comparably to genetic mutations.<sup>(4)</sup> For example, epigenetic mechanisms regulate the differentiation of naive T cells in T<sub>H</sub>1, T<sub>H</sub>2, and Treg. These mechanisms may also lead to transgenerational effects of pollution without involving direct DNA changes. A recent review details the evidence on humans, animals, and *in vitro*, supporting the hypothesis of the effect of air pollutants (PM and diesel exhaust particles) on epigenetic modifications.<sup>(87)</sup>

The interaction of ultrafine particles with membrane proteins may limit the activation of receptors for placental growth factors, resulting in reduced placental size and subsequent impaired supply of nutrients and oxygen.<sup>(88–92)</sup> Chronic exposure to air pollution may thus lead to a subclinical pulmonary and even systemic inflammation due to oxidative injuries<sup>(93)</sup> and innate immunity stimulation.<sup>(94)</sup> Increased blood coagulation and viscosity, in addition to endothelial and vascular function, represent further possible mechanisms of ultrafine matters' toxicity. These may also

lead to altered placental perfusion.<sup>(92,95–97)</sup> The effect on heart-rate variability due to reduction of autonomic system activity<sup>(98)</sup> may affect regulation of blood pressure and consequently change hemodynamic properties of the placenta.

## Conclusion

Humans have always been exposed to particulate matters, but since the industrial revolution their sources and their characteristics have been changed dramatically. Particulate matters derived from natural sources have a larger volume and smaller surface per unit mass, whereas those derived from humans, mainly combustion-generated, may exhibit a more harmful effect. They penetrate deeper into the lung, are able to interact with immune cells, and even exhibit systemic effects after entering the bloodstream. These human-derived particles have a higher rate of redox activity, glutathione depletion, and heme oxygenase-1 induction, possibly leading to a higher incidence of mitochondrial malfunction and genetic-epigenetic effects.<sup>(60,87)</sup> During pregnancy, these mechanisms may result in altered placental hemodynamics with subsequent reduction of nutrients and oxygen supply.<sup>(92)</sup>

Epidemiological studies of neonatal outcomes after exposure to air pollution during pregnancy consistently show harmful effects on lung function in infants and children and on respiratory symptoms during early childhood. Data of the effect on infant mortality, mainly for respiratory reasons, are consistent as well. Evidence on birth weight and prematurity is weaker, with some studies showing a strong association and others not able to confirm those results. Besides inappropriate adjustment for confounders, other hypotheses can be raised to be responsible for this incongruence. Studies with outcomes measured continuously and influenced by many factors, such as birth weight, need a precise exposure assessment. Minor misclassification errors have a large impact on the exposure–response relationship.<sup>(99)</sup> The inclusion of subjects who are more sensitive or more resistant to pollutants can also skew the effect. Perhaps prior classification of subjects according to sensitivity would produce a more consistent effect and offer a higher impact from a public health point of view. A better knowledge of the toxicodynamics of ultrafine particles may help to identify factors that could protect against air pollution in the future.

The effect on fetal development is particularly important in areas with higher outdoor pollution, where it is practically impossible for an individual to avoid exposure during pregnancy. Especially in these areas, strong evidence for the association between prenatal exposure to air pollution and infant mortality exists, clearly indicating the need for more stringent measures to reduce air pollution.

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**ETH 2013**

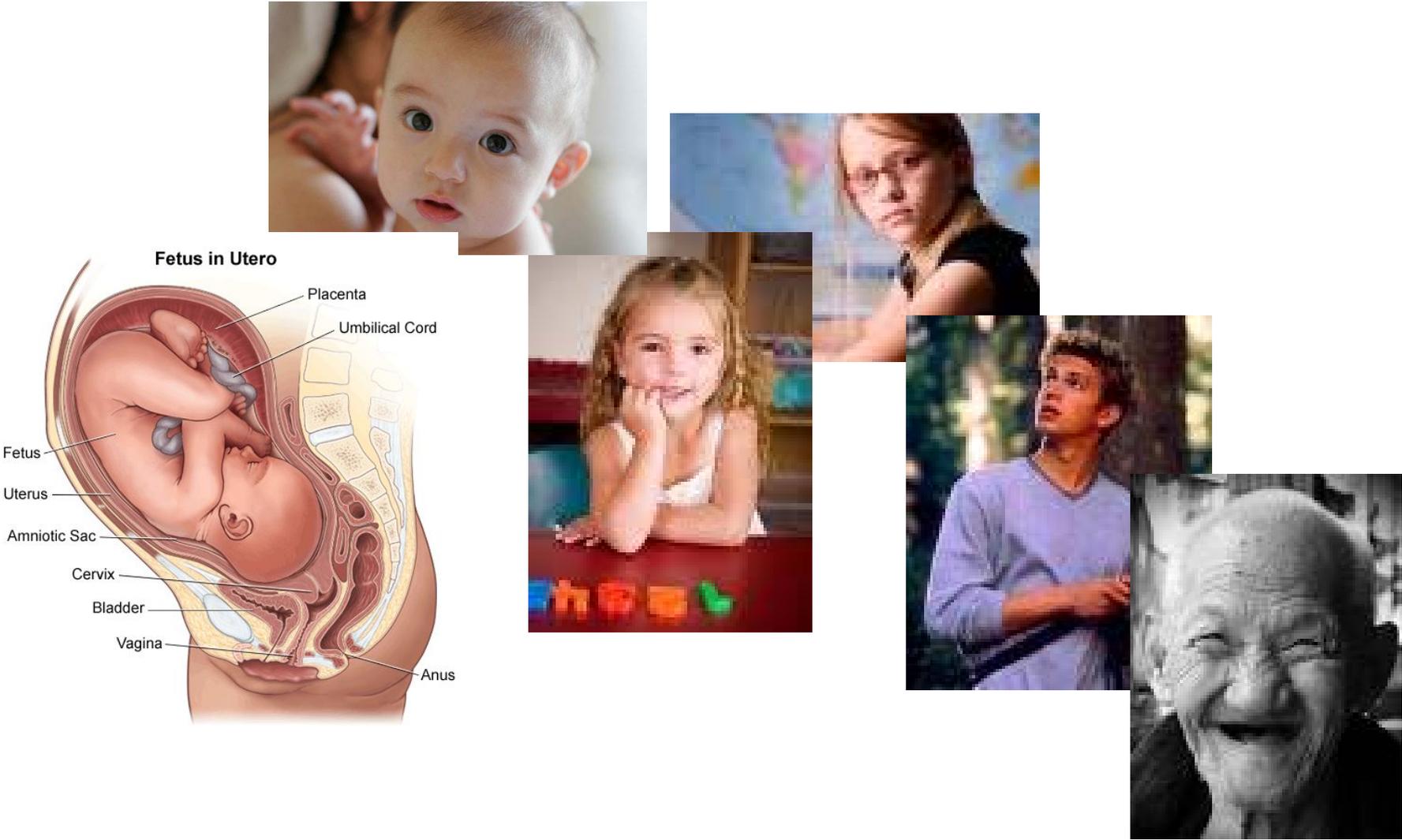
# **Effect of air pollution on newborns**

