Why do intrauterine exposure to air pollution and cigarette smoke increase the risk of asthma?

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Abstract

The prevalence of childhood asthma is increasing worldwide and increased in-utero exposure to environmental toxicants may play a major role. As current asthma treatments are not curative, understanding the mechanisms underlying the aetiology of asthma will allow better preventative strategies to be developed. This review focuses on the current understanding of how in-utero exposure to environmental factors increases the risk of developing asthma in children. Epidemiological studies show that maternal smoking and particulate matter exposure during pregnancy are prominent risk factors for the development of childhood asthma. We discuss the changes in the developing foetus due to reduced oxygen and nutrient delivery affected by intrauterine environmental change. This leads to foetal underdevelopment and abnormal lung structure. Concurrently an altered immune response and aberrant epithelial and mesenchymal cellular function occur possibly due to epigenetic reprogramming. The sequelae of these early life events are airway remodelling, airway hyperresponsiveness, and inflammation, the hallmark features of asthma. In summary, exposure to inhaled oxidants such as cigarette smoking or particulate matter increases the risk of childhood asthma and involves multiple mechanisms including impaired foetal lung development (structural changes), endocrine disorders, abnormal immune responses, and epigenetic modifications. These make it challenging to reduce the risk of asthma, but knowledge of the mechaisms can still help to develop personalised medicines.

Keywords: asthma; foetus; placental; smoking; particulate matter.

Introduction

Asthma is a disease that generally affects 5-20% of children globally (1, 2). It is a complex condition in which symptoms are mainly caused by bronchoconstriction (3). Airway constriction occurs rapidly in response to a variety of inhaled substances, for example, allergens such as pollen and house dust mite, and environmental sources such as dust and smoke, which usually can be fully or partially reversed by bronchodilators. Pathologically it is defined by airway remodelling, typified by increased smooth muscle and epithelial layer thickness, and increased numbers of inflammatory cells. However, the type of inflammation varies. For example, sputum based phenotyping of inflammation categorises people into eosinophilic, neutrophilic, or paucigranulocytic asthma. The other factors that can add to the complexity of asthma including the age of onset, aetiological cause (if known), co-existence of other respiratory diseases, comorbidities, the degree of reversibility, and the ability for the symptoms being effectively controlled by pharmaceutical interventions.

The susceptibility to asthma is complex, which involves both genetic sucipitibility, environmental insults (both pre and post birth), and is further complicated by asthma syptoms initating and sometimes ceasing at different ages, as well as differences in asthma prevalence between the male and female sexes.

It is known that boys are more susceptible than girls before puberty, but less than girls after puberty. Many therories exsist to explain this phenomina including: dysnapsis due to different sized lungs in boys and girls, increased allergy (more IgE production in boys), different innate and adaptive immune responces in boys and grils, and the influence of sex hormones (4-6). The incidence of asthma is also related to the use of life saving medical inteventions in premiture and newborn children such as oxygen supplementation or mechanical ventilation due to physical permanent damage to the newborn's lungs (7).

However, it has increasingly been recognised that certain factors during the intrauterine period affects childhood asthma susceptibility. In particular, maternal smoking (MSE) and particulate matter (PM) exposure (8, 9), are the best described/researched *in-utero* challenges which affect asthma sucipitibility. This review will discuss the current understanding of multiple mechanisms underlying these two factors, which may help to develop personalised medicines.

Epidemiology of asthma

The prevalence of allergic disorders has been rising since the early 1980s. The average global rate of allergic disorders is 22%, ranging from 15%-35% of the population in different countries (10). According to the WHO, the number of children with asthma is around 14% globally (11). Severe asthma is common in children. A recent study reported that the prevalence of severe asthma was 4.9% in 6-7 years old children, however, the incidence was increased to 6.9% in 13-14 years olds. These phenomena demonstrated that age is an important factor for the onset of asthma (12).

Environmental toxicant exposure during pregnancy is a significant factor that has been shown to increase the incidence of asthma (13). In particular, maternal smoke exposure (MSE) is the largest modifiable risk factor for the development of asthma. Although the harmful effect of smoking is well-known in the general public, smoking mothers find it difficult to quit due to nicotine addiction, even during pregnancy when nicotine metabolism is faster than non-pregnant status(14). A systematic review and meta-analysis in the Lancet showed that the top 3 countries with the highest smoking rate during pregnancy are Ireland (38.4%), Uruguay (29.7%) and Bulgaria (29.4%) (15). Even in Australia where anti-smoking legislation is one of the most aggressive in the world, the smoking rate in pregnant women is 11.7% (16).

