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Air pollution during pregnancy and lung development in the child

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EDUCATIONAL AIMS

The reader will come to appreciate that:

- Air pollution in pregnancy leads to adverse birth effects.
- Air pollution in pregnancy influences postnatal lung development and respiratory health.
- There is interplay of direct and indirect impacts of prenatal air pollution on lung health.
- Environmental and epigenetic factors and individual exposure may contribute to the heterogeneous effects in different subjects.

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SUMMARY

Air pollution exposure has increased extensively in recent years and there is considerable evidence that exposure to particulate matter can lead to adverse respiratory outcomes. The health impacts of exposure to air pollution during the prenatal period is especially concerning as it can impair organogenesis and organ development, which can lead to long-term complications. Exposure to air pollution during pregnancy affects respiratory health in different ways. Lung development might be impaired by air pollution indirectly by causing lower birth weight, premature birth or disturbed development of the immune system. Exposure to air pollution during pregnancy has also been linked to decreased lung function in infancy and childhood, increased respiratory symptoms, and the development of childhood asthma. In addition, impaired lung development contributes to infant mortality. The mechanisms of how prenatal air pollution affects the lungs are not fully understood, but likely involve interplay of environmental and epigenetic effects. The current epidemiological evidence on the effect of air pollution during pregnancy on lung function and children's respiratory health is summarized in this review. While evidence for the adverse effects of prenatal air pollution on lung development and health continue to mount, rigorous actions must be taken to reduce air pollution exposure and thus long-term respiratory morbidity and mortality.

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INTRODUCTION

Exposure to air pollution *in-utero* has long-term implications for respiratory health. Exposure events during pregnancy can significantly influence foetal and postnatal development and maturation. Germ and foetal cells are particularly sensitive to external exposure events due to their faster rates of replication, faster differentiation and higher sensitivity to surrounding signals compared with mature cells [1]. Prenatal environmental exposures may lead to an impaired organ development resulting in long term complications and disease in later life [2]. There is also growing evidence that environmental factors may affect gene expression permanently with trans-generational effects of intrauterine exposures. Children whose grandmothers smoked during pregnancy have a higher risk of developing asthma, independent of the smoking activity of the mother [3]. These data suggest an interplay

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of environmental and epigenetic effects [4,5], and thus exposure events might influence prenatal development heterogeneously in individuals.

The importance of air pollution on respiratory health is amplified through its broad exposure. Although the health impact of air pollution on the individual might be smaller than other dangerous exposures, such as tobacco smoke, its significance as an environmental toxicant is ubiquitous as it cannot be avoided and affects large numbers of individuals. Evidence on the effects of prenatal exposure to tobacco smoke [6] and adverse effects of air pollution on neonatal health in general are reviewed elsewhere in detail [7–10]. Exposure to air pollution during pregnancy plays also an important role in lung development and has been shown to affect respiratory health in different ways. Lung disease is a leading cause of morbidity and mortality world-wide, therefore, the effect of air pollution on lung health is of great interest, especially from a public health point of view [11]. This review will summarize current epidemiological evidence on the effects of air pollution exposure during pregnancy on lung function in childhood and children's respiratory health. As premature birth, lower birth weight and impaired development of the immune system could be associated with later respiratory disease in life, we also briefly summarize the influence of air pollution on these risk factors in this review.

LUNG AND AIRWAY DEVELOPMENT

Lung morphogenesis and development of airways begin at 4-7 weeks of gestation and reaches the alveolar phase at around 36 weeks of gestational age. Alveolarisation continues until adolescence or even early adulthood [12], thus, compared to other organs, the maturational process of the lung takes place over a relatively long time period. During early pregnancy, cellular differentiation and branching morphogenesis can be disturbed, whereas in late pregnancy, an impairment of structural and functional growth of the lung can occur [2]. Environmental exposures, including air pollution, can lead to a disturbed alveolarisation and thus impairment of lung development and function after birth [13,14]. In addition, repair mechanisms of the developing lung tissue are not as efficient as those of the mature lung and therefore, the immature lung is more vulnerable to respiratory insults [2]. Evidence exists for a negative effect of postnatal air pollution exposure on lung function outcomes. Large epidemiological studies have shown that increased exposure to outdoor air pollutants during early postnatal life is associated with reduced lung growth and impaired development in children [11,15,16]. Evidence for an effect of prenatal exposure to outdoor air pollution on lung development and respiratory health is less well established, but some studies exist and those will be summarized in the following sections.