**Focus:**

**Specific vulnerability and  
public health aspects**

Urs Frey, MD PhD  
University Children's  
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# Early origin of adult lung disease



## Proposed mechanisms

- Systemic effects of pollutants in the mother <sup>1</sup> with
  - decreased placental blood flow / hypoxia
  - reduced transfer of nutrients
- Direct effects of pollutants crossing the placental barrier (e.g. nanoparticles) <sup>2</sup>
- Developmental changes of the immune system <sup>3</sup>
- Adverse effects on lung development <sup>4</sup>

<sup>1</sup> Slama et al., EHP, 2008;

<sup>2</sup> Wick et al., EHP, 2010

<sup>3</sup> Hertz-Picciotto et al., EHP, 2005

<sup>4</sup> Kajekar, Pharm Ther 2007

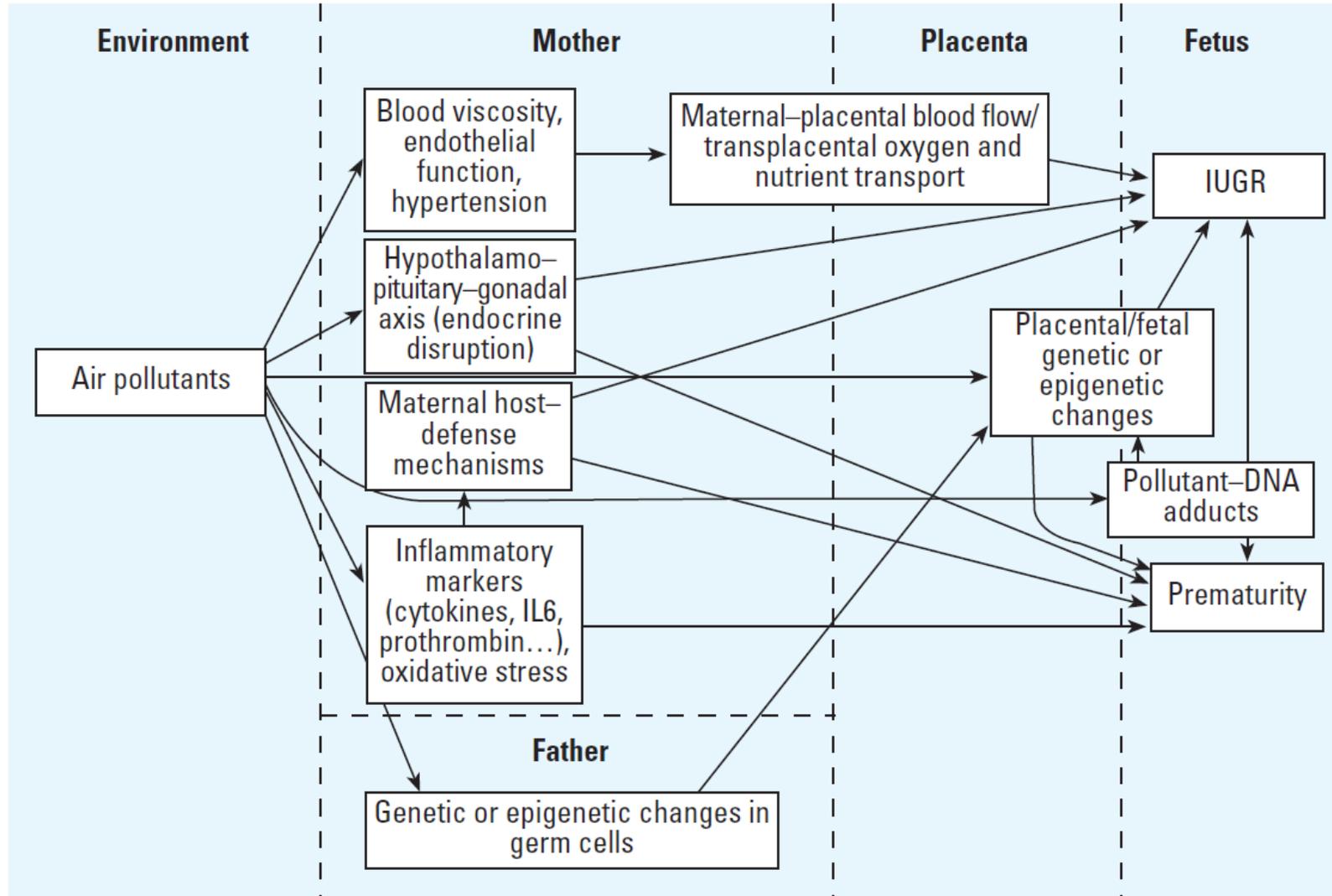
# Handout with detailed literature

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## Air Pollution During Pregnancy and Neonatal Outcome: A Review

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# Neonatal outcome of systemic effects



