OXFORD UNIVERSITY PRESS | Toxicological Sciences

Early life exposure to nicotine: Postnatal metabolic, neurobehavioral and metabolic outcomes and the development of childhood cancers

Journal:	*Toxicological Sciences*
Manuscript ID	TOXSCI-20-0264.R2
Manuscript Type:	Contemporary Review
Date Submitted by the Author:	16-Jul-2020
Complete List of Authors:	Jamshed, Laiba; McMaster University, Department of Obstetrics and Gynecology Perono, Genevieve; McMaster University, Department of Obstetrics and Gynecology Jamshed, Shanza; McMaster University, Department of Obstetrics and Gynecology Holloway, Alison; McMaster University, Department of Obstetrics and Gynecology;
Key Words:	nicotine, pregnancy, fetal programming of adult disease, nicotine replacement therapy, electronic nicotine delivery systems, dysmetabolism, lung development, developmental neurotoxicity, childhood cancer, neurobehavior
Category - Please select 1-2 Categories most applicable to your manuscript, in priority order.:	Developmental and Reproductive Toxicology, Clinical and Translational Toxicology

Article Title: Early life exposure to nicotine: Postnatal metabolic, neurobehavioral and metabolic outcomes and the development of childhood cancers

Laiba Jamshed, Genevieve A Perono, Shanza Jamshed. Alison C Holloway[1]

1. Department of Obstetrics and Gynecology, McMaster University, Hamilton, ON., Canada L8N 3Z5

Correspondence to:

Dr. Alison Holloway
Department of Obstetrics and Gynecology
McMaster University
Hamilton, ON
L8N 3Z5
Canada
Phone: 905-525-9140 x 22130
FAX: 905-524-2911
Email: hollow@mcmaster.ca

Abstract

Cigarette smoking during pregnancy is associated with numerous obstetrical, fetal and developmental complications, as well as an increased risk of adverse health consequences in the adult offspring. Nicotine replacement therapy (NRT) and electronic nicotine delivery systems (e-cigarettes) have been developed as a pharmacotherapy for smoking cessation and are considered safer alternatives for women to smoke during pregnancy. The safety of NRT use during pregnancy has been evaluated in a limited number of short-term human trials, but there is currently no information on the long-term effects of developmental nicotine exposure in humans. However, animal studies suggest that nicotine alone may be a key chemical responsible for many of the long-term effects associated with maternal cigarette smoking on the offspring and increases the risk of adverse neurobehavioral outcomes, dysmetabolism, respiratory illness and cancer. This review will examine the long-term effects of fetal and neonatal nicotine exposure on postnatal health.

Keywords: nicotine, pregnancy, fetal programming of adult disease, nicotine replacement therapy (NRT), electronic nicotine delivery system (e-cigarettes), dysmetabolism, lung development, neurotoxicity, childhood cancer

1. Introduction

There is compelling evidence from multiple epidemiological studies and meta-analyses that cigarette smoking during pregnancy is associated with a number of adverse obstetrical outcomes including: spontaneous pregnancy loss (Pineles et al. 2014), placenta previa (Shobeiri and Jenabi 2017), placental abruption (Shobeiri et al. 2017), preterm birth (Shah and Bracken 2000; Dahlin et al. 2016; Moore et al. 2016), stillbirth (Marufu et al. 2015; Bjørnholt et al. 2016), impaired fetal growth (Blatt et al. 2015; Abraham et al. 2017; Pereira et al. 2017) and sudden infant death syndrome (Zhang and Wang 2013; Anderson et al. 2019). Smoking cessation, or at least a reduction in cigarette smoking during pregnancy can improve many of these outcomes. Indeed, smoking cessation during pregnancy has been shown to reduce the incidence of impaired fetal growth (low birthweight or intrauterine growth restriction), prematurity and stillbirth (Hodyl et al. 2014; Räisänen et al. 2014; Soneji and Beltrán-Sánchez 2019; Veisani et al. 2019).

Although cigarette smoking during pregnancy has been identified as a significant modifiable risk factor for adverse pregnancy outcomes, recent data suggests that many women still smoke during their pregnancies with prevalence rates ranging from 1.7% globally, to as high as 59% in some regions (Cui et al. 2014; Drake et al. 2018; Lange et al. 2018). While approximately 75% of pregnant smokers want to quit, studies indicate that only half of women successfully abstain completely from smoking during pregnancy (Greaves et al. 2011; Tong et al. 2013; Orton et al. 2014; Gilbert et al. 2015). Nicotine dependence is a significant element of most women's smoking behavior and a significant negative predictor of smoking abstinence during pregnancy (Benowitz 2010; Riaz et al. 2016; Baraona et al. 2017). Consequently, nicotine replacement therapy (NRT; *e.g.*, nicotine containing gum, lozenges and transdermal patches) has been widely developed as a pharmacotherapy of smoking cessation (Moerke et al. 2020) and should be considered if the patient is unable to quit smoking by other means (Zwar et al. 2011; Behrakis 2016; Bar-Zeev et al. 2017; Ordean et al. 2017). Recently, electronic nicotine delivery systems (e-cigarettes) have become available and marketed as effective smoking cessation tools (Patel et al. 2016; Ramamurthi et al. 2016; Farsalinos 2018; Collins et al. 2019). Notably, in a recent study of pregnant smokers, the use of e-cigarettes to quit smoking was more common than any other FDA-approved smoking cessation pharmacotherapy (Oncken et al. 2017).

In pregnant women who use NRT or e-cigarettes for smoking cessation, nicotine crosses the placenta, concentrates in fetal blood and amniotic fluid, and is detectable in breast milk during lactation in some cases at higher concentrations than in maternal plasma (Jordanov 1990; Lambers and Clark 1996; Rowe et al. 2015; Napierala et al. 2016). NRT products were previously categorized as Pregnancy Category C (gum, nasal spray and lozenges) or D (transdermal patches) drugs (Bruin et al. 2010). New FDA Pregnancy and Lactational Labeling Rules include additional details about the risks of drugs in pregnancy (Pernia and DeMaagd 2016). In general, NRT product monographs suggest that NRT should only be considered for smoking cessation in pregnancy if the risk to the fetus or mother of continued smoking outweighs any potential adverse effects of NRT exposure (Drugs.com). Guidelines from a number of countries recommend that NRT be offered to pregnant women who are unable to quit smoking using non-pharmacologic means (National Institute for Health and Care Excellence 2010; Zwar et al. 2011; Canadian Action Network for the Advancement, Dissemination and Adoption of Practice-informed Tobacco Treatment

2011; The Royal Australian and New Zealand College of Obstetricians and Gynaecologists 2017). Although NRT is highly effective for smoking cessation in non-pregnant smokers (Cahill et al. 2013), the evidence is much less clear during pregnancy. A recent Cochrane review of pharmacological interventions for promoting smoking cessation during pregnancy found evidence that in a pooled analysis of 9 studies and 2336 participants, NRT and behavioral support did increase cessation rates relative to control (RR 1.37, 95% CI 1.08-1.74), but when the analysis was limited to placebo-controlled randomized control trials there was no clear benefit of NRT use on cessation rates (RR 1.21, 95% CI 0.95-1.55) (Claire et al. 2020). The lack of a clear benefit of NRT for smoking cessation during pregnancy may be related to the low adherence to NRT among pregnant smokers; in studies where adherence was reported, complete adherence with the treatment protocol occurred in less than 40% of participants (Claire et al. 2020). Despite the lack of evidence to support the efficacy of NRT use during pregnancy, estimates suggest that approximately 10-20% of pregnant women are offered or prescribed NRT for smoking cessation (Dhalwani et al. 2014; Kapaya et al. 2015). Moreover, there has been an increase in e-cigarette usage during pregnancy; Cardenas and colleagues published a small cohort study using self-reports and non-invasive smoking biomarkers in 232 pregnant women and found that 6.8% of pregnant women were e-cigarette users, with most being concurrent smokers (75%) (Cardenas et al. 2019).

1.1 NRT, smokeless tobacco and e-cigarette use in pregnancy: human studies

As of 2019, there have only been 9 clinical trials which have investigated the efficacy and/or safety of NRT for smoking cessation during pregnancy (Claire et al. 2020); most of these have focused on obstetrical outcomes and the short-term (<2 years) effects on the offspring. There are also a number of observational studies and retrospective cross-sectional studies which have looked at the effects of exposure to smoke-free nicotine containing products including NRT, snus/snuff, smokeless tobacco, Alaskan iq'mik and e-cigarettes (Glover and Phillips 2020). Although Claire et al. (2020) did not find evidence for increased rates of adverse pregnancy or infant outcomes (*e.g.*, miscarriage, stillbirth, low birthweight, preterm birth, neonatal intensive care unit admissions, neonatal death and congenital anomalies) in randomized control trials of NRT use during pregnancy (Claire et al. 2020), there is some, albeit inconsistent, evidence from cohort studies that exposure to smoke-free nicotine products during pregnancy can increase the risk of congenital malformations, stillbirth, preterm birth and low birthweight (Glover and Phillips 2020). Using data from the Swedish Medical Birth Registry (1999-2009), Gunnerbeck et al. (2014) reported an increased risk of oral cleft malformations in infants whose mothers used snuff compared to non-tobacco users (aOR 1.48, 95% CI 1.00-2.21). Similarly, using data from the Danish National Birth Cohort (1997-2003), Morales-Suárez-Varela and colleagues showed an increased prevalence of congenital malformations in pregnant NRT users compared to nonsmokers (Morales-Suárez-Varela et al. 2006). Conversely, analysis of primary care data from the UK (2001-2012) did not find an increased association between maternal NRT exposure and major congenital anomalies compared to the control group (aOR 1.12, 99% CI 0.84-1.48) (Dhalwani et al. 2015). However, Although NRT use was not associated with an increased risk of stillbirth (Strandberg-Larsen et al. 2008), the use of smokeless tobacco, which delivers doses of nicotine similar to cigarette smoking (Benowitz 2011), has been reported to increase rates of stillbirth (Gupta and Subramoney 2006; Suliankatchi and Sinha 2016; Hossain et al. 2018). Moreover, while smoking is