AIR POLLUTION DURING PREGNANCY AND LUNG FUNCTION IN CHILDHOOD

A number of studies, in both unselected and in asthmatic children, have reported associations between maternal exposure to different pollutants during pregnancy and impaired lung function during infancy and childhood. Those studies are summarized in Table 1.

In the BILD (Basel-Bern infant lung development cohort) study [17], a prospective birth cohort study of unselected infants, air pollution exposure was assessed during pregnancy and lung function measurements were performed at the postnatal age of five weeks in 241 neonates [18]. Increased minute ventilation, higher respiratory rate and tidal breathing flows in newborns were associated with higher maternal PM_{10} exposure during pregnancy, with the association strongest for the last trimester of pregnancy [18]. This suggests that prenatal exposure to air pollution may affect lung development. Importantly, the exposure to air pollution during the comparably short postnatal period was also assessed, but no consistent association for the examined pollutants was found, indicating that prenatal exposure had a greater influence on lung development. While this is the only study to investigate the association between prenatal air pollution exposure and lung function in infancy, a number of studies have examined associations with lung function later in childhood. One study in 620 children in the USA showed that higher NO_2 and benzene levels in pregnancy were associated with decreased lung function parameters (forced expiratory volume (FEV_1), forced vital capacity (FVC), peak expiratory flow (PEF)) at the age of 4.5 years [19]. Results were mainly driven by a high association in the second trimester and were significant after adjustment for maternal and paternal smoking during pregnancy. Postnatal and current air pollution exposure measurements were not associated with lung function measures, thus supporting the findings of the BILD study. Other studies have investigated the effect of prenatal air pollution exposure on pulmonary outcomes in childhood. A number of studies by Jedrychowski and colleagues used Personal Environmental Monitoring Samplers (PEMS) to monitor individual exposure to air pollution, although this method did not allow for indoor and outdoor pollution to be distinguished. In one study, exposure to prenatal and residential polycyclic aromatic hydrocarbons (PAH) was associated with a decrease in FEV_1 and forced expiratory flow 25-75% (FEF_{25-75}) when measured between 5 and 9 years of age in non-asthmatic children. The results suggested a possible additive effect of prenatal and postnatal exposure of PAH on lung function outcomes [20]. Both parameters showed significant associations if analysed in the same model, although further studies might be needed to clearly disentangle pre- and postnatal effects. The authors also demonstrated reduced FVC and FEV_1 values at the age of five years, if mothers were exposed to higher $PM_{2.5}$ during pregnancy [21]. A limitation of these studies is that $PM_{2.5}$ was only measured at one time point, in the second trimester of pregnancy, and postnatal exposure was not assessed. Investigation into prenatal and early childhood air pollution exposure on lung function in asthmatic children at 6-11 years of age showed consistent evidence for negative associations between prenatal exposure to air pollution and FVC, PEF and FEV_1 [22]. The strongest effects were found for NO_2 in the second trimester and PM_{10} in the first trimester of pregnancy, while CO seemed to have the strongest effect post-natally.

In summary, there is some evidence for an adverse impact of prenatal air pollution exposure on lung function in infancy and childhood in both unselected and asthmatic children. Effects were seen using various lung function measurements and remained significant after taking postnatal air pollution exposure as well as tobacco exposure into account. Nevertheless, data remains scarce. It is unclear which stage of pregnancy the developing lung is most vulnerable to air pollution exposure. In addition, publication bias may be a factor as no negative studies have been published. Further air pollution research is needed to better understand the specific effects of different pollutants at various stages of lung development.

AIR POLLUTION DURING PREGNANCY AND RESPIRATORY HEALTH IN CHILDREN

If prenatal exposure to air pollution leads to impaired lung growth and airway development, it is likely that air pollution also leads to increased respiratory morbidity in those children. Indeed, a number of studies have found associations between prenatal exposure to air pollution and respiratory symptoms (detailed results are presented in Table 2). Jedrychowski and co-authors

Table 1
Air pollution during pregnancy and effects on postnatal lung function.