Slama et al., EHP, 2008

## Epidemiological evidence

- Birth weight (heterogeneous findings, confounders)
- Neonatal prematurity
- Infant mortality
- Association with autism, cognitive development
- Association with congenital heart disease
- Respiratory symptoms and asthma

## Positive association of pollution and low birth weight

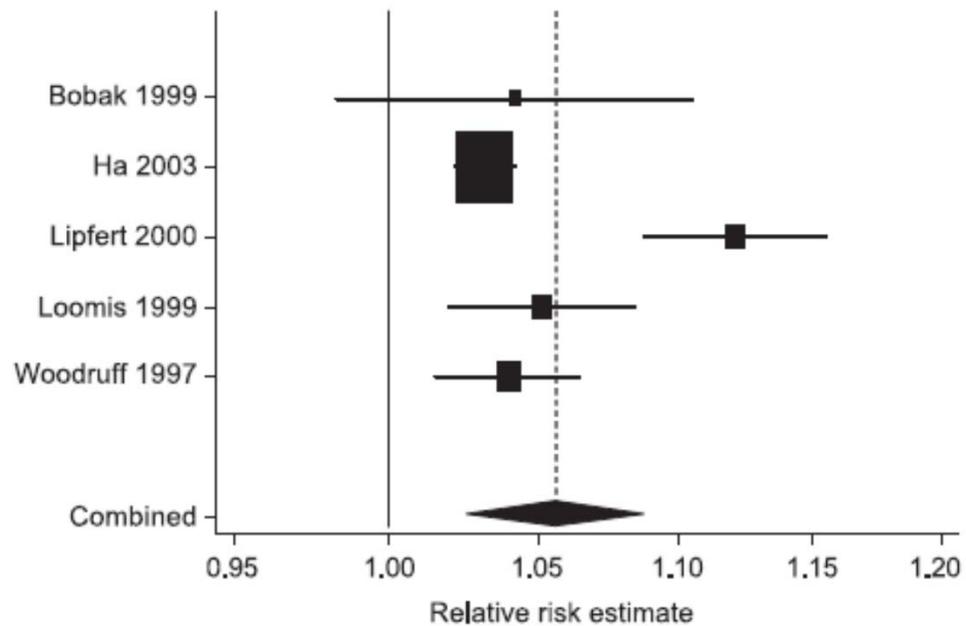
- Munich, Germany – Slama et al., EHP 2007
- California, USA – Morello-Frosch et al., Env Health 2010
- PA, USA – Xu et al., Int Arch Occup Med 2011
- Poland – Jedrychowski et al., Env Res 2009

## No effect of maternal exposure to pollution & birth weight

- Norway – Madsen et al., Env Res 2010
- PIAMA, Holland – Gehring et al., Env Res 2011
- ABCD, Holland – Gehring et al., Occup Env Med 2011

## Effect on infant mortality

Meta-analysis of 5 cohorts (per  $10\mu\text{g}/\text{m}^3$  increase in PM10)



### Effects for Switzerland

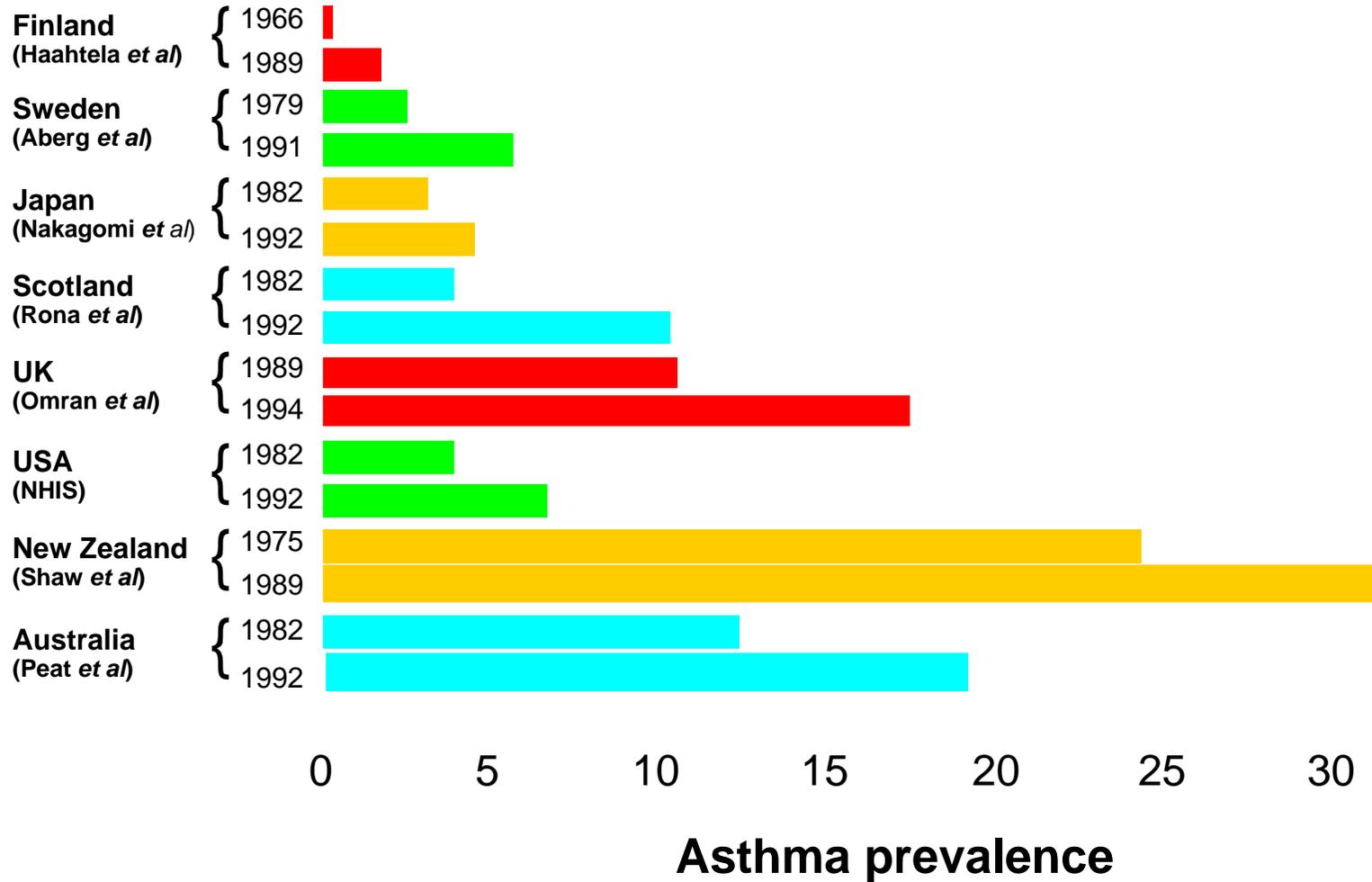
77800 birth in 2000  
 average PM10  $19.6\mu\text{g}/\text{m}^3$   
 Relative risk 1.056