clearly associated with preterm birth and intrauterine growth restriction (Shah and Bracken 2000; Pereira et al. 2017), the role of nicotine in causing this effect is unclear. Randomized control trials of NRT use in pregnancy have not shown increased rates of either low birthweight or preterm birth (Claire et al. 2020), yet retrospective studies have reported associations between nicotine exposure and these outcomes. For example, data from the 2004 Phase V Pregnancy Risk Assessment Monitoring System indicated that self-reported NRT use during pregnancy was associated with an approximate 2-fold increased risk of low birth weight and preterm birth compared to non-smokers (Gaither et al. 2009). Similarly, maternal snuff and smokeless tobacco use have also been associated with preterm birth and low birthweight (Ratsch and Bogossian 2014; Dahlin et al. 2016; Suliankatchi and Sinha 2016). Finally, relative to pregnant women who did not use nor were exposed to tobacco or e-cigarettes, e-cigarette-only use during pregnancy increased the risk of having a small for gestational age infant (RR 5.1, 95% CI 1.2-22.2) (Cardenas et al. 2019).

Taken together, evidence from human studies on the safety of NRT use (including e-cigarettes) during pregnancy remains uncertain (World Health Organization 2013; Committee on Underserved Women and Committee on Obstetric Practice 2017), yet there is some consensus that NRT may be a safer alternative to smoking during pregnancy because the mother and fetus are exposed to one chemical instead of the thousands of chemicals found in cigarette smoke (Benowitz et al. 2000). Indeed, it has been shown that conventional NRT use during pregnancy while abstinent from smoking results in lower maternal nicotine exposure than seen with smoking (Hickson et al. 2019), suggesting that the fetus will also be exposed to much less nicotine than children born to women who smoke during pregnancy. The same is not necessarily true for e-cigarette use. In fact, e-cigarette use has been reported to result in higher or comparable levels of nicotine exposure when compared to traditional tobacco cigarette use (Jarvis et al. 1984; Etter 2014; St Helen et al. 2016). While some studies have reported that amongst pregnant women there is a perception that e-cigarettes are less harmful than traditional cigarettes (Mark et al. 2015; Breland et al. 2019), e-cigarette use exposes the fetus to other chemicals including flavorants and thermal degradation products whose toxicity is largely unknown (Ward et al. 2020).

There is still considerable concern that there is no safe dose of nicotine during pregnancy (Bar-Zeev et al. 2017). Indeed, animal studies have demonstrated evidence of adverse behavioral, developmental, cardiovascular, respiratory, endocrine and metabolic outcomes in the offspring following maternal nicotine exposure (Bruin et al. 2010; Holbrook 2016; England et al. 2017). However, the evidence in human studies is less clear as most human studies of nicotine exposure use during pregnancy generally consider the acute risks of nicotine exposure on the developing fetus and in some cases, the long-term neurological effects. Moreover, nicotine exposure as a result of cigarette smoking or e-cigarette use also exposes the fetus to a multitude of other compounds. Nevertheless, considerable insight into the long-term effects of developmental nicotine exposure can be gained from animal models. Therefore, the goal of this review is to assess the current evidence regarding the long-term effects of fetal and neonatal nicotine exposure in animal and human studies. Searches were conducted on PubMed to collect relevant papers from 2010 to May 2020 based on the following keywords: “nicotine” “nicotine replacement therapy”, “e-cigarette”,

"smokeless tobacco", "snus", "snuff", "iq'mik" and "pregnancy" with, "fetal", "dysmetabolism", "obesity" "diabetes" "adiposity", "cardiovascular" "neurotoxicity", "lung development" and "childhood cancer". Although most papers utilized animal and cell models, studies that involved human participants were prioritized where possible. These searches were not intended for the purpose of a systematic review but rather to evaluate recent findings on the effects of early life exposure to nicotine; as such, relevant studies prior to 2010 were included as appropriate. We will use these animal studies to consider the potential contribution of nicotine to the long-term toxicity associated with cigarette smoke exposure and ENDS use during fetal and neonatal development in human populations.

2. Long-term effects of fetal and neonatal exposure to nicotine

2.1 Neurodevelopmental and behavioral outcomes

Nicotine functions as a neurotransmitter, acting on nicotinic acetylcholine receptors (nAChR) which are distributed in specific brain regions throughout neurodevelopment (Dwyer et al. 2009). Nicotine has been clearly established as a neuroteratogen and numerous animal studies have shown that early life exposure to nicotine results in adverse neurodevelopmental outcomes including disrupted synaptic plasticity and neuronal maturation, deficits in the number of neurons, and changes in brain volume (Thomas et al. 2000; Slotkin et al. 2007; Mahar et al. 2012; Muhammad et al. 2012; Zhu et al. 2012; Sailer et al. 2019; Kazemi et al. 2020). These morphological and functional changes in brain development have been associated with altered behaviors including, increased risk of cognitive impairments, attention deficit/hyperactivity disorder (ADHD), depression, impaired behavioral flexibility, increased anxiety and somatosensory deficits in the nicotine-exposed offspring (Reviewed in: (Abbott and Winzer-Serhan 2012; Liao et al. 2012; Holbrook 2016; Sailer et al. 2019)). Interestingly, evidence from rodent studies suggests that many of these outcomes are sex-dependent (Balsevich et al. 2014; Cross et al. 2017; Zhang et al. 2018). For example, maternal exposure to nicotine resulted in anxiety-like behaviors in male offspring but not female offspring, whereas ADHD-like behaviors were reported in both male and female offspring (Polli et al. 2020).

Adverse effects of nicotine exposure on neurodevelopment have also been reported following exposure to nicotine in e-cigarette vapors in animal and cell culture models (Nguyen et al. 2018; Church et al. 2020; Ruszkiewicz et al. 2020). Briefly, *in vitro* and *in vivo* rodent models investigating the influence of prenatal e-cigarette exposure on brain development suggest that exposure to e-cigarette aerosols increases neuronal death, reduces neuronal viability, worsens neonatal brain injury and decreases learning and memory in adolescent offspring with a brain injury (Sifat et al. 2020). Similarly, maternal e-cigarette exposure in mice has resulted in increased short-term memory deficits, reduced anxiety and hyperactivity in the offspring (Nguyen et al. 2018). Even though e-cigarette aerosols contain toxicants other than nicotine (Ward et al. 2020) the similarities in neurodevelopmental and behavioral outcomes following exposure to nicotine alone or nicotine as a component of e-cigarette aerosols suggest that exposure to nicotine, regardless of source, results in deficits in neurodevelopment and behavioral outcomes in rodent

models and supports the hypothesis that nicotine exposure may explain many of the adverse neurobehavioral outcomes in children born to women who smoke during pregnancy.

In humans, *in utero* exposure to cigarette smoke has been associated with adverse behavioral outcomes including greater irritability, hyperactivity, attention deficits, lower language comprehension and lower IQ (Reviewed in: (Abbott and Winzer-Serhan 2012; Liao et al. 2012; Smith et al. 2016)). Of the numerous behavioral disorders that have been reported in the offspring of women who smoke, the strongest evidence is for an association between maternal smoking and ADHD in the offspring. A meta-analysis of prospective cohort studies reported an association between maternal smoking and an increased risk of ADHD in the offspring (pooled RR 1.58, 95% CI 1.33-1.88) (He et al. 2017). Moreover, there is evidence that the severity of ADHD symptomology is positively correlated with the number of cigarettes smoked per day (Willoughby et al. 2009). Importantly, many rodent models of prenatal nicotine exposure have reported hyperactivity, attention deficit, working memory deficits, and impulsive-like behaviors in nicotine-exposed offspring (Zhu et al. 2012; El Marroun et al. 2014; Zhu et al. 2017; Polli et al. 2020).

While animal models have demonstrated that exposure to nicotine alone can affect neurodevelopment and offspring behavior, there is little information available in human populations (Reviewed in: (Sailer et al. 2019)). The single trial of NRT use in pregnancy, the SNAP trial, evaluated infant outcomes beyond the immediate perinatal period and reported that at 2 years of age, infants born to mothers who used NRT during pregnancy did not have an increased risk of impairments across 5 domains: communication, gross motor skills, fine motor skills, problem solving and personal social development (Cooper et al. 2014). While these results are reassuring, it is important to note that the compliance rate in the NRT study arm was below 10% at 1 month (Coleman et al. 2012). Therefore, the effect of early life exposure to nicotine alone, on neurodevelopment and postnatal behavior in children still remains largely unknown.

2.2 Metabolic outcomes

Maternal smoking during pregnancy is consistently linked to an increased risk of obesity and dysmetabolism (*i.e.*, aberrant glucose and lipid homeostasis) in the offspring. Indeed, a recent meta-analysis, based on 39 studies of 236,687 children, reported an increased risk of obesity in children born to mothers who smoked during pregnancy (pooled aOR 1.55, 95% CI 1.40-1.73) (Rayfield and Plugge 2017). Pediatric obesity is associated with cardiovascular and metabolic comorbidities previously considered to be "adult" diseases (*i.e.*, type 2 diabetes mellitus (T2DM), hypertension, nonalcoholic fatty liver disease (NAFLD) and dyslipidemia), lower health-related quality of life indicators and increased health care utilization and costs (Pelone et al. 2012; Buttitta et al. 2014; Lobstein and Jackson-Leach 2016). Recent estimates suggest that the health care costs associated with childhood obesity attributable to maternal smoking are over $9 billion/year in the US and $600 million/year in Canada (Chaiton and Holloway 2016).