Epidemiological studies have demonstrated a dose-dependent increase in asthma risk in offspring due to MSE (Table 1). Currently, several cohort studies have confirmed the association between MSE and asthma risk in the offspring (17-20). For example, a birth cohort study has found that women smoking during pregnancy could increase asthma incidence in the offspring with an adjusted hazard ratio of 1.79 (95% CI 1.20–2.67) (21). The same outcome has been found in another cohort study where MSE during pregnancy caused higher asthma risk in the child in the first year of life with an odds ratio (OR) of 1.83 (22). Similarly, a systematic review of 14 studies revealed a wheezing (OR 1.41 (95% CI 1.19–1.67)) and asthma risk (OR 1.85 (95% CI 1.35–2.53)) in 2 years old and younger children, followed by a higher asthmatic risk in 5–18 years old children (OR 1.23 (95% CI 1.12–1.36)) caused by smoking during pregnancy (18). One study found a strong asthma risk in 14 year old girls whose mothers smoked during pregnancy, however this was not found in boys (23); whereas a different study found that boys at the age of 11 are more susceptible to the maternal and postnatal secondhand smoke (24). These differences might be related to the changes in asthma prevelance in boys and girls around puberty.

Around 91% of the world's population are living in the areas where the levels of air pollutants exceed the WHO limits (25). Epidemiological studies demonstrated a strong association between pulmonary disease and particular matter (PM) exposure(9). Compared to cigarette smoking which can be avoided through quitting, the dangers of airborne pollution are hard to avoid in heavily polluted countries, such as China and India. In China, 74,000 premature deaths were attributed to $PM_{2.5}$ exposure in the year 2013 (26). It was estimated that 22% of these deaths could have been avoided if indoor $PM_{2.5}$ level met National Class I standards (26).

There are many different types of airborne pollution, but simplistically these can be divided into gasses and particulate matter (PM). PM is considered as particularly dangerous as respirable particles can remain airborne over large distances.

As shown in Table 2, prenatal PM exposure is also associated with childhood asthma. A cohort study found that prenatal PM_{10} exposure could cause pulmonary function changes with higher minute ventilation in newborns (27). Another birth cohort study including pre-school and school-age children demonstrated that prenatal PM_{10} exposure increased the risk of developing asthma in both age groups, especially for those pregnant mothers who lived near the highways (28). The correlation between maternal PM exposure and asthma risk in different genders was also investigated. High levels of $PM_{2.5}$ exposure during mid-gestation increased the development of asthma by the age of 6 years in boys, but not in girls (29). The above evidence indicates that maternal PM exposure during pregnancy has similar effects to MSE in terms of increasing the risks of developing asthma in childhood.

The difference of asthma prevalence between boys and girls and the change in prevalence which occurs around pubertiy naturally gives credance to the involvement of sex hormones. Animal models of estrogen receptor knockouts suggests that estrogen promotes the development of the asthma (30); while male mice lacking testosterone showed more severe asthma symptom (31). These studies help to explain why boys are more susceptible to asthma before puberty, and girls more susceptible after puberty. However, the eitology of asthma is complex and is multifactorial.

The role of oxidative stress in the development of asthma in children

Various chemicals can be found in both cigarette smoke and PM. It is unlikely that a single chemical is responsible for all the adverse effects of in-utero exposure to cigarette smoke or

PM on lung health in the offspring. Cigarette smoke and PM are two major environmental sources of inhaled free radicals and strong oxidants. The balance between excessive oxidant activity and the antioxidant capacity can tip in favour of excess oxidants causing oxidative stress. However, it is important to note that the production of oxidants is necessary to maintain healthy cell function, and important in regulating processes such as inflammatory responses. Oxidative stress induces adverse effects in tissues. The developing foetus is highly vulnerable to oxidative stress injury, as the immune system remains immature during the prenatal period (32). Free radicals and chemicals inhaled during MSE and maternal PM exposure can pass the blood-placental barrier to directly increase the level of oxidative stress in the offspring. Therefore, we propose the first common and prominent mechanism underlying these two factors to induce pathological changes in the offspring is oxidative stress.

