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REVIEW

Cardiovascular and metabolic influences of fetal smoke exposure

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Abstract Many epidemiological studies showed associations of low birth weight with cardiovascular disease, type 2 diabetes and obesity. The associations seem to be consistent and stronger among subjects with a postnatal catch up growth. It has been suggested that developmental changes in response to adverse fetal exposures might lead to changes in the fetal anatomy and physiology. These adaptations may be beneficial for short term, but may lead to common diseases in adulthood. Maternal smoking during pregnancy is one of the most important adverse fetal exposures in Western countries, and is known to be associated with a 150–200 g lower birth weight. An accumulating body of evidence suggests that maternal smoking during pregnancy might be involved in pathways leading to both low birth weight and common diseases, including cardiovascular disease, type 2 diabetes and obesity, in adulthood. In this review, we discuss epidemiological studies focused on the associations of maternal smoking with fetal growth and development and cardiovascular and metabolic disease in later life. We also discuss potential biological mechanisms, and challenges for future epidemiological studies.

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Introduction

Cardiovascular disease, type 2 diabetes and obesity are common diseases with major impact on morbidity and mortality in adulthood [1–4]. Multiple epidemiological studies, of which many have been published in *the European Journal of Epidemiology*, identified various risk factors in childhood and adulthood for these diseases [5–35]. The *developmental origins of health and disease* hypothesis postulates that adverse fetal exposures lead to permanent fetal adaptations in structure, physiology and metabolism [36]. These adaptations might be beneficial for short term fetal survival, but may lead to fetal growth retardation and cardiovascular and metabolic diseases in adulthood [36]. Strong support for this hypothesis comes from many epidemiological studies showing that low birth weight is associated with increased risks of cardiovascular disease, type 2 diabetes and obesity [37–41]. However, the effect estimates for the associations between low birth weight and diseases in later life seem to be small and underlying causal mechanisms are unknown [38–41]. Since the same birth weight might be the result of various fetal exposures and growth patterns, low birth weight is unlikely to be the causal factor per se leading to of cardiovascular disease, diabetes and obesity. Maternal smoking is one of the most important modifiable adverse risk factors for low birth weight in Western countries, and might be involved in the underlying mechanisms [29].

In this review, we discuss epidemiological studies focused on the associations of maternal smoking during pregnancy with fetal growth and cardiovascular and

metabolic disease in the offspring, the potential role of fetal smoke exposure in the mechanisms underlying the associations between low birth weight and diseases in later life, and challenges for future epidemiological studies.

Maternal smoking during pregnancy and fetal development

Although the negative effects of smoking during pregnancy on fetal growth are well known, the prevalence of smoking during pregnancy is still high. In western countries, up to 25% of all pregnant women smoke during pregnancy [41]. Maternal smoking is one of the most important modifiable risk factors for low birth weight in Western countries [29]. The effects of maternal smoking during pregnancy on fetal outcomes seem to be dose and trimester dependent [42, 43]. It has been suggested that smoking during first trimester only and quitting thereafter, does not lead to increased risks of neonatal complications [42, 43]. Maternal smoking may primarily affect fetal peripheral tissue and skeletal growth. Fetal femur length is already affected from second trimester onwards [44]. Recently, it has been shown that first trimester fetal growth, as measured by crown-rump length, is also affected by maternal smoking [45].