Reference	Area	Exposure Assessment	Pollutant mean (IQR)	Study size	Age at lung function	Results	Exposure unit
			NO_2 μg/m³				
Latzin 2009 [18]	Switzerland	LUR	15.8 (14.7 – 17.0) prenatal 15.1 (10.9 – 19.7) postnatal	241	5 weeks	adjusted Coef (95% CI): MV: 12.5 (-12.4 – 37.5) TEF: 0.61 (-0.33 – 1.54) RR: 1.50 (0.52 – 2.49) TIF: 0.07 (-0.81 – 0.95) TV: -0.78 (-1.30 – -0.27)	1 μg/m³ increase in mean
Morales 2014 [19]	USA	LUR	25.60 (17.40 – 31.66)* 25.80 (16.76 – 33.48)** 25.63 (16.96 – 33.10)*** 25.87 (16.88 – 33.26)**** 27.59 (19.84 – 33.59)*****	620	4.5 years	**FVC** estimates (ml), adjusted Coef (95% CI): -28.9 (-58.5 – 0.6) * -19.8 (-48.7 – 9.0) ** -32.8 (-61.2 – -4.4)*** -25.5 (-54.4 – 3.5) **** -13.5 (−41.3 – 14.3) ***** **FEV_1** estimates (ml), adjusted Coef (95% CI): -26.1 (-51.9 – -0.2) * -20.4 (-45.6 – 4.8) ** -28.0 (-52.9 – -3.2) *** -21.9 (-47.2 – 3.4) **** -18.1 (-42.4 – 6.2) *****	IQR increase
Mortimer 2008 [22]	USA			232	6 – 11 years	FVC: -7.1% FEV_1: -1.2%	effect size per IQR increase
			$PM_{2.5}$ μg/m³				
Jedrychowski 2010 [21]	Poland	PEMS	32.4 (30.1)	176	5 years	adjusted Coef (95% CI): FVC: -10.97 (-80.37 – 58.42)⁺ -42.04 (-111.58 – 27.49)⁺⁺ -91.92 (-159.60 – -24.24)⁺⁺⁺ adjusted Coef (95% CI): FEV_1: -32.84 (-98.61 – 32.92) ⁺ -39.79 (-105.68 – 26.10)⁺⁺ -87.71 (-151.85 – -23.57) ⁺⁺⁺	quartiles of $Pm_{2.5}$ levels (reference lowest quartile)
			PM_{10} μg/m³				
Latzin 2009 [18]	Switzerland	LUR	prenatal 22.1 (20.2 – 23.8) postnatal: 20.0 (16.6 – 23.4)	241	5 weeks	adjusted Coef (95% CI): MV: 24.9 (9.3 – 40.5) TEF: 0.81 (0.22 – 1.40) TIF: 0.81 (0.26 – 1.36) RR: 1.15 (0.52 – 1.77) TV: -0.23 (-0.56 – 0.10)	μg/m³ increase in mean
Mortimer 2008 [22]	USA - Atlanta	n.a.	n.a.	232	6-11 years	PEF -7.8% FEF25: -5.6%	effect size per IQR increase
			Other pollutants				
Morales 2014 [19]	USA	LUR	Benzene μg/m³ 0.83 (0.66 – 0.96)* 0.83 (0.62 – 0.98)** 0.83 (0.62 – 0.98)*** 0.84 (0.65 – 0.99)**** 0.87 (0.70 – 1.01)*****	620	4.5 years	**FVC** estimates (ml), adjusted Coef (95% CI): -15.0 (-33.9 – 4.0) * -10.2 (-28.6 – 8.3) ** -18.0 (-36.7 – 0.7) *** -13.9 (-32.6 – 4.9) **** -3.2 (-21.7 – 15.2) ***** **FEV1** estimates (ml), adjusted Coef (95% CI): -16.3 (-32.9 – 0.2) * -13.4 (-29.5 – 2.7) ** -18.4 (-34.8 – -2.1) *** -13.8 (-30.2 – 2.6) **** -8.8 (-24.9 – 7.3) *****	IQR increase
Jedrychowski 2014 [20]	Poland	PEMS	PAH ng/m³ Prenatal 20.1 (95% CI 17.1 – 23.7) Postnatal indoor 21.3 (17.8 – 28.5) Postnatal outdoor 32.5 (25.5 – 39.9)	195	5 - 9 years	FVC: -36.4 (-89.3 – 16.5) -39.7 (-96.7 – 17.4) # Fev1: -34.8 (-83.2 – 13.6) -61.6 (-113.8 – -9.4) # FEF_{25-75}: 6.8 (-113.92 – 126.8) -167.3 (-297.0 – -38.0) #	tertiles of PAH, (reference lowest tertile)
Mortimer 2008 [22]	USA		CO n.a.	232	6 – 11 years	FEF25-75: - 0.9% FEV1/FVC: - 2.5% FEF25: - 6.7%	effect size per IQR increase

*entire pregnancy; **first trimester; ***second trimester; ****third trimester;*****first year of life; [i]indoor, [o]outdoor.
''in utero values adjusted for postnatal values of air pollution data.
⁺second quartile, ⁺⁺ third quartile, ⁺⁺⁺fourth quartile; #second tertile, ## third tertile.
MV: Minute ventilation'' $mLmin^{-1}$, RR: Respiratory rate breaths?min-1, TV: Tidal volume mL, TEF: Mean tidal expiratory flow mLs^{-1}, TIF: Mean tidal inspiratory flow mLs^{-1}.
PEMS: personal environmental monitoring sampler, LUR: land use regression, IDW: inverse distance weighted.
AOR: adjusted Odds Ratio, ARR: adjusted relative risk, AIRR: adjusted incidence rate ratios, Coef: Coefficent; CI: Confidence interval.