Our previous studies in mice have repeatedly shown that MSE can reduce the level of endogenous antioxidant Manganese Superoxide Dismutase in the brain, kidney, and lungs of adult offspring accompanied by increased Reactive Oxygen Species (ROS) levels in those organs; interestingly, antioxidant supplementation during pregnancy could completely or partially reverse the adverbse effects on those organs induced by MSE (33-35). The endogenous antioxidant enzyme system is established in the second and third trimester of pregnancy and continues to develop in early childhood (36). Interestingly, lung development also matures in the early postnatal period, suggesting that the antioxidant system may protect early-life lung development from the adverse impacts of environmental oxidant pollutants (37). After all, the function of the respiratory system is vital for survival immediately after birth. Vitamin C is an antioxidant which contributes to cellular antioxidant defence(38, 39). A study in pigs found that vitamin C deficiency during pregnancy could cause brain damage in the offspring (40). Giving smoking women vitamin C during pregnancy was shown to improve lung function (better airflow and less wheezing) in children during the first year of life (41). This again provided evidence that oxidative stress and insufficient capacity of antioxidants play a key role in organ dysfunction in the offspring due to MSE. PM consists of metals and endotoxins (polycyclic aromatic hydrocarbons) which also can generate ROS (42) and produce oxidative damage (43). Therefore, the pathways associated with oxidative stress are regarded as playing an important role in inducing adverse respiratory outcomes after the exposure to environmental pollutants (44, 45).

In utero, any adverse effects that occur during foetal development can have long-lasting

negative influences on organ development and later function after birth (46, 47). In fact, local tissue oxidative stress and injury due to the imbalance between free radicals and antioxidant capacity is a key factor in asthma pathogenesis. As such we propose that oxidative stress is the pathological insult that drives changes in the intrauterine environment and disturbs normal foetal development which subsequently increases the risks of developing asthma. It is also worth noting that maternal smoking is a strong risk factor for miscarriage, a process also linked to oxidative stress (48).

Intrauterine growth restriction – The Barker Hypothesis

In 1990, the epidemiologist David Barker presented his hypothesis which linked chronic and degenerative diseases, such as heart disease, to the poor intrauterine environment caused intrauterine growth retardation (IUGR), low birth weight, and premature birth. This theory inspired scientists and has been expanded to the other organ systems including the respiratory system (49). Numerous studies have confirmed that environmental toxicant exposure during pregnancy, such as cigarette smoke, can cause IUGR and subsequently abnormal lung development in the offspring (49). Nicotine is the most widely studied component in cigarette smoke due to its addictive effects. Early studies showed that cotinine, the stable metabolite of nicotine, can be found in foetal circulation and body fluids (50). This indicates that chemicals in cigarette smoke can cross the blood-placental barrier and reach the foetus. A more recent study by Geelhoed *et al* showed that MSE can decrease blood flow in the ascending aorta because of higher arterial resistance in the uterus, which can reduce the oxygen and nutrient delivery to the growing foetus resulting in IUGR (51). Inadequate nutrient availability in the developing foetus, especially during the periods of rapid lung growth, has been shown to induce lung developmental defects (52, 53) and respiratory morbidity in the offspring (54, 55). Animal studies have demonstrated a decrease in both alveolarisation and vessel density in the lung of sheep with IUGR (56).

How do MSE and maternal PM exposure impact on foetal lung development?

In brief, MSE can induce such effects in two ways: the direct influence on the developing foetus, and indirect effects on the fetoplacental unit. Recently, studies have demonstrated that a small fraction of the circulating nicotine in the mothers can cross the trophoblastic membrane and reach the unborn child, and as such cotinine can accumulate in the foetal circulation and fluids in measurable concentrations (57, 58). Furthermore, a similar concentration of cotinine in both foetal lung tissue and blood was found, suggesting cotinine may bind to the receptors

in the lung to directly affect foetal lung development (59). Maternal air pollution exposure can also cause foetal growth restriction (60). Polycyclic aromatic hydrocarbons on the surface of PM can easily cross the blood-placental barrier and circulate in the foetal blood because of its small size (61). Therefore, lung development in the foetus can be directly affected by the PM inhaled by the mothers.