The biological mechanisms by which maternal smoking during pregnancy influences fetal growth are not fully known. Various substances related to maternal smoking might be involved. Nicotine is an important teratogen and it induces vasoconstriction which leads to reduced placental blood flow and oxygen deprivation in the fetus [46]. Fetal vasoconstriction and impaired blood flow may lead to suboptimal hemodynamic stimulus for placental and fetal vascular development [47, 48]. Other toxins from maternal smoking also lead to reduced placental and fetal perfusion [48–51]. Some studies suggest that nicotine directly influences cell proliferation and differentiation, hereby affecting neural cell survival and the development of fetal neurotransmitter systems [49]. Another teratogenic element in smoking is carbon monoxide, which is rapidly absorbed in the blood where it binds to haemoglobin and forms carboxyhaemoglobin which results in hypoxia, and might be teratogenic and fetotoxic [50]. Animal studies show a direct negative effect of prenatal carbon monoxide exposure on cardiac maturation [51]. Cadmium is also a toxic constituent of tobacco smoke. It is known to accumulate in the placenta. In human trophoblast cells, cadmium inhibits activity of 11-β-hydroxysteroid dehydrogenase type 2 (11-β-HSD2). Reduced placental 11-β-HSD2 enzyme activity, needed for the metabolism of cortisol into the inactive cortisone, may lead to fetal growth restriction [52]. Other constituents, including additives present in cigarettes, have shown to be teratogenic or fetotoxic in animals, but their effect on the human fetus are largely unknown [53].

Although, the association of maternal smoking with low birth weight is well known, not much is known about the effects of maternal smoking on fetal organ function and development [54–61]. Among the offspring of mothers who continued smoking during pregnancy, the estimated fetal weight and birth weight were most severely affected in those with the highest umbilical artery resistance, suggesting that the effect of maternal smoking during pregnancy on fetal growth is at least partly mediated by placental and fetal circulatory adaptations. Third trimester umbilical artery resistance indices seem also to be associated with a reduced aortic root diameter in postnatal life [62]. These findings may suggest that increased arterial resistance in response to fetal smoke exposure affects the left atrium and aortic root development in postnatal life. The persistence of the increased arterial resistance during life may predispose a person to the development of critical hypertension, left ventricular hypertrophy and cardiovascular disease in adulthood [62]. It has also been suggested that continued smoking during pregnancy affects fetal kidney development. The effect size and direction depends on the number of cigarettes smoked. Smoking less than five cigarettes per day was associated with larger fetal combined kidney volume, whereas smoking more cigarettes leads to smaller fetal kidneys [63]. Thus far, epidemiological studies on the associations of maternal smoking during pregnancy on other fetal cardiac structures and metabolic profiles are lacking.

Maternal smoking and risk factors for cardiovascular disease and type 2 diabetes in adulthood

Accumulating body of evidence suggests that maternal smoking during pregnancy also affects the development of risks factors for cardiovascular disease and type 2 diabetes in the offspring. Fetal smoke exposure might lead to programming of the cardiovascular system [64]. Several studies have shown that blood pressure is higher among children of mothers who smoked during pregnancy [65–69]. However this association was not always clearly present [70]. It has been suggested that quitting smoking during early pregnancy prevent the adverse effects on the offspring blood pressure [66, 71]. Brion et al. assessed the associations of both maternal and paternal smoking during pregnancy on blood pressure in the offspring, and observed similar effect estimates for both maternal and paternal smoking. If maternal smoking would program the fetal cardiovascular system due to direct fetal exposure, stronger effect estimates would be observed for maternal than for paternal smoking [69]. Their finding may therefore suggest

that rather than direct intra uterine effects, general environmental mechanisms might be involved in the underlying mechanisms. Thus far, the study with the longest follow up has been performed in the United Kingdom. Power et al. demonstrated that maternal smoking during pregnancy was associated with higher blood pressure in adults aged 45 years [72].

The increase in blood pressure in childhood may predispose to development of hypertension and cardiovascular disease in later life. The association between smoking during pregnancy and elevated childhood blood pressure indicates that there might be an increase in peripheral vascular resistance which leads to decreased blood flow and oxygen delivery. One study with a small number of children showed that on the first postnatal day there is indeed less tissue oxygenation in children exposed to smoking in utero [73].

A long term follow-up study showed that fetal smoke exposure is associated with an increased rise in total cholesterol levels and appears to lead to an adverse lipoprotein profile. It has to be noticed that this effect was restricted to the offspring in the highest body mass index tertile [74]. Fetal smoke exposure may also negatively affect the vascular wall and eventually lead to atherosclerosis [75]. Recent studies in animals and young children support the hypothesis that maternal smoking during pregnancy negatively affects the lipid profile in childhood [76, 77].