Since it is well-established that maternal cigarette smoking results in intrauterine growth restriction (Pereira et al. 2017) and that low birthweight is a significant risk factor for the development of cardiometabolic disease (Erkamp et al. 2019; Fall and Kumaran 2019;

Nakano 2020), it has been suggested that the association of cigarette smoking with an increased risk of adverse postnatal health outcomes is simply a reflection of intrauterine growth restriction. However, maternal smoking increases the risk of adult-onset diseases in the offspring even after adjustment for a wide range of confounding factors including birthweight, infancy BMI and socioeconomic status (Weng et al. 2012; Behl et al. 2013; Morgen et al. 2018; Rogers 2019); suggesting that it may be a direct effect of intrauterine exposure to the chemicals in cigarette smoke that accounts for the increased risk of adverse health outcomes in the offspring of women who smoke during pregnancy. Of the thousands of chemicals in cigarette smoke, animal studies suggest that fetal exposure to nicotine alone may result in dysmetabolism (*i.e.*, increased weight gain/adiposity, aberrant glucose homeostasis and cardiovascular disease) in postnatal life.

2.2.1 Weight Gain, Adiposity and Dyslipidemia

Prenatal nicotine exposure has been shown to result in increased postnatal body weight and higher levels of body fat in animal models (Behl et al. 2013). The mechanisms by which early life exposure to nicotine can impact body weight homeostasis in animals are varied and include increased energy intake, reduced energy expenditure and effects on adipose tissue development and function. There is evidence that early life exposure to nicotine increases the hypothalamic expression of neuropeptide Y (NPY), an important orexigenic neuropeptide (Huang and Winzer-Serhan 2007; Chen et al. 2012; Younes-Rapozo et al. 2013). The effects of nicotine on energy intake are complex as nicotine has been shown to increase food efficiency and preference for sugar but not overall food intake (Somm et al. 2008; Younes-Rapozo et al. 2013; Pinheiro et al. 2015). Interestingly, a rat model of early life exposure to cigarette smoke results in hyperphagia and an increased preference for a high-fat diet (Peixoto et al. 2019); these results are similar to what has been reported in the Saguenay Youth Study, a population-based cross sectional study investigating the long-term consequences of prenatal exposure to cigarette smoke (Haghighi et al. 2013; Ken W. K. Lee et al. 2015). Similarly, children exposed *in utero* to cigarette smoke had significantly higher *ad libitum* energy intake at a palatable lunch buffet but not over a 7-day period (Cameron et al. 2018). Taken together, these data suggest that early life exposure to nicotine in humans may influence body weight homeostasis via changes in energy intake and food preferences; although the effects of exposure to nicotine in the absence of the other components of cigarette smoke remains to be determined.

As obesity is a disorder of energy imbalance between energy intake and energy expenditure, it is also possible that nicotine exposure in early life increases obesity risk in the offspring via persistent changes in energy expenditure. Indeed, decreased spontaneous activity and perturbed thermogenesis was reported in rats exposed prenatally to nicotine (Somm et al. 2008). Recent work has shown that brown adipose tissue (BAT) is a thermogenic tissue which regulates energy expenditure (Villarroya et al. 2018). In rats, perinatal exposure to nicotine has been shown to increase the accumulation of unilocular lipid droplets in BAT (*i.e.*, whitening of BAT) along with decreased expression of thermogenesis-specific genes and sympathetic nervous system activity (*i.e.*, reduced BAT activity) (Fan, Ping, et al. 2016; Peixoto et al. 2019). Neonatal exposure to cigarette smoke had similar effects (Peixoto et al. 2019). The influence of nicotine exposure on energy expenditure and/or BAT activity in humans is not well known as there are few studies

which have investigated these outcomes in the offspring of women who smoke or use nicotine during pregnancy. To our knowledge, the single study which assessed energy expenditure in children born to women who smoke did not report any differences in resting energy expenditure (Cameron et al. 2018); however, there was no assessment of any markers of BAT activity. Given that reduced energy expenditure is a key component of obesity that has been shown to be affected by nicotine exposure, studies investigating these outcomes in children with early life exposure to nicotine are warranted.

Prenatal nicotine exposure has also been shown to lead to increased storage of lipids in both white adipose tissue (WAT) and peripheral tissues, an effect which is central to the development of obesity and insulin resistance (Blüher 2013). Rats exposed *in utero* to nicotine have elevated expression of adipogenic markers in WAT and increased fat pad weights (Somm et al. 2008; Behl et al. 2013; Fan, Zhang, et al. 2016). These effects may be due to direct effects of nicotine on the developing adipocytes as *in vitro* studies have shown that nicotine exposure can increase lipid accumulation and adipocyte maturation in mouse 3T3-LI cells in a dose-dependent manner (Zhang et al. 2020). Similarly, increased percent body fat and fat mass have also been reported in children born to women who smoke (Moschonis et al. 2017; Cameron et al. 2018). Nicotine exposure in animal models has also been reported to increase hepatic fat accumulation (Ma et al. 2014) which is a key component of NAFLD (Tiniakos et al. 2010). The effect of nicotine on hepatic fat accumulation may be mediated via epigenetic changes in genes important for lipid homeostasis (Suter et al. 2010). For example, *in utero* exposure to nicotine causes elevated hepatic triglyceride levels in association with increased histone H3 [K9,14] acetylation in the promoter of hepatic fatty acid synthase, a key gene involved in *de novo* lipogenesis, in nicotine-exposed offspring at 6 months of age (Ma et al. 2014). Importantly, liver fat is often associated with obesity and insulin resistance (Bellentani 2017). These changes in insulin sensitivity may explain increased diabetes risk in children born to women who smoke (Reviewed in (Rogers 2019)). Alternatively, the increased risk of diabetes following *in utero* exposure to cigarette smoke (Rogers 2019) may be attributed, in part, to nicotine-induced reductions in beta cell mass as has been reported in animal studies (Reviewed in (Bruin et al. 2010)).

2.2.2 Hypertension

Hypertension is another health consequence associated with *in utero* exposure to cigarette smoking in humans (Bruin et al. 2010; Cabral et al. 2018; Rogers 2019) and animal studies suggest that this may be mediated via nicotine exposure. Indeed, fetal and neonatal nicotine exposure in rodents results in increased blood pressure in adult life (Pausová et al. 2003; Gao et al. 2008; Xiao et al. 2015). A recent study has reported that children exposed *in utero* to snus, a smokeless tobacco that delivers nicotine but not the combustion products found in cigarette smoke, had increased blood pressure at 5-6 years of age (Felicia et al. 2019). The mechanisms underlying increased blood pressure following early life exposure to nicotine are not fully known but may involve abnormalities in heart development and/or function as has been reported in animal studies (Wang et al. 2015; Barra et al. 2017). Alternatively, perinatal nicotine exposure may induce vasoconstriction and facilitate the hypertensive phenotype in adulthood via epigenetic mechanisms (Xiao et al. 2014). Indeed, one study conducted in rats found that perinatal exposure to nicotine altered epigenetic

regulation of vascular angiotensin II receptors (ATRs), as evidenced by reduced DNA methylation at ATR-specific gene promoter regions (Xiao et al. 2014). Other studies suggest that increased blood pressure following nicotine exposure could be related to increased fat mass, glucose abnormalities, or elevated circulating triglyceride levels, all of which have been identified as determinants of childhood hypertension (Liang et al. 2020) and reported in nicotine-exposed offspring (Bruin et al. 2010; Ma et al. 2014).

There is clear evidence from animal studies that early life exposure to nicotine can cause profound cardiometabolic deficits. Although many of these metabolic perturbations are similar to what has been reported in children born to mothers who smoked during pregnancy, cigarette smoke contains numerous constituents making it difficult to attribute these outcomes to nicotine alone. As there are no clinical studies of NRT use in pregnancy which have reported metabolic outcomes in children, the consequences of early life exposure to nicotine in humans remains to be determined and is a significant research gap in the field.

2.3 Respiratory Outcomes

2.3.1 Lung Function and Development

The developing lung is sensitive to exogenous compounds such as those found in maternal tobacco smoke (Dasgupta et al. 2012; Stocks et al. 2013; Gibbs et al. 2016). There are several epidemiological studies which have reported that perinatal tobacco smoke exposure increases the risk of upper and lower respiratory tract infections, bronchitis, asthma, wheezing, pulmonary hypertension and impaired lung function in the offspring (Kalliola et al. 2013; den Dekker et al. 2015; Spindel and McEvoy 2016). In fact, 2 meta-analyses have reported that maternal smoking during the prenatal period was associated with an increased risk of wheezing (Burke et al. 2012) and asthma (Silvestri et al. 2015) in childhood. Importantly, there is compelling evidence from several animal studies that suggest that majority of adverse effects associated with perinatal smoke exposure on the developing lung are mediated by nicotine alone (Reviewed in: (Maritz and Harding 2011; Spindel and McEvoy 2016; McEvoy and Spindel 2017; Kuniyoshi and Rehan 2019)).