Table 2
Air pollution during pregnancy and effects on respiratory symptoms and asthma prevalence.

Reference	Area	Exposure Assessment	Pollutant – mean (IQR)	Study size	Age of symptom assessment	Results	Exposure unit
			NO_2 μg/m³				
Esplugues 2011 [26]	Spain	LUR	39.1 (31.6 – 48.6)* 38.8 (28.7 – 50.2)** 39.8 (29.3 – 50.3)*** 38.7 (29.8 – 48.6)**** 19.7 (11.6 – 26.1)*****i 27.4 (18.6 – 37.1)*****o	352	First year	LRTI AOR (95% CI): 1.18(0.92 – 1.53)* 1.18 (0.94 – 1.48)** 1.13 (0.89 – 1.43)*** 1.14 (0.90 – 1.46)**** 1.02 (0.82 –1.27)*****i 0.94 (0.78 – 1.15)*****o Persist. cough AOR (95% CI): 1.50 (0.91 – 2.48)* 1.37 (0.90 – 2.09)** 1.47 (0.93 – 2.33)*** 1.35 (0.85 – 2.14)**** 1.34 (0.96 – 1.86)*****i 1.40 (1.02 – 1.92)*****o	per 10 μg/m³ increase
Aguilera 2013 [27]	Spain	LUR	n.a.	2199	12– 18 months	ARR (95% CI)): 1.05 (0.98 – 1.12)* 1.06 (1.00 – 1.12)** 1.08 (1.02 – 1.15)*** 1.00 (0.93 – 1.07)**** 1.03 (0.95 – 1.11)*****	10 μg/m³ increase
Deng 2016 [30]	China	IDW	46 (40 – 52)* 45 (37 – 53)** 46 (39 – 54)*** 46 (38 – 53)****	2598	3 – 6 years	AOR (95% CI):: 1.63 (0.99 – 2.70)* 1.43 (0.89 – 2.28)** 1.74(1.15 – 2.62)*** 1.40 (0.90 – 2.19)****	Per IQR increase
Clark 2010 [29]	Canada	IDW/LUR	IDW: controls: 30.74 (24.96 – 36.54) asthma: 31.37 (25.17 – 37.57) LUR: controls: 31.68 (25.7 – 35.07) asthma: 31.73 (25.96 – 35.16	37401	3 – 4 years	AOR (95% CI):: IDW: 1.10 (1.05 – 1.15) LUR: 1.02 (0.97 – 1.07) LUR": 0.98 (0.92 – 1.03)	Per 10 μg/m³
			$PM_{2.5}$ μg/m³				
Hsu 2014 [32]	USA	LUR	11.2 (10.2 – 11.8)	736	6 years	-	10 μg/m³ increase
Clark 2010 [29]	Canada	LUR/IDW	IDW: controls: 4.74 (4.07 – 5.58) asthma 4.71 (4.00 – 5.57) LUR: controls: 4.67 (3.08 – 5.98) asthma: 4.78 (3.19 – 6.02)	37401	3 – 4 years	AOR (95% CI): IDW: 0.95 (0.91 – 1.00) LUR: 1.02 (1.00 – 1.03)	μg/m³
Jedrychowski 2010 [23]	Poland	PEMS	33.3 (22.3 – 50.7)	339	0 – 2 years 3 – 4 years	AIRR (95% CI): Age < 2y: 1.38 (1.25 – 1.51) Age 3-4 y: 1.06 (0.92 – 1.22)	-
Jedrychowski 2013 [25]	Poland	PEMS	42.37 (27.55)	214	0 – 7 years	AOR (95% CI): 2.44 (1.12 – 5.36)	-
			PM_{10} μg/m³				
Deng 2016 [30,31]	China	IDW	110 (103 – 115)* 113 (102 –121)** 110 (101 – 118)*** 108 (97 – 116)****	2598	3 – 6 years	AOR (95% CI):: 0.90 (0.70 – 1.17)* 0.91 (0.69 – 1.19)** 0.86 (0.69 – 1.09)*** 0.76 (0.60 – 0.97)****	per IQR increase
Clark 2010 [29]	Canada	IDW	controls: 11.94 (11.08 – 12.85) asthma: 12.03 (11.21 – 12.89)	37401	3 – 4 years	AOR (95% CI): 1.09 (1.05 – 1.13) 1.10 (1.04 – 1.15)"	μg/m³
			Other pollutants				
Clark 2010 [29]	Canada	IDW/LUR	NO μg/m³ IDW: Controls: 19.82 (12.76 – 25.69) Asthma: 20.32 (12.74 – 27.15) LUR: Controls: 30.38 (21.71 – 35.99) Asthma: 31.03 (22.00 – 36.62)	37401	3 – 4 years	AOR (95% CI): IDW: 1.07 (1.03 – 1.12) LUR: 1.05 (1.02 – 1.09) LUR: 1.06 (1.01 – 1.11)	10 μg/m³
Clark 2010 [29]	Canada	IDW	CO μg/m³ Controls: 612.2 (507.7 – 698.8) Asthma: 618.8 (520.2 – 705.8)	37401	3 – 4 years	AOR (95% CI): 1.07 (1.04 – 1.10)	100 μg/m³
Clark 2010 [29]	Canada	IDW	SO_2 μg/m³ Controls: 5.11 (3.7 – 6.2) Asthma: 5.25 (3.69 – 6.74)	37401	3 – 4 years	AOR (95% CI): 1.03 (1.02 – 1.05)	1 μg/m³