The fetoplacental unit has a significant influence on foetal development. The damage to fetoplacental unit caused by maternal smoking can be seen during early pregnancy. For example, MSE significantly increases villous membrane thicknesses and trophoblastic layer in the placenta during the first trimester (58). There are also signs of reduced capillary volume in placental vasculature in pregnant smokers (62). The consequence of reduced capillary volume is nutrient delivery decrement. Intrauterine nutrient deficiency has been suggested as the major factor contributing to foetal growth restriction and low birth weight due to MSE (63). Low birth weight can increase the asthma risk in later life, evidenced by a meta-analysis including 1.1 million people (64). In rat models, maternal PM exposure was found to change placental morphology, and decrease placental weight, size and surface area (65). Similar findings have also been confirmed in humans, where PM_{10} exposure can decrease placental weight with higher anti-angiogenic factors in cord blood (66). As a result, increased vascular resistance can be predicted, which will reduce uteroplacental perfusion and lead to various maternal and foetal complications, such as low birth weight and miscarriage (67-69).

The abovementioned evidence indicates that MSE and maternal PM exposure during pregnancy can impair foetal lung development through a direct effect on the foetus and indirect influence on placental morphology and function. However, the molecular mechanisms underlying the increased risk of asthma due to MSE and maternal PM exposure are not well understood. In monkeys, MSE upregulated nicotinic acetylcholine receptors in the foetal lung, associated with lung function decline after birth (70, 71). Several *in vitro* and *in vivo* animal models have also shown that both MSE and PM exposure during pregnancy affects the development of the neonatal immune system, lung structure, and lung function in the offspring, making them more susceptible to the development of asthma(72, 73). These will be discussed in greater detail later.

The development of asthma in children

The role of altered lung structure

Just as discussed above, MSE and maternal PM exposure during pregnancy can result in oxidative stress, and cause nutrition deficiency resulting in IUGR, which eventually alters lung development and structure. Foetal lung development starts from embryo Weeks 3-5 when the laryngotracheal groove forms on the floor of the foregut and matures during the early postnatal year. Therefore, inhaled environmental toxicants by pregnant mothers may change lung morphology and function as early as gestational Weeks 5-17 when epithelial and smooth muscle cell differentiation takes place. Epidemiological evidence well supports this theory, where significant lung function impairment was found in the newborns of mothers who smoked during pregnancy or inhaled high levels of PM (74, 75). Such lung function disorders can last until later childhood (76, 77). It needs to be noted that lung function deficiency in early life has been correlated with increased asthma incidence later on (78).

Lung dysfunction after birth can be attributed to lung structural changes during foetal development. Animal studies have shown that both MSE and maternal PM exposure could decrease lung volume, alveoli number and mean linear intercept in the offspring as well as reduced alveolar–bronchiolar attachment points (72, 73, 79). Nicotine as the 'addictive substance' in tobacco smoke has often been used in animal models to investigate the potential mechanisms underlying the adverse effects of maternal tobacco smoking. For example, increased airway collagen deposition and altered vascular structure were found in a monkey model after prenatal nicotine exposure (80, 81). However, it is uncertain if these results can be translated to humans as nicotine replacement therapy during pregnancy has not been found to be associated with the same adverse outcomes as maternal cigarette smoking (82) or nicotine administration in animal models (80, 81). This suggests that the whole constituent of tobacco smoke is needed to study the mechanism in animals.

The role of endocrine disorders.

Endocrine disruption during pregnancy is a potential cause of adverse pregnancy outcomes. Endocrine glands form an important part of the fetoplacental unit that can secrete a significant amount of hormones including the oestrogen to support pregnancy. Oestrogen plays a key role in regulating neuroendocrine homeostasis in the developing foetus and promotes Th2 immune cell development in the foetus (83, 84). A human study demonstrated that abnormal oestrogen level in pregnant mothers affects foetal development (85). A reduction in oestrogen and oestrone (a weak oestrogen) levels in the cord blood has been found if the mother smoked during pregnancy (86),(87). This is because smoking can produce an anti-oestrogenic effect

and induce androgenisation in pregnant mothers to disturb hormonal homeostasis (88). Such changes may influence the risk of asthma in offspring (89).