Avoidable years lost per  
 $10\mu\text{g}/\text{m}^3$  in Switzerland

**= 1705 years**

Röösli M et al. Int J Epidemiol 2005: 34: 1029-35..

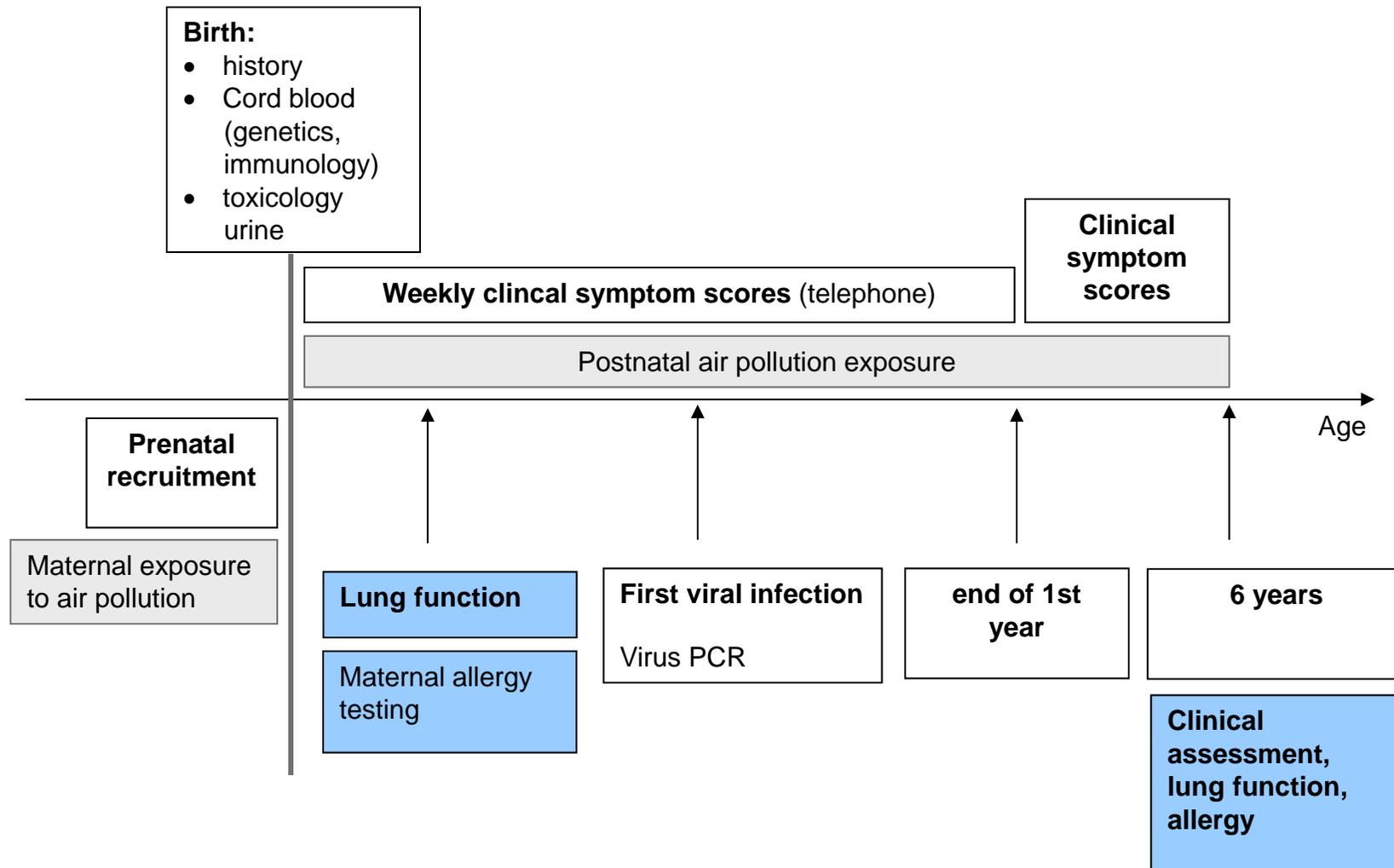
# Respiratory Symptoms: secular trends (school age)