Table 2 (*Continued*)

Reference	Area	Exposure Assessment	Pollutant – mean (IQR)	Study size	Age of symptom assessment	Results	Exposure unit
Aguilera 2013 [27]	Spain	LUR	Benzene $\mu g/m^3$	2199	12 – 18 months	ARR (95% CI): 1.05 (0.96 – 1.14)* 1.06 (0.99 – 1.13)** 1.10 (1.01 – 1.20)*** 0.99 (0.87 – 1.12)**** 1.02 (0.93 – 1.11)*****	1 $\mu g/m^3$ increase
Jedrychowski 2010 [23]	Poland	PEMS	PAH ng/m^3	339	0 – 2 years 3 – 4 years	AIRR (95% CI): age < 2 y: 1.69 (1.52 – 1.88) age 3-4y: 0.96 (0.83 – 1.09)	-
Jedrowski 2005 [24]	Poland	PUF	PAH ng/m^3 26.1 (22.9 – 29.7)	333	first year	ARR (95% CI): cough: 4.80 (2.73 – 8.44) wheeze: 3.83 (1.18 – 12.43)	per logunit PAH ng/m^3
Miyake 2010 [28]	Japan	-	Distance to main road	756	16 – 24 months	AOR (95% CI): <50 m: 4.01 (1.44 – 11.24) 50 to <100 m: 1.39 (0.36 – 4.54) 100 to <200 m: 2.38 (0.91 – 6.28) >=200 m: 1.00	distance in m (50m and 200 m)
Deng 2016 [30,31]	China	IDW	So2 $\mu g/m^3$ 82 (62 – 98)* 86 (60 – 103)** 82 (60 – 95)*** 79 (52 – 94)****	2598	3 – 6 years	AOR (95% CI): 1.00 (0.65 – 1.56)* 1.08 (0.78 – 1.50)** 1.03 (0.80 – 1.33)*** 0.95 (0.68 – 1.31)****	per IQR increase

*entire pregnancy; **first trimester; ***second trimester; ****third trimester;*****first year of life; [i]indoor, [o]outdoor.
''in utero values adjusted for postnatal values of air pollution data.
[+]second quartile, [++] third quartile, [+++]fourth quartile; [#]second tertile, [##] third tertile.
MV: Minute ventilation'' $mLmin^{-1}$, RR: Respiratory rate breaths?min-1, TV: Tidal volume mL, TEF: Mean tidal expiratory flow mLs^{-1}, TIF: Mean tidal inspiratory flow mLs^{-1}, LRTI: lower respiratory tract infection, persist.: persistent.
PEMS: personal environmental monitoring sampler, LUR: land use regression, IDW: inverse distance weighted.
AOR: adjusted Odds Ratio, ARR: adjusted relative risk, AIRR: adjusted incidence rate ratios, Coef: Coefficent; CI: Confidence interval.