The evidence to prove the relationship between maternal PM exposure and its impact on endocrine homeostasis are scarce. It has been shown that the endocrine-disrupting chemicals (EDCs) on the surface of PM can disrupt sex hormone synthesis (90). Polycyclic aromatic hydrocarbons in both tobacco smoke and PM, can also affect steroidogenesis through inhibiting steroidogenic enzymes (91). However, there is no direct evidence suggesting the correlation between hormone change induced by maternal PM exposure and foetal lung development, neither is known about the risk of asthma in the offspring (92).

However, the information collected from cord blood at birth can't accurately reflect the changes in foetal lung development during particular sensitive windows of embryo development induced by MSE and Maternal PM exposure. Amniocentesis is an alternative method to measure hormone levels at different time points and explore endocrine disruption, but access is limited. Animal modelling may shed a light on the correlation between placental hormone changes and foetal lung development, as well as postnatal lung function and susceptibility to asthma. Future research can focus on this aspect to better understand the niche factors contributing to lung development and the risk of asthma.

The role of epigenetic programming

Programming is a term used to describe an altered phenotype due to changes in the *in utero* environment. Epigenetic programming describes stable inheritable phenotypic changes without the alteration in the DNA sequence. Such a process controls mRNA expression and protein production through changing the transcriptome, including DNA methylation and histone modifications. Mounting evidence has closely linked asthma to epigenetic programming due to intrauterine environmental changes. For example, asthma is also an inheritable disease (93). The parent-of-origin effect which is usually due to epigenetic mechanism, also shows a prominent influence on the development of asthma, eg. asthmatic mothers are more likely to have offspring with asthma than the asthmatic fathers (94). As mitochondrial DNA is 100% inherited from the mothers, epigenetic modification of this genome may largely contribute to this phenomenon. In addition, the foetal period is a vulnerable stage and thus very sensitive to environmental toxicant exposure, when maternal protection is vital. During embryogenesis,

cells divide rapidly and therefore the genome is in a relatively unstable status. During this period, oxidative stress induced by environmental toxicant exposure may easily interrupt genomic duplication process (95), leading to abnormal epigenetic modifications or even mutation, rendering the foetus susceptible to future chronic diseases after birth, such as asthma.

In a cohort study on MSE, CpGs methylation has been found on genes responding to the pollutants in tobacco smoke in the newborns of smokers who smoked during pregnancy (96). In addition, CpG methylation was also found in the genes involved in foetal development in cord blood by MSE, suggesting a mechanism by which MSE results in intrauterine underdevelopment (96). Previous studies have shown that maternal PM exposure could alter DNA methylation in the offspring. Prenatal PM_{10} exposure induced superoxide dismutase 2 (SOD2) protomer methylation in cord blood cells (97), which is related to phthalate and diisocyanate-induced asthma (98, 99). As the epigenetic changes are inheritable, they will change gene expression to affect normal embryo development and persist throughout life, resulting in the susceptibility to chronic diseases in later life (100). It may also result in the transfer of certain respiratory diseases to subsequent generations, such as asthma, establishing a family history. For a detailed review on epigenetic changes due to *in utero* oxidative challenges, please see Zakarya *et al*. 2019 (101).

The role of the immune response

The mother's immune system plays a central role in the protection of foetal development. The foetus and newborns need maternal antibodies (Ig) to protect them from infectious diseases (102). Previous studies have shown that parental smoking and PM exposure increased Ig E levels in the cord blood (43, 103). MSE and maternal PM exposure can also alter immune responses through activating inflammatory macrophages and memory B cells in the offspring (104, 105). These changes in immune responses suggest that MSE and maternal PM exposure can alter the innate and adaptive immune response in the offspring. In addition, MSE and maternal PM exposure have also been shown to delay the maturation of immune system [(106),(107)], which may also make such offspring more susceptible to allergic disorders.