# Respiratory symptoms and infections in infancy

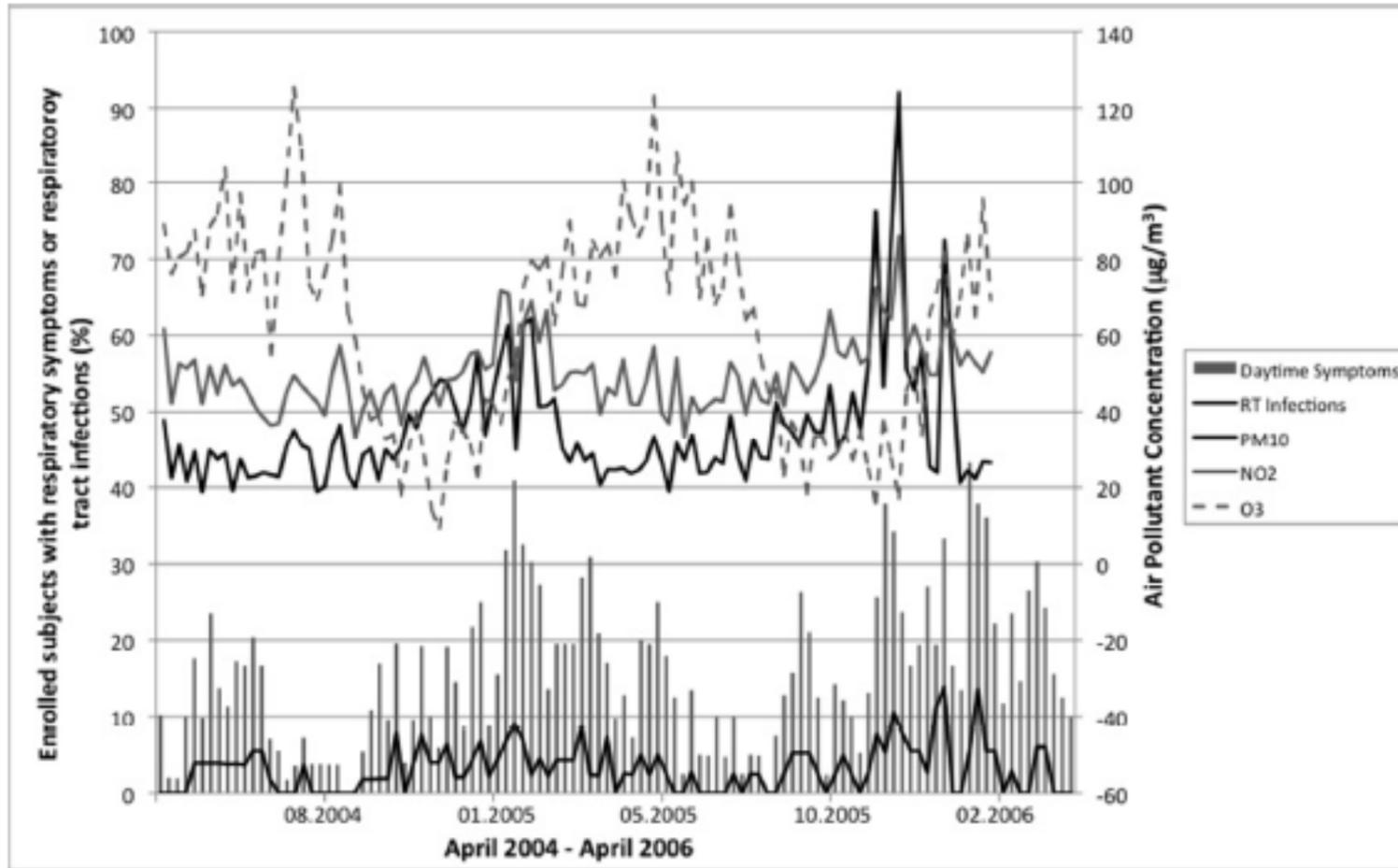
- Increased number of symptoms [NO<sub>2</sub>, PM10]
- Increased asthma prevalence in preschoolers [NO<sub>2</sub>]
- Longer periods of viral infections in infancy [PM10]

# SNF prospective BILD birth cohort (n= 500)



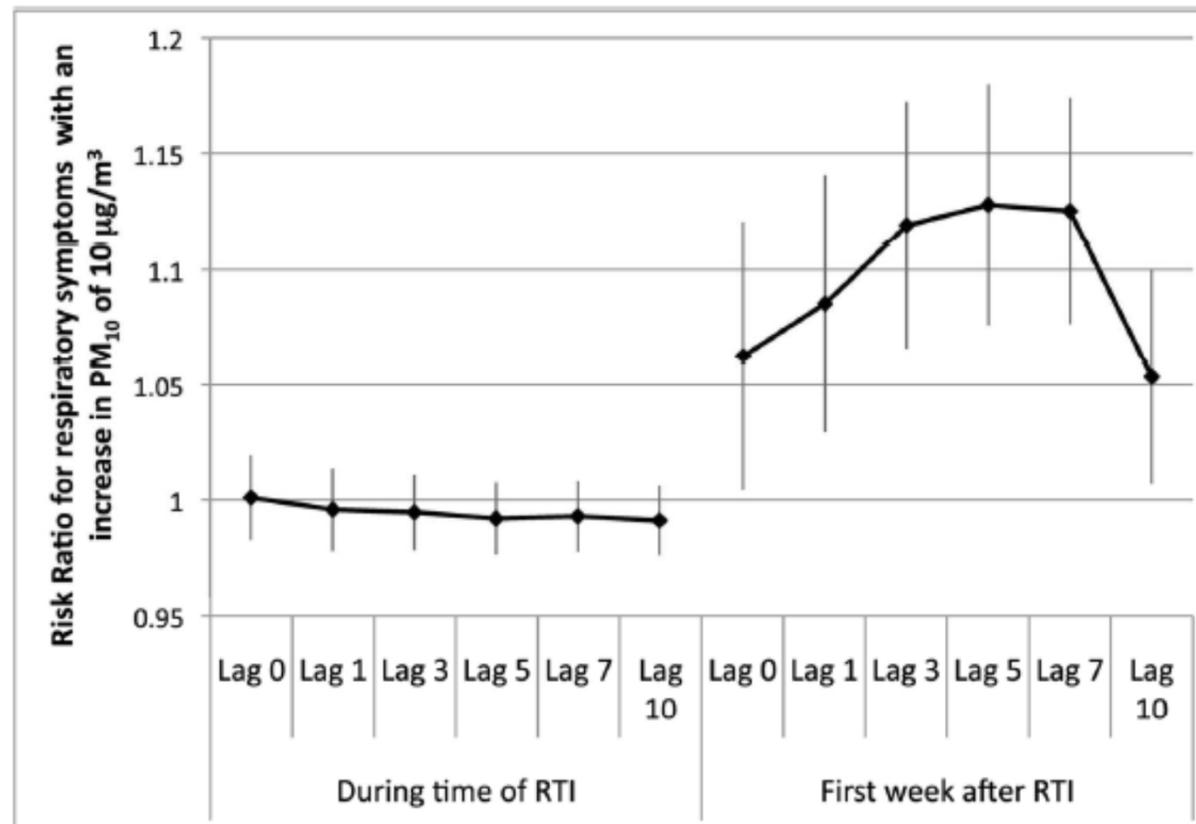
Fuchs et al. Int J Epidemiol. 2012; 41: 366-376.