Perinatal nicotine exposure alters normal lung development leading to reduced lung size and volume capacity, thickening of the airway walls and pulmonary vessels and reduced alveolar surface area (Sekhon et al. 1999; Sekhon et al. 2002; Krebs et al. 2010; Petre et al. 2011; Maritz 2013; Lavezzi et al. 2014; England et al. 2017). Collectively, these outcomes compromise the primary role of the respiratory system to mediate optimal blood-gas exchange (Wongtrakool et al. 2012; Spindel and McEvoy 2016). *In vitro* and *in vivo* studies reveal that the effects of nicotine on airway remodeling can be attributed to its activity at the α7 nAChR (Reviewed in: (Gibbs et al. 2016; Spindel and McEvoy 2016). Maternal nicotine exposure upregulates α7 nAChR expression in fetal lung macrophages and epithelial cells and fibroblasts (Sekhon et al. 1999; Sekhon et al. 2002; England et al. 2017) and it has been suggested that nicotine activity at α7 nAChR may play a role in altering lung development, morphogenesis and airway plasticity (Sekhon et al. 1999; Maritz and Harding 2011). In support of this hypothesis, perinatal nicotine exposure did not cause

impaired lung function (as measured by forced expiratory flows) in α7 nAChR knockout mice (Wongtrakool et al. 2012).

Defects in lung development are often associated with impaired lung function and an increased incidence of respiratory diseases including asthma and wheeze (Stocks et al. 2013). There is compelling evidence demonstrating that prenatal exposure to nicotine adversely alters pulmonary function parameters, with consistent reports of decreased forced expiratory flows. These findings are indicative of alterations to airway diameter and compliance during critical stages of lung development (Landau 2008; Spindel and McEvoy 2016). Similarly, results from epidemiological studies have reported impaired lung function and increased risk for wheezing, asthma and hospitalization due to respiratory complications in children exposed to tobacco smoke (Reviewed in: (McEvoy and Spindel 2017; Wang et al. 2020)). However, the impact of prenatal exposure to tobacco smoke on asthma risk is complex and cannot be solely attributed to nicotine exposure as evidenced by the fact that infants with prenatal exposure to paternal tobacco smoke also have an increased risk of asthma by age 6 (Wu et al. 2019). Despite this, there is some evidence in humans that early life exposure to nicotine alone can impact lung function in the offspring.

In a recent cohort study including 192,498 children, a small number of exposed cases showed that offspring born of women prescribed NRT patches during their first trimester of pregnancy demonstrated a significant association between maternal NRT use and respiratory anomalies (OR 4.65, 99% CI 1.76-12.25) (Dhalwani et al. 2015). While in humans the effects of nicotine exposure via e-cigarette use during pregnancy are unknown, a recent study that used a mouse whole-body environmental e-cigarette exposure model found that neonates exposed to aerosols containing nicotine had significant reductions in alveolar cell proliferation and impaired lung health (McGrath-Morrow et al. 2015). While it is unclear whether nicotine-containing e-cigarettes will have the same effect in humans, these findings suggest that the use of e-cigarette during pregnancy may adversely affect respiratory health of offspring.

2.3.2 Fibrosis

To date, several epidemiologic studies have reported an association between adult cigarette smoking and idiopathic pulmonary fibrosis (Taskar and Coultas 2006; Jensen et al. 2012; Kärkkäinen et al. 2017; Ebrahimpour et al. 2019). There is some evidence that nicotine may accelerate pathogenesis; *in vitro* and *in vivo* studies have shown that nicotine plays a role in key pro-fibrotic processes including increased pulmonary fibroblast transdifferentiation (Krebs et al. 2010; Rehan et al. 2012), activation of collagen-producing cells (Sekhon et al. 1999; Vicary et al. 2017; Wawryk-Gawda et al. 2018) and recruitment of inflammatory molecules (Nowak et al. 1990; Roomans et al. 2002). There is limited evidence demonstrating an association between early life exposure to nicotine and risk for idiopathic pulmonary fibrosis, however, one epidemiological study has reported an association between maternal smoking and risk for idiopathic pulmonary fibrosis in the offspring (OR 1.41, 95% CI 1.19-1.68) (Bellou et al. 2017). Based on animal and cell culture studies, it is plausible that this association is mediated via nicotine's effects on the developing lung.

The substitution of alveolar architecture with collagen and aberrant remodelling of lung structures are hallmarks of pulmonary fibrosis (Jensen et al. 2012; Pardo and Selman 2016). Emerging evidence in animal models suggests that fetal and neonatal nicotine exposure inhibits alveolar development and increases the risk for idiopathic pulmonary fibrosis in offspring via upregulation of transforming growth factor β1 signaling (Dasgupta et al. 2012). In fact, in multiple species (rat, mouse and monkey) prenatal nicotine-induced overexpression of transforming growth factor β1, and its downstream effectors such as connective tissue growth factor, has been shown to increase the risk of fibrosis, inflammation, epithelial-to-mesenchymal transdifferentiation and collagen deposition in the airways and pulmonary vessels of the offspring (Sekhon et al. 2002; Gauldie et al. 2003; Tarantal et al. 2010; Dasgupta et al. 2012; Wongtrakool et al. 2012). The nAChRs expressed on pulmonary fibroblasts and epithelial cells are responsive to exogenous stimulation by nicotine (Ebrahimpour et al. 2019), suggesting that the observed incidences of idiopathic pulmonary fibrosis in nicotine-exposed offspring may be attributed to nAChR signaling. In support of this hypothesis, genetic knock-out models of α7-nAChR reversed the inflammatory response and changes to the local microenvironment of the fibrotic lung in nicotine-exposed mice (Wongtrakool et al. 2012).

Interestingly some of these increases in inflammation-related genes appear to be mediated via epigenetic alterations as a result of early life nicotine exposure. Offspring exposed to nicotine *in utero* showed decreased HDAC activity and increased overall histone H3 acetylation in the lung (Rehan et al. 2012), paralleling *in vitro* and *in vivo* observations of cigarette smoke-induced methylation changes in histones H3 [K9] and increased expression of inflammatory genes, including interleukin-8 and tumor necrosis factor α (Chen et al. 2015). While further investigation is needed to identify disease-specific genes altered by nicotine exposure alone, these data suggest that nicotine treatment may alter the fetal lung epigenome and increase its susceptibility to adult lung diseases, such as asthma and idiopathic pulmonary fibrosis (Suter et al. 2015).

2.4 Childhood Cancers

Prenatal exposure to tobacco smoke has been associated with increased risk of childhood cancers, including childhood brain tumors, hepatoblastomas, and leukemias/lymphomas as well as genotoxic effects which may increase the risk of adult cancers (Reviewed in: (Pattemore 2013; Fucic et al. 2017). The most widely studied of these childhood cancers is acute lymphoblastic leukemia. Recent work suggests that prenatal maternal smoke exposure increased leukemogenic somatic deletions found in acute lymphoblastic leukemia (de Smith et al. 2017). In women who smoke, maternal and neonatal blood samples found increased/altered signaling pathways related to cancer, including: tumor suppressor p53, ErbB, hedgehog and WNT signaling, all of which are essential signal transduction pathways related to cancer pathogenesis (Gu 2014). Likewise, other studies have reported that the largest cluster of biological pathways in newborns impacted by maternal smoking were related to cancer (Rotroff et al. 2016). Importantly, altered DNA methylation patterns associated with these pathways have been found to persist in exposed offspring into adolescence (Ken W.K. Lee et al. 2015; Rotroff et al. 2016). Taken together, these data suggest that early life exposure to tobacco smoke mediates genetic and epigenetic changes

resulting in increased risk of childhood cancers, with potentially long-term effects. However, tobacco smoke contains many known carcinogens (i.e., polycyclic hydrocarbons and tobacco-smoke specific nitrosamines derivatives) that may also cross the placenta, making it difficult to attribute the increased risk of cancer to nicotine alone (Reviewed in: (Fucic et al. 2017). There are now studies that have shown that nicotine can affect several pathways mediating cancer as well as chromosomal aberrations and DNA double-strand breaks important in cancer development (Reviewed in: (Sanner and Grimsrud 2015)). While this evidence suggests that NRT use during pregnancy has the potential to increase cancer risk in children, this has not been demonstrated in human clinical trials or cohort studies.

The mechanism(s) by which nicotine may affect the development of cancer are not well known, but it may involve activation of the nAChR. Nicotine activation of nAChR has been shown to influence signaling pathways involved in survival (mitogenic and anti-apoptotic), proliferation, epithelial to mesenchymal transition, angiogenesis and metastasis; promoting a cancer-supporting microenvironment that can aid in the initiation and progression of many adult tumors and cancers (Reviewed in: (Improgo et al. 2011; Grando 2014; Mishra et al. 2015; Sanner and Grimsrud 2015; Haussmann and Fariss 2016). Despite the fact that nicotine can influence many pro-cancer pathways, nicotine is not presently considered a human carcinogen (International Agency for Research on Cancer 2004). While there are no long-term studies assessing the association between *in utero* exposure to NRT or e-cigarettes and cancer risk in children*, in vitro* studies and animal experiments suggest that the long-term effects of early life exposure to nicotine and cancer risk deserve further attention.

3. Conclusions

Cigarette smoking during pregnancy continues to be a significant modifiable risk factor for adverse pregnancy and fetal outcomes. Animal models have indicated that nicotine alone may be responsible for many of the long-term effects associated with maternal tobacco exposure including adverse metabolic (Pelone et al. 2012; Buttitta et al. 2014; Lobstein and Jackson-Leach 2016; Liang et al. 2020), pulmonary (Maritz and Harding 2011; Gibbs et al. 2016; McEvoy and Spindel 2017; Kuniyoshi and Rehan 2019) and neurobehavioral outcomes (Abbott and Winzer-Serhan 2012; Clifford et al. 2012; Liao et al. 2012; Tiesler and Heinrich 2014) and increased cancer risk in offspring (Bruin et al. 2010; England et al. 2017) (Fig.1). However, the contribution of nicotine to these same outcomes in humans remains unclear.