Toll-like receptors (TLRs) play an important role in the neonatal immune response (108). MSE can inhibit neonatal immune system maturation through impairing TLR mediated responses (such as TLR2 and TLR9) (109). We also have similar observations in the brains of mice who are offspring which had MSE. At postnatal day 1, mRNA expression of TLR4 was decreased

in the offspring from MSE compared to those from Sham-exposed mothers, suggesting suppressed immune response or delayed maturation of immune response (110). However, TLR4 mRNA expression was increased in 13 weeks old offspring which had MSE along with increased inflammatory cytokines expression (110), suggesting that MSE has a sustainable influence on the immune system leading to heightened inflammatory cytokines production. Maternal PM exposure could induce similar adverse effects. High levels of TLR2 and TLR4 expression were found in the human offspring and animals from mothers exposed to increased levels of PM during pregnancy(106).

Asthma is typified by T cell dysregulation, including Th1, Th2 and Th17 cells (111). In most asthmatic patients, accumulating evidence shows the suppression of Th1 cytokines (for example IFNγ) with higher Th2 cytokine expression (IL-4, IL-5, and IL-13) (112). Furthermore, clinical data showed that allergic responses are more prevalent among the children who have developed attenuated Th1 responses during infancy (113). Similar changes were found in animal studies. In pregnant C57BL/6 mice, intranasal exposure to diesel exhaust particles has been shown to increase the Th2 cell percentage in the bronchoalveolar lavage fluid with higher levels of pro-inflammatory cytokines (IL-4 and IL-5) in the offspring with asthma (114). MSE was also shown to increase Th2 cytokines (IL-4 and IL-5) and other pro-inflammatory cytokines (such as IL6) with suppressed Th1 cytokines (IFN-γ) due to reduced NK cell activities (115, 116).

However, the immune response is complicated, and difficult to investigate from a broader spectrum. A study has found that $PM_{2.5}$ exposure differentially impacts the immune system at different stages of gestation. High level of CD3+ and CD4+ lymphocytes and low percentage of CD19+ lymphocytes and NK cells can be found in the cord blood during the early gestation; however, the opposite changes with low level of CD3+ and CD4+ lymphocytes and high percentage of CD19+ lymphocytes and NK cells were found if PM exposure occurs during late gestation (117). These studies suggest that immune response has been programmed by *in-utero* exposure to air pollution, however, future studies are needed to fully understand the extent of the changes in this system.

Conclusion and perspectives

In conclusion, cigarette smoking and PM exposure during pregnancy is detrimental to foetal development and increase the risk of childhood asthma. As summarised in Fig 1, Fig 2 and Fig

3, oxidants inhaled by the mother result in increased oxidative stress in the intrauterine environment. This results in persistent changes to both the structure of the lung and the epigenome, altering immune and endocrine systems. Collectively these changes increase the risk of childhood asthma. Although smoking cessation is preferred, the success rate remains low during pregnancy. Given the similarity between MSE and maternal PM exposure, antioxidant supplementation during pregnancy may be a plausible prophylactic strategy, which is yet to be confirmed by large clinical trials.

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Figure 1. MSE and maternal PM exposure can increase the rate of childhood asthma. MSE and maternal PM exposure can induce various adverse impacts on the foetus during different intrauterine developmental stages, such as DNA methylation, oxidative stress, inflammatory responses, and placental dysfunction. The resulting intrauterine growth retardation, low birth weight, and premature birth can increase the risk of childhood asthma with a lower alveolar number and reduced lung function, as well as increased lung inflammation.

Figure 2. MSE and maternal PM exposure increase oxidative stress in the womb which increases the risk of developing asthma due to the epigenetic modification of fetal DNA. Environmental toxicants can induce histone modifications and DNA methylation, which results in Th2 cytokine overproduction, eosinophils accumulation, goblet cell hyperplasia, and mucin hypersecretion.

Figure 3. MSE and maternal PM exposure can dysregulate the immune system in the foetus. The numbers of Th2 and Th17 cells are increased with a lower number of Th1 cells. This is caused by several epigenetic mechanisms, for example, miRNA 223 is increased in Treg cells. B cell and macrophages differentiation are also affected, and a lower number of NK cells are found.