# Impact of air pollution in infancy



Stern&Latzin et al. Am J Resp Crit Care Med 2013, Jun 15; 187:1341-8.

# Air pollution (PM10): Longer periods of symptoms after respiratory infection in the first year of life



Stern&Latzin et al. Am J Resp Crit Care Med 2013, Jun 15; 187:1341-8.

## Proposed mechanisms

- Systemic effects of pollutants in the mother <sup>1</sup> with
  - decreased placental blood flow / hypoxia
  - reduced transfer of nutrients
- Direct effects of pollutants crossing the placental barrier (e.g. nanoparticles) <sup>2</sup>
- Developmental changes of the immune system <sup>3</sup>
- Adverse effects on lung development <sup>4</sup>

1 Slama et al., EHP, 2008;

2 Wick et al., EHP, 2010

3 Hertz-Picciotto et al., EHP, 2005

4 Kajekar, Pharm Ther 2007

## Exposure, placenta function, biological effects

- Large heterogeneity of effects, dynamic effects
- Dependent on particle size, chemical composition, immunological aspects, redox activity
- Epigenetic activity
- Time of exposure (change in placental function)
  - 1month (placenta barrier  $<20 \mu\text{m}$ , diffusion, no perfusion)
- Presence of pre-existing inflammatory process
- Programming effects

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- **Developmental changes of the immune system** <sup>3</sup>
- Adverse effects on lung development <sup>4</sup>

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<sup>4</sup> Kajekar, Pharm Ther 2007

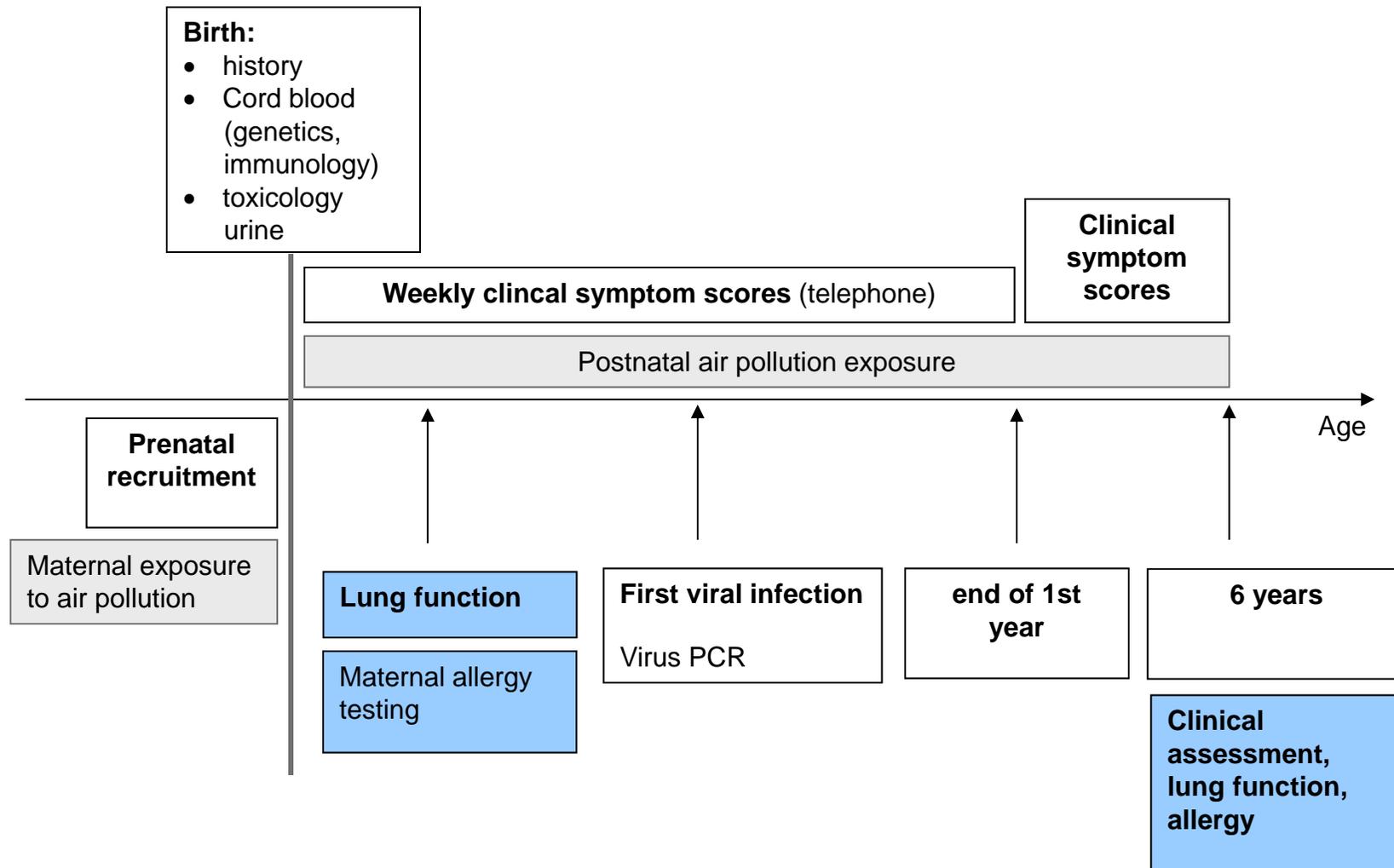
## Effect on immune system and development