While NRT and e-cigarette usage are thought to be harm reduction strategies to reduce tobacco use during pregnancy, the postnatal health consequences of exposure to these products in humans a limited. There are few trials investigating NRT use during pregnancy most of which do not explore the postnatal health outcomes in the exposed children. Until there are carefully designed cohort studies to investigate long-term health outcomes in children exposed to NRT in fetal and neonatal life, there can be no definitive answer to whether or not there is a safe dose of nicotine during pregnancy (Bar-Zeev et al. 2017, Glover and Phillips, 2020). The long term effects of maternal e-cigarette use on offspring health and the contribution of nicotine to any of these outcomes also remains largely

unknown. There is evidence that pregnant women are using e-cigarettes for smoking cessation (Breland et al., 2019, Oncken et al., 2017) which can result in fetal exposure to nicotine alongside other toxicants. Studies have shown that other components of e-cigarette liquids (base components and flavoring compounds) can affect nicotine yield and may themselves have the ability to independently affect key pathways important for fetal development (DeVito and Krishnan-Sarin 2018; Greene and Pisano 2019). Moreover, e-cigarette liquids do not contain consistent nicotine concentrations, and the nicotine yield depends on puffing topography, the type of device used, and the other constituents present in the e-cigarette liquids. Therefore, there will be considerable challenges to understand the contribution of nicotine alone to any long-term health outcomes in offspring exposed to e-cigarette aerosols. Given that there is considerable potential for women to use nicotine alone during pregnancy through NRT or e-cigarette use, carefully designed human cohort studies and animal experiments to investigate long-term outcomes in the offspring are urgently needed.

Funding
This work was supported by the Canadian Institutes of Health Research (PJT-155981). LJ was funded by a Canadian Graduate Scholarship – Master's Award.

Figure 1: Summary, from animal studies, of the effects of prenatal nicotine exposure on the brain, heart, lungs, metabolic-regulating tissues and cancer

References

Abbott LC, Winzer-Serhan UH. 2012. Smoking during pregnancy: lessons learned from epidemiological studies and experimental studies using animal models. Critical Reviews in Toxicology. 42(4):279–303. doi:10.3109/10408444.2012.658506.

Abraham M, Alramadhan S, Iniguez C, Duijts L, Jaddoe VWV, Dekker HTD, Crozier S, Godfrey KM, Hindmarsh P, Vik T, et al. 2017. A systematic review of maternal smoking during pregnancy and fetal measurements with meta-analysis. PLOS ONE. 12(2):e0170946. doi:10.1371/journal.pone.0170946.

Anderson TM, Ferres JML, Ren SY, Moon RY, Goldstein RD, Ramirez J-M, Mitchell EA. 2019. Maternal Smoking Before and During Pregnancy and the Risk of Sudden Unexpected Infant Death. Pediatrics. 143(4). doi:10.1542/peds.2018-3325. https://pediatrics.aappublications.org/content/143/4/e20183325.

Balsevich G, Poon A, Goldowitz D, Wilking JA. 2014. The effects of pre- and post-natal nicotine exposure and genetic background on the striatum and behavioral phenotypes in the mouse. Behavioural Brain Research. 266:7–18. doi:10.1016/j.bbr.2014.02.038.

Baraona LK, Lovelace D, Daniels JL, McDaniel L. 2017. Tobacco Harms, Nicotine Pharmacology, and Pharmacologic Tobacco Cessation Interventions for Women. Journal of Midwifery & Women's Health. 62(3):253–269. doi:10.1111/jmwh.12616.

Barra NG, Lisyansky M, Vanduzer TA, Raha S, Holloway AC, Hardy DB. 2017. Maternal nicotine exposure leads to decreased cardiac protein disulfide isomerase and impaired mitochondrial function in male rat offspring. Journal of Applied Toxicology. 37(12):1517–1526. doi:10.1002/jat.3503.

Bar-Zeev Y, Lim LL, Bonevski B, Gruppetta M, Gould GS. 2017. Nicotine replacement therapy for smoking cessation during pregnancy. The Medical Journal of Australia. 208(1):46–51. doi:10.5694/mja17.00446.

Behl M, Rao D, Aagaard K, Davidson TL, Levin ED, Slotkin TA, Srinivasan S, Wallinga D, White MF, Walker VR, et al. 2013. Evaluation of the Association between Maternal Smoking, Childhood Obesity, and Metabolic Disorders: A National Toxicology Program Workshop Review. Environ Health Perspect. 121(2):170–180. doi:10.1289/ehp.1205404.

Behrakis P. 2016. TOB-G: Tobacco Cessation Guidelines for High risk Populations. Tob Prev Cessation. 2(April Supplement). doi:10.18332/tpc/62428. http://www.tobaccopreventioncessation.com/TOB-G-Tobacco-Cessation-Guidelines-for-High-risk-Populations,62428,0,2.html.

Bellentani S. 2017. The epidemiology of non-alcoholic fatty liver disease. Liver Int. 37 Suppl 1:81–84. doi:10.1111/liv.13299.

Bellou V, Belbasis L, Konstantinidis A, Evangelou E. 2017. Tobacco smoking and risk for idiopathic pulmonary fibrosis: a prospective cohort study in UK Biobank. European

Respiratory Journal. 50(suppl 61). doi:10.1183/1393003.congress-2017.PA4887. https://erj.ersjournals.com/content/50/suppl_61/PA4887.

Benowitz NL. 2010. Nicotine Addiction. N Engl J Med. 362(24):2295–2303. doi:10.1056/NEJMra0809890.

Benowitz NL. 2011. Smokeless Tobacco as a Nicotine Delivery Device: Harm or Harm Reduction? Clinical Pharmacology & Therapeutics. 90(4):491–493. doi:10.1038/clpt.2011.191.

Benowitz NL, Dempsey DA, Goldenberg RL, Hughes JR, Dolan-Mullen P, Ogburn PL, Oncken C, Orleans CT, Slotkin TA, Whiteside HP, et al. 2000. The use of pharmacotherapies for smoking cessation during pregnancy. Tob Control. 9 Suppl 3:III91-94. doi:10.1136/tc.9.suppl_3.iii91.

Bjørnholt SM, Leite M, Albieri V, Kjaer SK, Jensen A. 2016. Maternal smoking during pregnancy and risk of stillbirth: results from a nationwide Danish register-based cohort study. Acta Obstetricia et Gynecologica Scandinavica. 95(11):1305–1312. doi:10.1111/aogs.13011.

Blatt K, Moore E, Chen A, Van Hook J, DeFranco EA. 2015. Association of Reported Trimester-Specific Smoking Cessation With Fetal Growth Restriction. Obstetrics & Gynecology. 125(6):1452–1459. doi:10.1097/AOG.0000000000000679.

Blüher M. 2013. Adipose tissue dysfunction contributes to obesity related metabolic diseases. Best Practice & Research Clinical Endocrinology & Metabolism. 27(2):163–177. doi:10.1016/j.beem.2013.02.005.

Breland A, McCubbin A, Ashford K. 2019. Electronic nicotine delivery systems and pregnancy: Recent research on perceptions, cessation, and toxicant delivery. Birth Defects Research. 111(17):1284–1293. doi:10.1002/bdr2.1561.

Bruin JE, Gerstein HC, Holloway AC. 2010. Long-term consequences of fetal and neonatal nicotine exposure: a critical review. Toxicol Sci. 116(2):364–374. doi:10.1093/toxsci/kfq103.

Burke H, Leonardi-Bee J, Hashim A, Pine-Abata H, Chen Y, Cook DG, Britton JR, McKeever TM. 2012. Prenatal and passive smoke exposure and incidence of asthma and wheeze: systematic review and meta-analysis. Pediatrics. 129(4):735–744. doi:10.1542/peds.2011-2196.

Buttitta M, Iliescu C, Rousseau A, Guerrien A. 2014. Quality of life in overweight and obese children and adolescents: a literature review. Qual Life Res. 23(4):1117–1139. doi:10.1007/s11136-013-0568-5.

Cabral M, Fonseca MJ, González-Beiras C, Santos AC, Correia-Costa L, Barros H. 2018. Maternal Smoking: A Life Course Blood Pressure Determinant? Nicotine Tob Res. 20(6):674–680. doi:10.1093/ntr/ntx117.

Cahill K, Stevens S, Perera R, Lancaster T. 2013. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. Cochrane Database of Systematic Reviews.(5). doi:10.1002/14651858.CD009329.pub2. https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD009329.pub2/full.

Cameron JD, Doucet É, Adamo KB, Walker M, Tirelli A, Barnes JD, Hafizi K, Murray M, Goldfield GS. 2018. Effects of prenatal exposure to cigarettes on anthropometrics, energy intake, energy expenditure, and screen time in children. Physiology & Behavior. 194:394–400. doi:10.1016/j.physbeh.2018.06.020.

Canadian Action Network for the Advancement, Dissemination and Adoption of Practice-informed Tobacco Treatment. 2011. Canadian Smoking Cessation Clinical Practice Guideline - Overview of Summary Statements. :8.

Cardenas V, Cen R, Clemens M, Moody H, Ekanem U, Policherla A, Fischbach L, Eswaran H, Magann E, Delongchamp R, et al. 2019. Use of Electronic Nicotine Delivery Systems (ENDS) by pregnant women I: Risk of small-for-gestational-age birth. Tob Induc Dis. 17(May). doi:10.18332/tid/106089. [accessed 2020 May 13]. http://www.journalssystem.com/tid/Use-of-Electronic-Nicotine-Delivery-Systems-by-Pregnant-Women-I-Risk-of-Small-for,106089,0,2.html.

Chaiton M, Holloway A. 2016. Population attributable risk of smoking during pregnancy on obesity in offspring. Can J Public Health. 107(3):e336–e336. doi:10.17269/CJPH.107.5686.