show that prenatal $PM_{2.5}$ and PAH exposure are associated with more frequent episodes of wheezing in the first 2 years of life, but not at age 3 – 4 years [23]. One methodological drawback the authors point out is that postnatal environmental measurements were not performed and the effect of environmental tobacco smoke (ETS) could not clearly be disentangled due to high co-linearity with $PM_{2.5}$. The authors also found an association between PAH exposure and increased frequency and duration of respiratory symptoms in general [24] and of $PM_{2.5}$ with recurrent pulmonary infections until the age of 7 years [25]. The latter effect was independent of current indoor levels of $PM_{2.5}$. Outdoor exposure to $PM_{2.5}$ was not assessed and repeated $PM_{2.5}$ measurements during pregnancy were only performed in a subgroup of the study population, which could have biased the results. Two studies in Spain investigated prenatal and early postnatal exposure to NO_2 and respiratory symptoms during the first year of life [26,27]. A study in 2,199 children showed an association of respiratory symptoms with pre- and postnatal NO_2 exposure. However, as both were highly correlated, the authors were not able to disentangle the relative importance of each exposure [27]. A smaller study in 352 children found significant associations only for postnatal NO_2 measurements and a non-significant trend for prenatal exposure [26]. A Japanese study showed a correlation between residency close to main roads and doctor diagnosed asthma at the age of two, but not with the risk of wheeze [28]. However, asthma diagnosis at this age is difficult, especially if not consistent with wheezing episodes.

Concordant with findings in lung function measurements, air pollution does not only affect early respiratory symptoms, but also the development of asthma later in life. In a large case-control study including 37,401 subjects, a positive association of the incidence of asthma at age of 3-4 years with individual exposure to air pollution during gestational time and the first year of life could be found [29]. The results were confirmed in different smaller studies [30–32]. An association between NO_2 in the second trimester and PM_{10} in the first trimester of pregnancy and asthma prevalence at age 3-6 years was found even after the model was adjusted for exposure to ETS and different pollutants in the statistical model [30]. Because pre- and postnatal measurements of air pollution were highly correlated, the effect exposures at different time periods could not been distinguished [31]. In addition, estimated maternal air pollution exposure was calculated retrospectively, using the monitoring stations nearest to the later kindergarten of the child, verifying the measured values during the gestational period, irrespective of the home address of the families. A recent study in 736 children showed an association between prenatal $PM_{2.5}$ exposure and later asthma in boys. The authors frequently assessed PM values during pregnancy to achieve accurate results and detect vulnerable time windows during pregnancy, but postnatal $PM_{2.5}$ was not assessed [32].

The available studies clearly suggest an association between air pollution exposure in pregnancy and respiratory health in childhood. However, they also reveal how difficult it can be to distinguish between the effects of different environmental exposures as well as different exposure periods during pre- and post-natal development.

AIR POLLUTION DURING PREGNANCY AND PREMATURITY AND LOW BIRTH WEIGHT

It is well established, that premature birth and/or low birth weight (LBW) are risk factors for a worse respiratory outcome later in life, including more frequent respiratory symptoms and lower lung function measurements [33–37]. Thus, the association between air pollution and premature birth and/or LBW needs to be taken into account. Both premature birth and LBW are important markers of intrauterine growth and development and are important predictors of morbidity. Both of these markers are routinely measured and easily obtainable from hospital charts, and are therefore often used as an outcome parameter for the impact of

prenatal air pollution. The association of prenatal exposure to air pollution with prematurity and LBW has been studied extensively. A number of studies show a clear impact of different air pollutants on prematurity [38–42] and LBW [43–45]. A large multicentre, multi-country study reported a clear effect of prenatal air pollution on LBW [46]. While most studies found positive associations between exposure to air pollution and adverse birth outcomes, results differ between studies [10,45,47]. Meta-analyses and reviews of the topic suggest that comparison between studies is difficult due to study heterogeneity, including different methods of exposure assessment, differences in absolute levels of pollutants, different study sizes and differences in land use between studies.

AIR POLLUTION DURING PREGNANCY AND THE DEVELOPMENT OF THE IMMUNE SYSTEM

Another aspect that has to be taken into account when investigating the impact of prenatal air pollution on respiratory health is the role of the immune system early in life, as it is known to strongly influence later asthma development [48,49]. Immune maturation and immune responses can be influenced by environmental exposures in early life [50] and thus, exposure to air pollution may influence immune programming [51]. Several studies have shown that maternal smoke exposure during pregnancy has strong influences on the immune system of neonates [52–54], however, data on maternal exposure to outdoor air pollution and an altered neonatal immune system remain scarce. A sub-study of the BILD cohort found an association between an attenuated expression of the cytokines IL-10 and IL-1ß in cord blood of unselected infants and higher prenatal exposure towards PM_{10} [55]. Other studies found an association of increased prenatal PAH and $PM_{2.5}$ exposure with decreased T lymphocytes, increased B lymphocytes, and higher natural killer cells in cord blood [56,57]. These studies postulated different mechanisms of action, which they related to the different stages of pregnancy they found to be the most vulnerable. Although further studies are needed, these results suggest that prenatal air pollution can play a role in the development of the immune system of the foetus.