- Increased inflammatory markers (CRP) [PM10]
- Attenuated expression of IL10, IL1 $\beta$  [PM10]
- Dysbalance of T and B Lymphocytes, NK cells [PAH]
- Elevated Ig-E levels in cord blood [PAH]

## Proposed mechanisms

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# SNF prospective BILD birth cohort (n= 500)



Fuchs et al. Int J Epidemiol. 2011



**Plethysmographie**



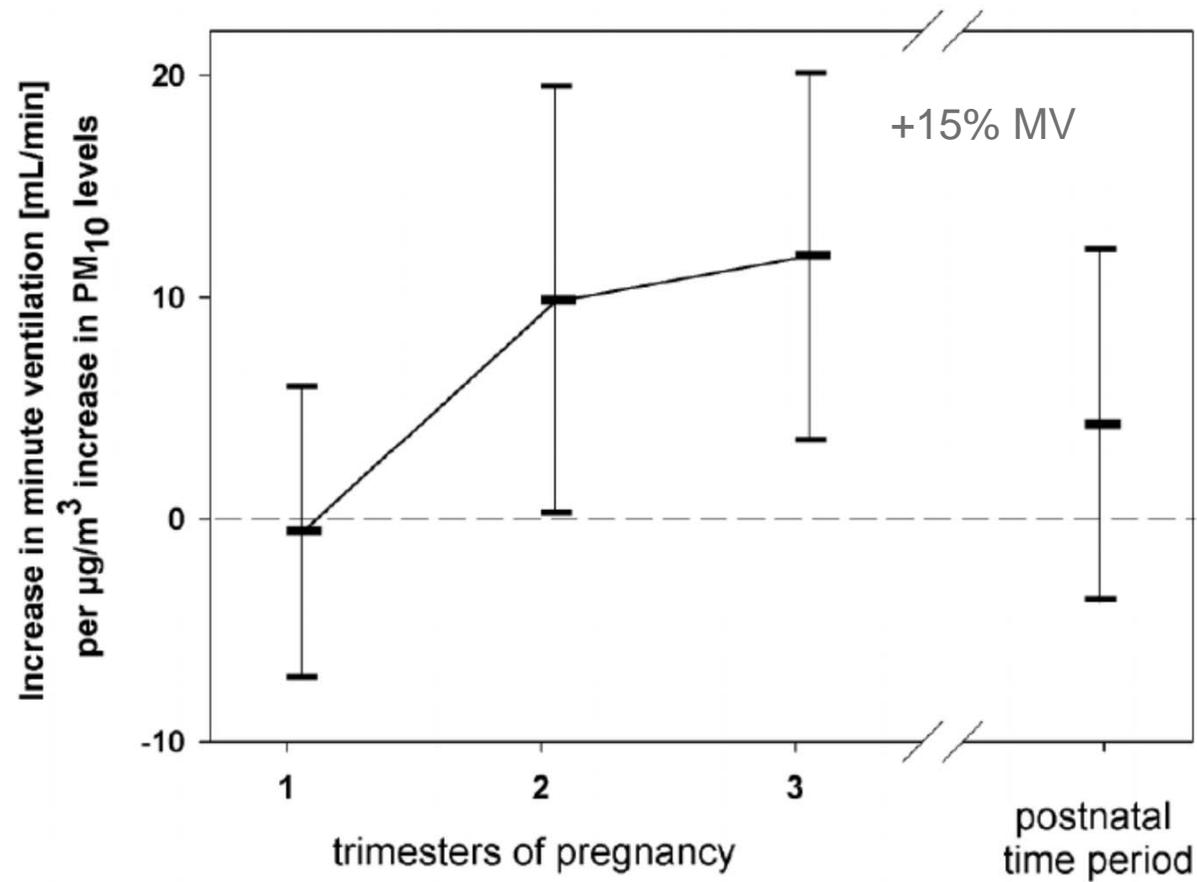
## **International standards for infant lung function tests**

Frey U et al. Respir J 2000; 16: 731-741.

Frey U et al. Eur Respir J 2000; 16: 1016-1022.

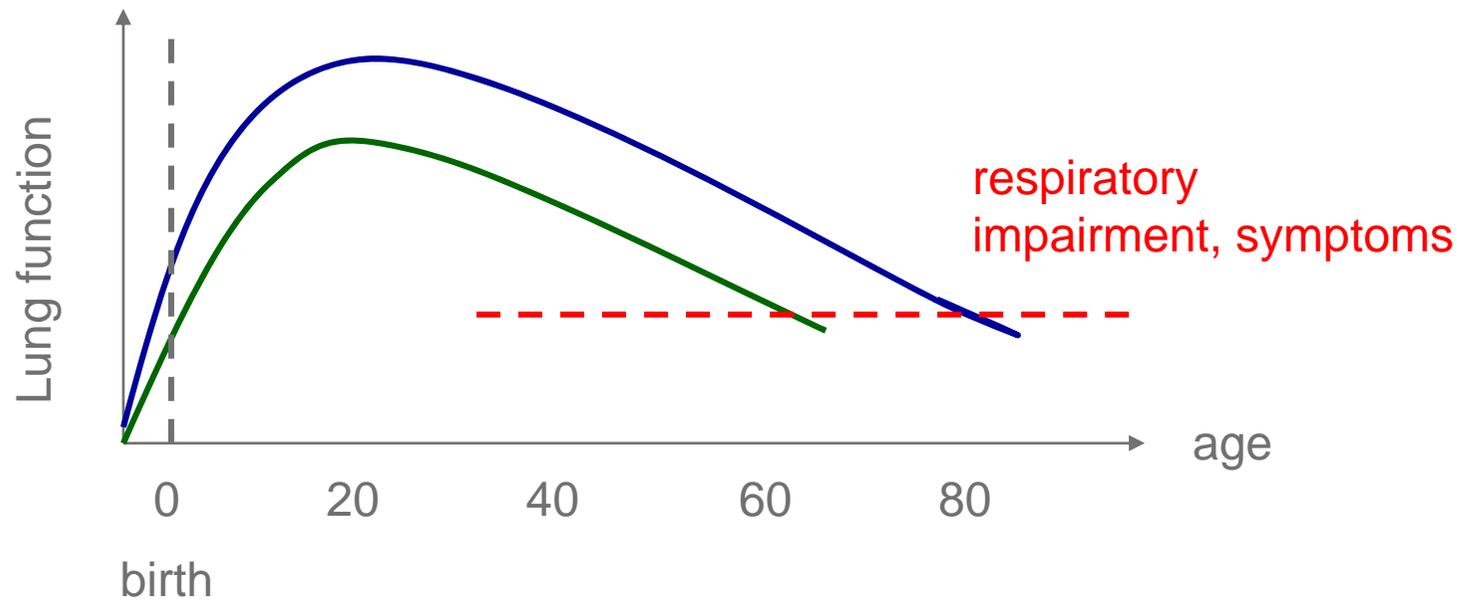
## **Non-invasive lung function in unsedated infants**