Chen H, Saad S, Sandow S, Bertrand P. 2012. Cigarette Smoking and Brain Regulation of Energy Homeostasis. Front Pharmacol. 3. doi:10.3389/fphar.2012.00147. https://www.frontiersin.org/articles/10.3389/fphar.2012.00147/full.

Chen X, Guan X, Peng X, Cui Z, Luan C, Guo X. 2015. Acetylation of lysine 9 on histone H3 is associated with increased pro-inflammatory cytokine release in a cigarette smoke-induced rat model through HDAC1 depression. Inflamm Res. 64(7):513–526. doi:10.1007/s00011-015-0832-y.

Church JS, Chace-Donahue F, Blum JL, Ratner JR, Zelikoff JT, Schwartzer JJ. 2020. Neuroinflammatory and Behavioral Outcomes Measured in Adult Offspring of Mice Exposed Prenatally to E-Cigarette Aerosols. Environmental Health Perspectives. 128(4):047006. doi:10.1289/EHP6067.

Claire R, Chamberlain C, Davey M-A, Cooper SE, Berlin I, Leonardi-Bee J, Coleman T. 2020. Pharmacological interventions for promoting smoking cessation during pregnancy. Cochrane Database of Systematic Reviews.(3). doi:10.1002/14651858.CD010078.pub3. https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD010078.pub3/full.

Clifford A, Lang L, Chen R. 2012. Effects of maternal cigarette smoking during pregnancy on cognitive parameters of children and young adults: A literature review. Neurotoxicology and Teratology. 34(6):560–570. doi:10.1016/j.ntt.2012.09.004.

Coleman T, Cooper S, Thornton JG, Grainge MJ, Watts K, Britton J, Lewis S. 2012. A Randomized Trial of Nicotine-Replacement Therapy Patches in Pregnancy. New England Journal of Medicine. 366(9):808–818. doi:10.1056/NEJMoa1109582.

Collins L, Glasser AM, Abudayyeh H, Pearson JL, Villanti AC. 2019. E-Cigarette Marketing and Communication: How E-Cigarette Companies Market E-Cigarettes and the Public Engages with E-cigarette Information. Nicotine Tob Res. 21(1):14–24. doi:10.1093/ntr/ntx284.

Committee on Underserved Women, Committee on Obstetric Practice. 2017. Committee Opinion No. 721: Smoking Cessation During Pregnancy. Obstet Gynecol. 130(4):e200–e204. doi:10.1097/AOG.0000000000002353.

Cooper S, Lewis S, Thornton JG, Marlow N, Watts K, Britton J, Grainge MJ, Taggar J, Essex H, Parrott S, et al. 2014. The SNAP trial: a randomised placebo-controlled trial of nicotine replacement therapy in pregnancy--clinical effectiveness and safety until 2 years after delivery, with economic evaluation. Health Technol Assess. 18(54):1–128. doi:10.3310/hta18540.

Cross SJ, Linker KE, Leslie FM. 2017. Sex-dependent effects of nicotine on the developing brain. Journal of Neuroscience Research. 95(1–2):422–436. doi:10.1002/jnr.23878.

Cui Y, Shooshtari S, Forget EL, Clara I, Cheung KF. 2014. Smoking during pregnancy: findings from the 2009-2010 Canadian Community Health Survey. PLoS ONE. 9(1):e84640. doi:10.1371/journal.pone.0084640.

Dahlin S, Gunnerbeck A, Wikström A-K, Cnattingius S, Bonamy A-KE. 2016. Maternal tobacco use and extremely premature birth – a population-based cohort study. BJOG: An International Journal of Obstetrics & Gynaecology. 123(12):1938–1946. doi:10.1111/1471-0528.14213.

Dasgupta C, Xiao D, Xu Z, Yang S, Zhang L. 2012. Developmental nicotine exposure results in programming of alveolar simplification and interstitial pulmonary fibrosis in adult male rats. Reproductive Toxicology. 34(3):370–377. doi:10.1016/j.reprotox.2012.05.100.

den Dekker HT, Voort AMMS der, de Jongste JC, Reiss IK, Hofman A, Jaddoe VWV, Duijts L. 2015. Tobacco Smoke Exposure, Airway Resistance, and Asthma in School-age Children. Chest. 148(3):607–617. doi:10.1378/chest.14-1520.

DeVito EE, Krishnan-Sarin S. 2018. E-cigarettes: Impact of E-Liquid Components and Device Characteristics on Nicotine Exposure. Curr Neuropharmacol. 16(4):438–459. doi:10.2174/1570159X15666171016164430.

Dhalwani NN, Szatkowski L, Coleman T, Fiaschi L, Tata LJ. 2014. Prescribing of nicotine replacement therapy in and around pregnancy: a population-based study using primary care data. Br J Gen Pract. 64(626):e554-560. doi:10.3399/bjgp14X681361.

Dhalwani NN, Szatkowski L, Coleman T, Fiaschi L, Tata LJ. 2015. Nicotine Replacement Therapy in Pregnancy and Major Congenital Anomalies in Offspring. Pediatrics. 135(5):859–867. doi:10.1542/peds.2014-2560.

Drake P, Driscoll AK, Mathews TJ. 2018. Cigarette Smoking During Pregnancy: United States, 2016. NCHS Data Brief.(305):1–8.

Drugs.com. Nicotine Monograph for Professionals. Drugs.com. https://www.drugs.com/monograph/nicotine.html.

Dwyer JB, McQuown SC, Leslie FM. 2009. The dynamic effects of nicotine on the developing brain. Pharmacology & Therapeutics. 122(2):125–139. doi:10.1016/j.pharmthera.2009.02.003.

Ebrahimpour A, Shrestha S, Bonnen MD, Eissa NT, Raghu G, Ghebre YT. 2019. Nicotine Modulates Growth Factors and MicroRNA to Promote Inflammatory and Fibrotic Processes. J Pharmacol Exp Ther. 368(2):169–178. doi:10.1124/jpet.118.252650.

El Marroun H, Schmidt MN, Franken IHA, Jaddoe VWV, Hofman A, van der Lugt A, Verhulst FC, Tiemeier H, White T. 2014. Prenatal Tobacco Exposure and Brain Morphology: A Prospective Study in Young Children. Neuropsychopharmacology. 39(4):792–800. doi:10.1038/npp.2013.273.

England LJ, Aagaard K, Bloch M, Conway K, Cosgrove K, Grana R, Gould TJ, Hatsukami D, Jensen F, Kandel D, et al. 2017. Developmental toxicity of nicotine: A transdisciplinary synthesis and implications for emerging tobacco products. Neurosci Biobehav Rev. 72:176–189. doi:10.1016/j.neubiorev.2016.11.013.

Erkamp JS, Jaddoe VWV, Mulders AGMGJ, Steegers EAP, Reiss IKM, Duijts L, Gaillard R. 2019. Customized versus population birth weight charts for identification of newborns at risk of long-term adverse cardio-metabolic and respiratory outcomes: a population-based prospective cohort study. BMC Medicine. 17(1):186. doi:10.1186/s12916-019-1424-4.

Etter J-F. 2014. Levels of saliva cotinine in electronic cigarette users. Addiction. 109(5):825–829. doi:10.1111/add.12475.

Fall CHD, Kumaran K. 2019. Metabolic programming in early life in humans. Philosophical Transactions of the Royal Society B: Biological Sciences. 374(1770):20180123. doi:10.1098/rstb.2018.0123.

Fan J, Ping J, Zhang W, Rao Y, Liu H, Zhang J, Yan Y. 2016. Prenatal and lactation nicotine exposure affects morphology and function of brown adipose tissue in male rat offspring. Ultrastructural Pathology. 40(5):288–295. doi:10.1080/01913123.2016.1223243.

Fan J, Zhang W, Rao Y, Xue J, Wang F, Zhang L, Yan Y. 2016. Perinatal Nicotine Exposure Increases Obesity Susceptibility in Adult Male Rat Offspring by Altering Early Adipogenesis. Endocrinology. 157(11):4276–4286. doi:10.1210/en.2016-1269.

Farsalinos K. 2018. Electronic cigarettes: an aid in smoking cessation, or a new health hazard? Ther Adv Respir Dis. 12:1753465817744960. doi:10.1177/1753465817744960.

Felicia N, Mikael N, Ronny W. 2019. Blood Pressure and Heart Rate Variability in Preschool Children Exposed to Smokeless Tobacco in Fetal Life. Journal of the American Heart Association. 8(21):e012629. doi:10.1161/JAHA.119.012629.

Fucic A, Guszak V, Mantovani A. 2017. Transplacental exposure to environmental carcinogens: Association with childhood cancer risks and the role of modulating factors. Reproductive Toxicology. 72:182–190. doi:10.1016/j.reprotox.2017.06.044.

Gaither KH, Brunner Huber LR, Thompson ME, Huet-Hudson YM. 2009. Does the use of nicotine replacement therapy during pregnancy affect pregnancy outcomes? Matern Child Health J. 13(4):497–504. doi:10.1007/s10995-008-0361-1.

Gao Y-J, Holloway AC, Su L-Y, Takemori K, Lu C, Lee RMKW. 2008. Effects of fetal and neonatal exposure to nicotine on blood pressure and perivascular adipose tissue function in adult life. European Journal of Pharmacology. 590(1):264–268. doi:10.1016/j.ejphar.2008.05.044.

Gauldie J, Galt T, Bonniaud P, Robbins C, Kelly M, Warburton D. 2003. Transfer of the active form of transforming growth factor-beta 1 gene to newborn rat lung induces changes consistent with bronchopulmonary dysplasia. Am J Pathol. 163(6):2575–2584. doi:10.1016/s0002-9440(10)63612-7.