AIR POLLUTION DURING PREGNANCY AND INFANT MORTALITY

Good evidence exists for an association between air pollution exposure during pregnancy and infant mortality as reported in a 2005 World Health Organisation review [58]. As the leading cause of post-neonatal mortality is for respiratory reasons, the impact of air pollution exposure on infant mortality may be significant [59]. A large study with a population of 3,583,495 births including 6,639 post neonatal deaths in 96 counties throughout the United States showed elevated odds for respiratory mortality for infants exposed to the highest quartile of pollution (PM_{10} and $PM_{2.5}$) compared to the lowest quartile. Similar findings were reported in a study performed in South Korea [60], as well as in a meta-analysis of five studies on infant mortality in a framework of an estimation of years of life lost attributable to air pollution [61].

METHODOLOGICAL CONSIDERATIONS AND POSSIBLE MECHANISMS

To completely understand the associations between air pollution during pregnancy and lung health, important methodological issues regarding exposure assessment need to be considered. The precision of assessing individual exposure is crucial in estimating effects of air pollution on health. Estimating exposure during pregnancy is especially difficult, as women change their life style dramatically during pregnancy (e.g. stopping working, not performing the same sporting activities as usual or becoming less mobile in general). This occurs at individually different time points and as such cannot be estimated generally, but ideally is assessed individually. Importantly, the susceptibility of different organs to air pollutants strongly depends on the timing of exposure in relation to the stages of pregnancy and developmental process involved [55,57,62,63].

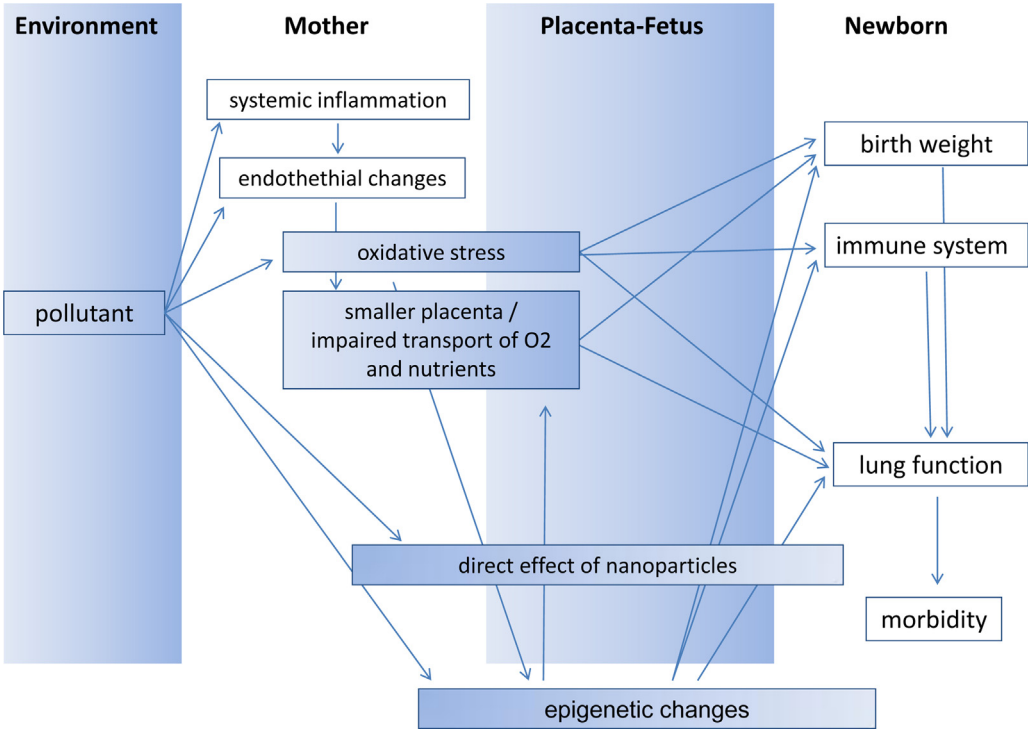

Figure 1. Direct and indirect impact of air pollution in pregnancy on adverse birth outcomes and lung development.