801 **Table 1. Maternal smoking during pregnancy and the risk of asthma in children**

Smoking exposure	Age	Relative risk Odds ratio (95% CI)		References
		Male	Female	
Smoker at some stage	14 years	1.15 (1.01-1.72)	1.25 (0.85-1.22)	(118)
>20 cigarettes (early and late)	14 years	0.57 (0.20-1.60)	1.09 (0.47-2.51)	(118)
Total of 1–9 cigarettes/day	4-16 years	1:19 (0.98, 1.43)		(119)
< 10 Cigarettes per day	7 years	1.20 (1.04, 1.38)		(120)
Total of ≥10 cigarettes/day	<5 years	1.68 (1.10 to 2.58)		(121)
> 10 Cigarettes per day	7 years	1.31 (1.09, 1.58)		(120)
Total of ≥10 cigarettes/day	4-16 years	1:66 (1.29, 2.15)		(119)
Smoking during pregnancy	First 3 years	1.88 (1.14 – 3.12)		(122)
Smoking during pregnancy	4-6 years	1.65 (1.18–2.31)		(123)
Smoking during pregnancy	2-7 years	1.7(1.2-2.2)		(124)
Smoking during pregnancy	5-9 years	0.97 (0.51 to 1.84)		(125)
Smoking during pregnancy	14 years	1.49 (0.91–2.45)		(126)
Smoking during pregnancy	7-16 years	0.99 (0.78 to 1.25)		(127)

802

803 **Table 2. Maternal PM exposure and the development of asthma in offspring**

Pollutant	Age	Concentration increase	Relative Risk	References
$PM_{2.5}$	6 years	1.7 μg/m^3 (per IQR)	1.15(1.03-1.26)	(128)
$PM_{2.5}$	3-4 years	1 μg/m^3 (exposure interval)	0.95 (0.91–1.00)	(129)
$PM_{2.5}$	0-5years	1.45 μg/m^3 (per IQR)	0.99 (0.97–1.01)	(130)
$PM_{2.5}$	6-10 years	1.46 μg/m^3 (per IQR)	1.01 (0.97–1.06)	(130)
$PM_{2.5}$	0-6years	3.7 μg/m^3 (per IQR)	1.01 (0.99 – 1.04)	(131)
PM_{10}	3-6 years	12 μg/m^3 (per IQR)	0.89 (0.68, 1.16)	(132)
PM_{10}	3-4 years	1 μg/m^3 (exposure interval)	1.09 (1.05–1.13)	(129)
PM_{10}	0-5years	1.3 μg/m^3 (per IQR)	1.12 (1.05–1.19)	(130)
PM_{10}	6-10 years	1.36 μg/m^3 (per IQR)	1.09 (0.96–1.24)	(130)

804 IQR: interquartile range.

805 **Table 3. Clinical evidence of the adverse impacts of MSE and maternal PM exposure**

Pollutant	Sample collecting time (gestation)	Adverse impact	References	
Maternal Smoking	9-14 weeks	High villous membrane and trophoblastic layer thicknesses	(133)	Placenta
Maternal Smoking	-	Smaller villous capillaries and high basement membrane thickness	(134)	
Maternal Smoking	-	High villous membrane thickness	(135)	
Maternal Smoking	28 +/- 1 weeks	Decreased uterine artery volume	(136)	
Maternal Smoking	1st trimester	More NK cells and macrophages, less regulatory T cells	(104)	Immune cells regulation
Maternal Smoking	34th week	Lower Treg cell numbers	(137)	
Maternal Smoking	After delivery	Attenuated innate immune responses	(107)	
Maternal Smoking	During gestation	DNA methylation in cord blood cells	(138)	Epigenetics
Maternal Smoking	6–28 weeks infants	Lower antioxidant level and high oxidative stress level	(139)	Oxidative stress
Maternal Smoking	3 months infants	higher markers of oxidative stress	(47)	
PM_{10}	1st and 2nd-trimester	Lower Pro- and anti-angiogenic factors and PlGF	(140)	Placenta
$PM_{2.5}$	Early /late gestation	Higher CD3+ and CD4+ lymphocytes and lower CD19+ and NK cell number during early gestation, which were opposite in the late gestation	(117)	Immune cells regulation
$PM_{2.5}$	After delivery	Higher GSTP1 methylation	(32)	Epigenetics
$PM_{2.5}$	During gestation	Higher 3-NTp levels (oxidative stress)	(141)	Oxidative stress

806

807 GSTP1: Glutathione S-Transferase Pi 1. 3-NTp: 3-nitrotyrosine; MSE: Maternal smoke
808 exposure; NK cells: Natural Killing cells. PlGF: Placental Growth Factor; PM: Particulate
809 Matter; Treg cells: T regular cells.