Gibbs K, Collaco JM, McGrath-Morrow SA. 2016. Impact of Tobacco Smoke and Nicotine Exposure on Lung Development. Chest. 149(2):552–561. doi:10.1378/chest.15-1858.

Gilbert NL, Nelson CRM, Greaves L. 2015. Smoking cessation during pregnancy and relapse after childbirth in Canada. J Obstet Gynaecol Can. 37(1):32–39. doi:10.1016/s1701-2163(15)30360-1.

Glover M, Phillips CV. 2020. Potential effects of using non-combustible tobacco and nicotine products during pregnancy: a systematic review. Harm Reduction Journal. 17(1):16. doi:10.1186/s12954-020-00359-2.

Grando SA. 2014. Connections of nicotine to cancer. Nat Rev Cancer. 14(6):419–429. doi:10.1038/nrc3725.

Greaves L, Poole N, Okoli CTC, Hemsing N, Qu A, Bialystok L, O'Leary R. 2011. Expecting to Quit: A Best-Practices Review of Smoking Cessation Interventions for Pregnant and Postpartum Girls and Women (2nd ed.).

http://bccewh.bc.ca/2014/02/expecting-to-quit-a-best-practices-review-of-smoking-cessation-interventions-for-pregnant-and-postpartum-girls-and-women/.

Greene RM, Pisano MM. 2019. Developmental toxicity of e-cigarette aerosols. Birth Defects Research. 111(17):1294–1301. doi:10.1002/bdr2.1571.

Gu L. 2014. Integrative Analysis of Prostate Cancer Methylome and Smoking-induced Transgenerational Epigenomic Reprogramming. doi:10.11588/HEIDOK.00016011. [accessed 2020 May 11]. http://archiv.ub.uni-heidelberg.de/volltextserver/id/eprint/16011.

Gunnerbeck A, Bonamy A-KE, Wikström A-K, Granath F, Wickström R, Cnattingius S. 2014. Maternal Snuff Use and Smoking and the Risk of Oral Cleft Malformations - A Population-Based Cohort Study. PLOS ONE. 9(1):e84715. doi:10.1371/journal.pone.0084715.

Gupta P, Subramoney S. 2006. Smokeless Tobacco Use and Risk of Stillbirth: A Cohort Study in Mumbai, India. Epidemiology. 17(1):47–51. doi:10.1097/01.ede.0000190545.19168.c4.

Haghighi A, Schwartz DH, Abrahamowicz M, Leonard GT, Perron M, Richer L, Veillette S, Gaudet D, Paus T, Pausova Z. 2013. Prenatal Exposure to Maternal Cigarette Smoking, Amygdala Volume, and Fat Intake in Adolescence. JAMA Psychiatry. 70(1):98–105. doi:10.1001/archgenpsychiatry.2012.1101.

Haussmann H-J, Fariss MW. 2016. Comprehensive review of epidemiological and animal studies on the potential carcinogenic effects of nicotine *per se*. Critical Reviews in Toxicology. 46(8):701–734. doi:10.1080/10408444.2016.1182116.

He Y, Chen J, Zhu L-H, Hua L-L, Ke F-F. 2017. Maternal Smoking During Pregnancy and ADHD: Results From a Systematic Review and Meta-Analysis of Prospective Cohort Studies. J Atten Disord. doi:10.1177/1087054717696766.

Hickson C, Lewis S, Campbell KA, Cooper S, Berlin I, Claire R, Oncken C, Coleman-Haynes T, Coleman T. 2019. Comparison of nicotine exposure during pregnancy when smoking and abstinent with nicotine replacement therapy: systematic review and meta-analysis. Addiction. 114(3):406–424. doi:10.1111/add.14473.

Hodyl NA, Grzeskowiak LE, Stark MJ, Scheil W, Clifton VL. 2014. The impact of Aboriginal status, cigarette smoking and smoking cessation on perinatal outcomes in South Australia. Medical Journal of Australia. 201(5):274–278. doi:10.5694/mja13.11142.

Holbrook BD. 2016. The effects of nicotine on human fetal development. Birth Defects Research Part C: Embryo Today: Reviews. 108(2):181–192. doi:10.1002/bdrc.21128.

Hossain MS, Kypri K, Rahman B, Milton AH. 2018. Smokeless tobacco consumption and stillbirth: Population-based case–control study in rural Bangladesh. Drug and Alcohol Review. 37(3):414–420. doi:10.1111/dar.12566.

Huang LZ, Winzer-Serhan UH. 2007. Nicotine regulates mRNA expression of feeding peptides in the arcuate nucleus in neonatal rat pups. Dev Neurobiol. 67(3):363–377. doi:10.1002/dneu.20348.

Improgo MaR, Tapper AR, Gardner PD. 2011. Nicotinic acetylcholine receptor-mediated mechanisms in lung cancer. Biochemical Pharmacology. 82(8):1015–1021. doi:10.1016/j.bcp.2011.05.020.

International Agency for Research on Cancer. 2004. Smokeless Tobacco and Some Tobacco-specific N-Nitrosamines. International Agency for Research on Cancer. https://publications.iarc.fr/Book-And-Report-Series/Iarc-Monographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans/Smokeless-Tobacco-And-Some-Tobacco-specific-Em-N-Em--Nitrosamines-2007.

Jarvis M, Tunstall-Pedoe H, Feyerabend C, Vesey C, Salloojee Y. 1984. Biochemical markers of smoke absorption and self reported exposure to passive smoking. J Epidemiol Community Health. 38(4):335–339. doi:10.1136/jech.38.4.335.

Jensen K, Nizamutdinov D, Guerrier M, Afroze S, Dostal D, Glaser S. 2012. General mechanisms of nicotine-induced fibrogenesis. FASEB J. 26(12):4778–4787. doi:10.1096/fj.12-206458.

Jordanov JS. 1990. Cotinine concentrations in amniotic fluid and urine of smoking, passive smoking and non-smoking pregnant women at term and in the urine of their neonates on 1st day of life. Eur J Pediatr. 149(10):734–737. doi:10.1007/BF01959534.

Kalliola S, Pelkonen AS, Malmberg LP, Sarna S, Hämäläinen M, Mononen I, Mäkelä MJ. 2013. Maternal smoking affects lung function and airway inflammation in young children with multiple-trigger wheeze. Journal of Allergy and Clinical Immunology. 131(3):730–735. doi:10.1016/j.jaci.2013.01.005.

Kapaya M, Tong V, Ding H. 2015. Nicotine replacement therapy and other interventions for pregnant smokers: Pregnancy Risk Assessment Monitoring System, 2009–2010. Preventive Medicine. 78:92–100. doi:10.1016/j.ypmed.2015.07.008.

Kärkkäinen M, Kettunen H-P, Nurmi H, Selander T, Purokivi M, Kaarteenaho R. 2017. Effect of smoking and comorbidities on survival in idiopathic pulmonary fibrosis. Respir Res. 18(1):160. doi:10.1186/s12931-017-0642-6.

Kazemi T, Avci NG, Keller RF, Akay YM, Akay M. 2020. Investigating the influence of perinatal nicotine exposure on genetic profiles of neurons in the sub-regions of the VTA. Scientific Reports. 10(1):2419. doi:10.1038/s41598-020-59248-0.

Krebs M, Sakurai R, Torday JS, Rehan VK. 2010. Evidence for in vivo nicotine-induced alveolar interstitial fibroblast-to-myofibroblast transdifferentiation. Exp Lung Res. 36(7):390–398. doi:10.3109/01902141003714023.

Kuniyoshi KM, Rehan VK. 2019. The impact of perinatal nicotine exposure on fetal lung development and subsequent respiratory morbidity. Birth Defects Research. 111(17):1270–1283. doi:10.1002/bdr2.1595.

Lambers DS, Clark KE. 1996. The maternal and fetal physiologic effects of nicotine. Semin Perinatol. 20(2):115–126. doi:10.1016/s0146-0005(96)80079-6.

Landau LI. 2008. Tobacco smoke exposure and tracking of lung function into adult life. Paediatric Respiratory Reviews. 9(1):39–44. doi:10.1016/j.prrv.2007.11.002.

Lange S, Probst C, Rehm J, Popova S. 2018. National, regional, and global prevalence of smoking during pregnancy in the general population: a systematic review and meta-analysis. The Lancet Global Health. 6(7):e769–e776. doi:10.1016/S2214-109X(18)30223-7.

Lavezzi AM, Corna MF, Alfonsi G, Matturri L. 2014. Possible role of the α7 nicotinic receptors in mediating nicotine's effect on developing lung – implications in unexplained human perinatal death. BMC Pulm Med. 14(1):11. doi:10.1186/1471-2466-14-11.

Lee Ken W. K., Abrahamowicz M, Leonard GT, Richer L, Perron M, Veillette S, Reischl E, Bouchard L, Gaudet D, Paus T, et al. 2015. Prenatal exposure to cigarette smoke interacts with OPRM1 to modulate dietary preference for fat. J Psychiatry Neurosci. 40(1):38–45. doi:10.1503/jpn.130263.

Lee Ken W.K., Richmond R, Hu P, French L, Shin J, Bourdon C, Reischl E, Waldenberger M, Zeilinger S, Gaunt T, et al. 2015. Prenatal Exposure to Maternal Cigarette Smoking and DNA Methylation: Epigenome-Wide Association in a Discovery Sample of Adolescents and Replication in an Independent Cohort at Birth through 17 Years of Age. Environmental Health Perspectives. 123(2):193–199. doi:10.1289/ehp.1408614.

Liang X, Xiao L, Luo Y, Xu J. 2020. Prevalence and risk factors of childhood hypertension from birth through childhood: a retrospective cohort study. Journal of Human Hypertension. 34(2):151–164. doi:10.1038/s41371-019-0282-z.