Several studies have been published showing associations of maternal smoking with obesity in later life. It has been suggested that maternal smoking during pregnancy is associated with an increase in body weight from childhood until adulthood [72, 78–82]. Fetal tobacco exposure is associated with an increase in body mass index and waist circumference in adulthood [72]. A systematic review showed that smoking exposure in utero appears to increase the rate of overweight already in childhood [78]. A study on body fat composition in infancy showed no association between maternal smoking and subcutaneous fat mass in early childhood [83]. Recently, it has been shown that children of mothers who smoke only in first trimester of pregnancy, do not have a higher risk of overweight, suggesting that the second half of pregnancy is the critical time period [84]. In the same study, it has been shown that paternal smoking was not associated with obesity in the offspring, suggesting direct intra uterine effects.

No extensive research has been performed on the associations of maternal smoking during pregnancy with type 2 diabetes or impaired glucose tolerance in the offspring. However, recent animal studies suggest that fetal smoking exposure might cause metabolic changes which lead to type 2 diabetes [85, 86].

In summary, an accumulating body of evidence suggest that fetal smoke exposure is associated with risk factors for cardiovascular disease, type 2 diabetes and obesity. Thus far, results seem to be inconsistent and not much is known about the mechanisms underlying these associations.

Hypothesis

Based on the above mentioned findings, we hypothesise that fetal smoke exposure might be involved in the mechanisms underlying the associations between low birth weight and cardiovascular disease, obesity and type 2 diabetes (Fig. 1).

Perspectives for future research

Current studies showing associations of maternal smoking during pregnancy with risk factors for cardiovascular disease, type 2 diabetes and obesity do still have some major limitations. As in any observational study, residual confounding due to unmeasured or insufficiently measured confounders might be an issue. Besides fetal smoking exposure, there are several related maternal factors of influence on pregnancy outcomes [87–92]. Recently, it was concluded from meta-analyses and a systematic review that heavy alcohol consumption during pregnancy increases the risks of low birth weight, preterm birth and small for gestational age [92]. It has been suggested that fish consumption and high caffeine intake during pregnancy does not significantly affect birth weight [93, 94]. However, job circumstances during pregnancy might cause adverse effects, and exposure to pesticides is associated with decreased birth weight [95].

Study designs accounting for potential confounders on the effect of maternal smoking on postnatal outcome are needed. For example, studies which look at effects of paternal smoking among non-smoking mothers and studies which look at the effects of siblings exposed and non-exposed to maternal smoking [69, 84] When these possible confounders will be taken into account, it might be able to identify the specific intra uterine or general environmental effects of fetal smoke exposure [96–109].

Furthermore, future studies might use more detailed measurements [110–113]. Maternal smoking during pregnancy is most frequently measured by questionnaires. More objective measurements, such as cotinin levels might be useful. Also, for the outcomes, more detailed measurements of cardiovascular properties, such as pulse wave velocity, endothelial function, lipid spectrums and glucose responses might lead to better insight in the underlying vascular and metabolic mechanisms. Measurements of body composition by dual X energy absorptiometry, or Magnetic Resonance Imaging (MRI) will provide information about body growth