# Air pollution during pregnancy and lung function in the neonates

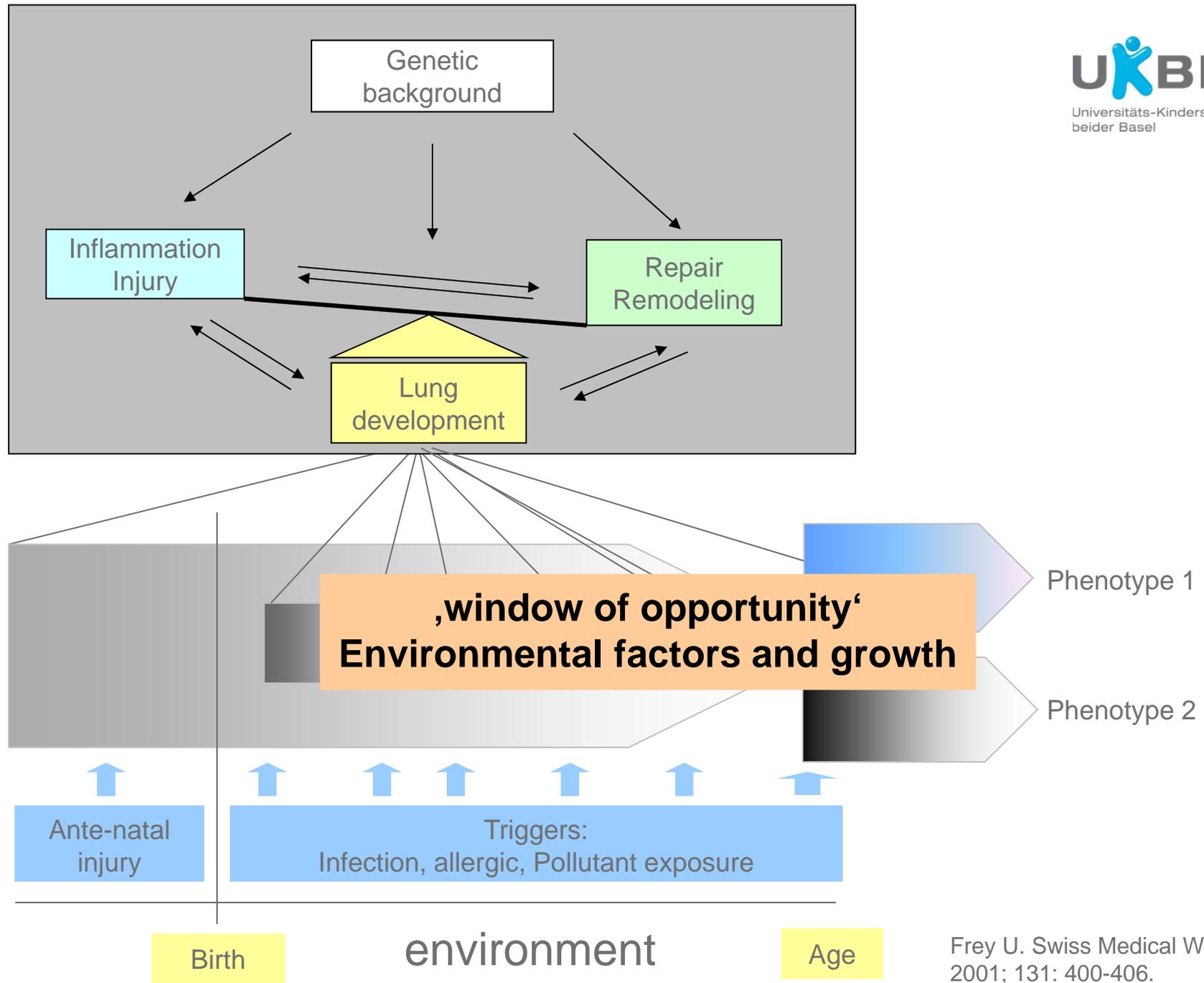


Latzin et al. Eur Resp J 2009; 33: 594-603

# Impact of lung development on respiratory morbidity in the elderly



Speizer FE, Tager IB. Epidemiol Rev 1979; 1: 124



# Summary

- **Pre and postnatal effects on infant mortality and morbidity are well established**
- **Effect have been shown for NO<sub>2</sub>, ozone and particulate matter, however no epidemiological studies exist for nanoparticles**
- **Nano-particles can cross placenta and further research in infants is needed**
- **There are especially vulnerable phases of lung and immun-development in early infancy ('window of opportunity')**
- **A small impact in early infancy may have a strong impact on respiratory morbidity in the elderly and may lead to significant health care costs.**

# University Children's Hospital Basel (UKBB)

Basel-Bern infant lung  
development cohort (SNF)

Botnar Research Professor for  
Paediatric Respiratory Medicine



Frey- ETH 2013



Strong collaboration with

Swiss TPH Basel  
SAPALDIA