Table 3
Further research directions.

Limitations of past studies	Further research questions	Possible approaches
Different air pollution models are used in different studies	Validation of air pollution assessment	Develop standardized procedure
Air pollution measurements are not performed repeatedly during pregnancy	Find the vulnerable time windows during pregnancy	Air pollution prediction modelling [32,73]
Air pollution measurements are not performed pre- and postnatally	Distinguish between pre- and postnatal air pollution	Sophisticated statistical modelling with tests for interaction
Air pollution measurements are assessed both indoors and outdoors	Distinguish between indoor and outdoor pollution	Develop standardized procedure
Most studies are performed in countries with low or moderate pollution	Investigation of air pollution exposure in different areas with low, medium and high pollution	Multicenter, multicountry studies

The mechanisms by which particulate matter affects the foetus are still unclear to a large extent. Different reviews addressing that subject conclude that there is large evidence that the interplay of epigenetic and environmental influences lead to impairment of lung development, although the exact interaction is not fully understood [13,64,65]. It has been suggested that epigenetic mechanisms of lung gene regulation, DNA methylation, ATP-dependent complexes, and noncoding RNA might play a role [13]. Regulation of tumour suppressor genes, fibrosis and asthma related genes might be altered. An interaction between maternal smoking during pregnancy and regions of the IL-13 gene in childhood asthma has been shown [66]. A detailed review of current knowledge on toxicokinetics and toxicodynamics of pollutants in relation to health effects was published recently [10]. In general it is thought that pollutants inhaled by the pregnant mother either cross the alveoli and the placental barrier and act directly on the foetus, or more likely, lead to systemic immune or inflammatory reactions of the mother, which ultimately decrease foetal supply of nutrients and/or oxygen [67] (Figure 1).

Through the on-going exchange of nutrients and other elements during the progressing pregnancy, the effects of air pollution on lung development depend on the specific period of exposure during pregnancy [68]. Apart from very small particles, such as nanoparticles, that can cross the placental barrier via passive diffusion [69], larger air pollutants can pass the placental barrier more easily with progressing pregnancy. The heterogeneous effects of air pollution on different subjects exposed to similar pollutants can be explained with different physical-chemic interactions. This mainly depends on the size and the surface of the particle, and the fluid surrounding the particle, which will determine the solid-liquid interaction and potentially result in different effects [70].

Exposure to air pollution has increased dramatically over the last decades. Although humans have always been exposed to particulate matter, increased industry has changed the characteristics of particles. Natural aerosols have a larger volume and smaller surface per unit mass, whereas human produced particles can exhibit a more harmful configuration. Depending on size, shape and solubility, they enter the body mostly through the lung, interacting with the immune and inflammatory system, leading to mitochondrial malfunction, genetic-epigenetic effects [71,72] and may cause or trigger a number of diseases. During pregnancy, air pollution exposure does not only harm the mother, but can possibly have adverse effects on the fetus, during the extremely susceptible time of early organ development. [67].

CONCLUSION

As organogenesis of the lung continues throughout pregnancy, harmful effects of prenatal exposure to air pollutants on lung development seems inevitable and may continue to impact lung development later in life. Evidence for impaired lung function outcomes and increased respiratory symptoms following prenatal air pollution exposure are clearly supported by epidemiological studies. In addition to affecting lung development directly, air pollution exposure during pregnancy increases the risks of preterm birth, reduced birth weight and impaired development of the immune system, which may significantly influence respiratory morbidity later in life. Epidemiological data suggest that air pollution adversely affects birth outcomes known to play a role in lung development. Nevertheless these studies present inconsistent results and it remains difficult to distinguish between the impact of pre- and postnatal exposure as well as to define the vulnerable time window in pregnancy for the different pollutants. A standardized approach to assess air pollution is clearly needed to have comparable results between studies, as different models might present different results [19]. A recent study presented an approach to model air pollution exposure prediction, which might help to give more specific data points for the pollutants and will help to distinguish time points of effects individually [73]. Moreover, as a high number of the past studies have been conducted in areas with moderate or low pollution, further research in areas of high pollution is needed for a comprehensive understanding. While those questions need to be answered in future studies (see Table 3), the overall effect of air pollution on lung development and adverse outcome on respiratory health cannot be denied, clearly indicating the need for more stringent measures to reduce air pollution.

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DIRECTIONS FOR FUTURE RESEARCH

- Summarized in Table 3

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