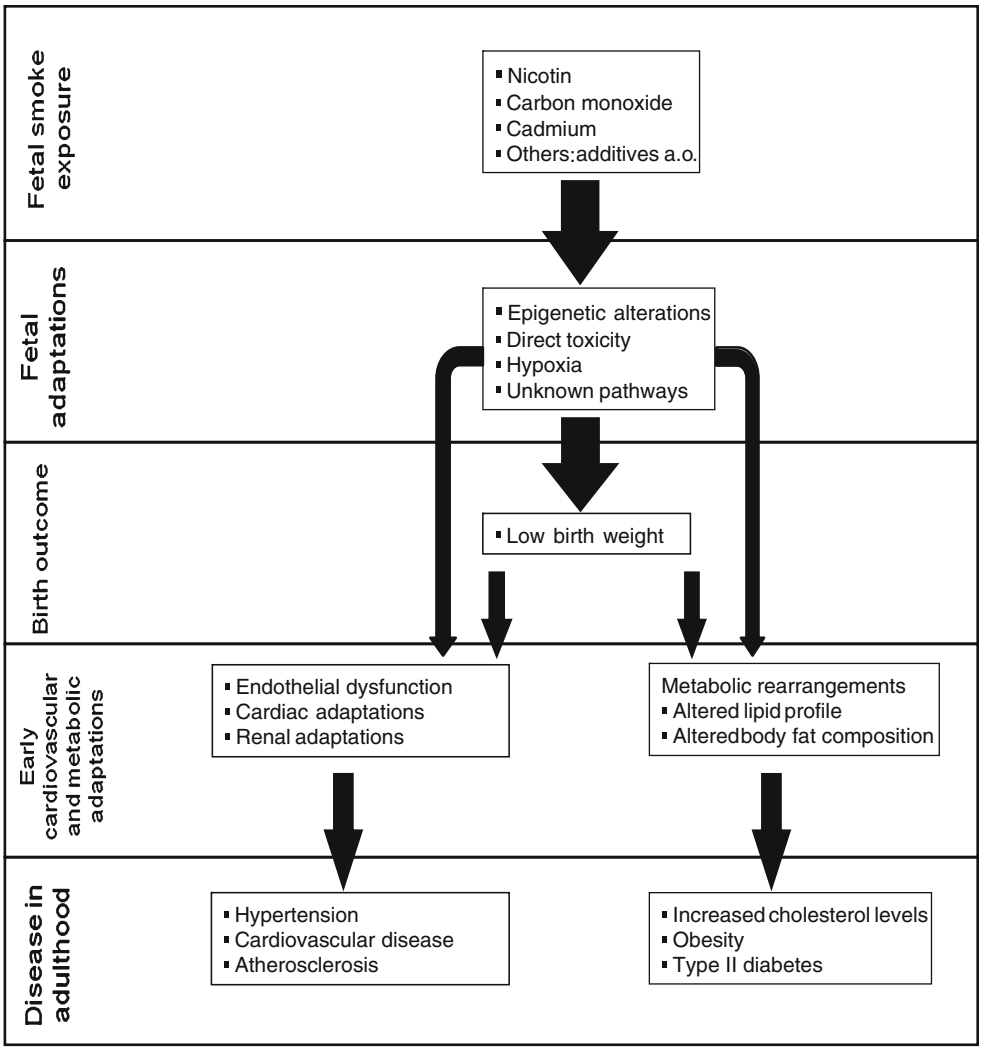

Fig. 1 Fetal smoke exposure and developmental changes

and composition in children who had been exposed to maternal smoking during pregnancy. MRI studies also enable studies on liver steathosis, visceral fat and thoracal fat [114–116].

The effects of maternal smoking on the fetus might differ between subjects. Genetic susceptibility might be important. Fetal exposures might cause epigenetic alterations. This is one mechanism by which adverse fetal environment might increase the risk of disease in later life. Smoking during pregnancy causes changes in fetal DNA methylation. A study of DNA methylation in buccal cells showed significant alterations in children with in utero smoke exposure [117]. Recently, another study confirmed the association between prenatal smoke exposure and methylation alterations. It was concluded that there is an inverse dose response relationship between DNA methylation in cord serum and serum cotinine levels [118].

In conclusion, fetal smoke exposure might be involved in the mechanisms underlying the associations between low birth weight and cardiovascular disease, obesity and type 2 diabetes. Well designed epidemiological studies, which take account for potential confounders are needed, and focus on specific underlying mechanisms are needed.

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