Liao C-Y, Chen Y-J, Lee J-F, Lu C-L, Chen C-H. 2012. Cigarettes and the developing brain: Picturing nicotine as a neuroteratogen using clinical and preclinical studies. Tzu Chi Medical Journal. 24(4):157–161. doi:10.1016/j.tcmj.2012.08.003.

Lobstein T, Jackson-Leach R. 2016. Planning for the worst: estimates of obesity and comorbidities in school-age children in 2025. Pediatr Obes. 11(5):321–325. doi:10.1111/ijpo.12185.

Ma N, Nicholson CJ, Wong M, Holloway AC, Hardy DB. 2014. Fetal and neonatal exposure to nicotine leads to augmented hepatic and circulating triglycerides in adult male offspring due to increased expression of fatty acid synthase. Toxicology and Applied Pharmacology. 275(1):1–11. doi:10.1016/j.taap.2013.12.010.

Mahar I, Bagot RC, Davoli MA, Miksys S, Tyndale RF, Walker C-D, Maheu M, Huang S-H, Wong TP, Mechawar N. 2012. Developmental hippocampal neuroplasticity in a model of nicotine replacement therapy during pregnancy and breastfeeding. PLoS ONE. 7(5):e37219. doi:10.1371/journal.pone.0037219.

Maritz GS. 2013. Perinatal Exposure to Nicotine and Implications for Subsequent Obstructive Lung Disease. Paediatric Respiratory Reviews. 14(1):3–8. doi:10.1016/j.prrv.2012.03.006.

Maritz GS, Harding R. 2011. Life-long programming implications of exposure to tobacco smoking and nicotine before and soon after birth: evidence for altered lung development. Int J Environ Res Public Health. 8(3):875–898. doi:10.3390/ijerph8030875.

Mark KS, Farquhar B, Chisolm MS, Coleman-Cowger VH, Terplan M. 2015. Knowledge, Attitudes, and Practice of Electronic Cigarette Use Among Pregnant Women. Journal of Addiction Medicine. 9(4):266–272. doi:10.1097/ADM.0000000000000128.

Marufu TC, Ahankari A, Coleman T, Lewis S. 2015. Maternal smoking and the risk of still birth: systematic review and meta-analysis. BMC Public Health. 15(1):239. doi:10.1186/s12889-015-1552-5.

McEvoy CT, Spindel ER. 2017. Pulmonary Effects of Maternal Smoking on the Fetus and Child: Effects on Lung Development, Respiratory Morbidities, and Life Long Lung Health. Paediatric Respiratory Reviews. 21:27–33. doi:10.1016/j.prrv.2016.08.005.

McGrath-Morrow SA, Hayashi M, Aherrera A, Lopez A, Malinina A, Collaco JM, Neptune E, Klein JD, Winickoff JP, Breysse P, et al. 2015. The Effects of Electronic Cigarette Emissions on Systemic Cotinine Levels, Weight and Postnatal Lung Growth in Neonatal Mice. Morty RE, editor. PLoS ONE. 10(2):e0118344. doi:10.1371/journal.pone.0118344.

Mishra A, Chaturvedi P, Datta S, Sinukumar S, Joshi P, Garg A. 2015. Harmful effects of nicotine. Indian J Med Paediatr Oncol. 36(1):24–31. doi:10.4103/0971-5851.151771.

Moerke MJ, McMahon LR, Wilkerson JL. 2020. More than Smoke and Patches: The Quest for Pharmacotherapies to Treat Tobacco Use Disorder. Pharmacol Rev. 72(2):527–557. doi:10.1124/pr.119.018028.

Moore E, Blatt K, Chen A, Van Hook J, Defranco EA. 2016. Relationship of trimester specific smoking patterns and risk of preterm birth. Am J Obstet Gynecol. 215(1):109.e1-109.e6. doi:10.1016/j.ajog.2016.01.167.

Morales-Suárez-Varela MM, Bille C, Christensen K, Olsen J. 2006. Smoking habits, nicotine use, and congenital malformations. Obstet Gynecol. 107(1):51–57. doi:10.1097/01.AOG.0000194079.66834.d5.

Morgen CS, Ängquist L, Baker JL, Andersen AMN, Michaelsen KF, Sørensen TIA. 2018. Prenatal risk factors influencing childhood BMI and overweight independent of birth weight and infancy BMI: a path analysis within the Danish National Birth Cohort. International Journal of Obesity. 42(4):594–602. doi:10.1038/ijo.2017.217.

Moschonis G, Kaliora AC, Karatzi K, Michaletos A, Lambrinou C-P, Karachaliou AK, Chrousos GP, Lionis C, Manios Y. 2017. Perinatal, sociodemographic and lifestyle correlates of increased total and visceral fat mass levels in schoolchildren in Greece: the Healthy Growth Study. Public Health Nutrition. 20(4):660–670. doi:10.1017/S1368980016002640.

Muhammad A, Mychasiuk R, Nakahashi A, Hossain SR, Gibb R, Kolb B. 2012. Prenatal nicotine exposure alters neuroanatomical organization of the developing brain. Synapse. 66(11):950–954. doi:10.1002/syn.21589.

Nakano Y. 2020. Adult-Onset Diseases in Low Birth Weight Infants: Association with Adipose Tissue Maldevelopment. Journal of Atherosclerosis and Thrombosis. 27(5):397–405. doi:10.5551/jat.RV17039.

Napierala M, Mazela J, Merritt TA, Florek E. 2016. Tobacco smoking and breastfeeding: Effect on the lactation process, breast milk composition and infant development. A critical review. Environmental Research. 151:321–338. doi:10.1016/j.envres.2016.08.002.

National Institute for Health and Care Excellence. 2010. Smoking: stopping in pregnancy and after childbirth | Public health guideline. https://www.nice.org.uk/guidance/ph26.

Nguyen T, Li GE, Chen H, Cranfield CG, McGrath KC, Gorrie CA. 2018. Maternal E-Cigarette Exposure Results in Cognitive and Epigenetic Alterations in Offspring in a Mouse Model. Chem Res Toxicol. 31(7):601–611. doi:10.1021/acs.chemrestox.8b00084.

Nowak D, Ruta U, Piaşęcka G. 1990. Nicotine increases human polymorphonuclear leukocytes chemotactic response —a possible additional mechanism of lung injury in cigarette smokers. Experimental Pathology. 39(1):37–43. doi:10.1016/S0232-1513(11)80218-5.

Oncken C, Ricci KA, Kuo C-L, Dornelas E, Kranzler HR, Sankey HZ. 2017. Correlates of Electronic Cigarettes Use Before and During Pregnancy. Nicotine Tob Res. 19(5):585–590. doi:10.1093/ntr/ntw225.

Ordean A, Wong S, Graves L. 2017. No. 349-Substance Use in Pregnancy. Journal of Obstetrics and Gynaecology Canada. 39(10):922-937.e2. doi:10.1016/j.jogc.2017.04.028.

Orton S, Bowker K, Cooper S, Naughton F, Ussher M, Pickett KE, Leonardi-Bee J, Sutton S, Dhalwani NN, Coleman T. 2014. Longitudinal cohort survey of women's smoking behaviour and attitudes in pregnancy: study methods and baseline data. BMJ Open. 4(5):e004915. doi:10.1136/bmjopen-2014-004915.

Pardo A, Selman M. 2016. Lung Fibroblasts, Aging, and Idiopathic Pulmonary Fibrosis. Annals ATS. 13(Supplement_5):S417–S421. doi:10.1513/AnnalsATS.201605-341AW.

Patel D, Davis KC, Cox S, Bradfield B, King BA, Shafer P, Caraballo R, Bunnell R. 2016. Reasons for current E-cigarette use among U.S. adults. Prev Med. 93:14–20. doi:10.1016/j.ypmed.2016.09.011.

Pattemore P. 2013. Tobacco or healthy children: the two cannot co-exist. Front Pediatr. 1. doi:10.3389/fped.2013.00020. [accessed 2020 May 11]. http://journal.frontiersin.org/article/10.3389/fped.2013.00020/abstract.

Pausová Z, Paus T, Šedová L, Bérubé J. 2003. Prenatal exposure to nicotine modifies kidney weight and blood pressure in genetically susceptible rats: A case of gene-environment interaction. Kidney International. 64(3):829–835. doi:10.1046/j.1523-1755.2003.00172.x.

Peixoto TC, Moura EG, Oliveira E, Younes-Rapozo V, Soares PN, Rodrigues VST, Torsoni MA, Torsoni AS, Manhães AC, Lisboa PC. 2019. Hypothalamic Neuropeptides Expression and Hypothalamic Inflammation in Adult Rats that Were Exposed to Tobacco Smoke during Breastfeeding: Sex-Related Differences. Neuroscience. 418:69–81. doi:10.1016/j.neuroscience.2019.08.006.

Pelone F, Specchia ML, Veneziano MA, Capizzi S, Bucci S, Mancuso A, Ricciardi W, de Belvis AG. 2012. Economic impact of childhood obesity on health systems: a systematic review. Obes Rev. 13(5):431–440. doi:10.1111/j.1467-789X.2011.00968.x.

Pereira PP da S, Da Mata FAF, Figueiredo ACG, de Andrade KRC, Pereira MG. 2017. Maternal Active Smoking During Pregnancy and Low Birth Weight in the Americas: A Systematic Review and Meta-analysis. Nicotine Tob Res. 19(5):497–505. doi:10.1093/ntr/ntw228.

Pernia S, DeMaagd G. 2016. The New Pregnancy and Lactation Labeling Rule. P T. 41(11):713–715.

Petre MA, Petrik J, Ellis R, Inman MD, Holloway AC, Labiris NR. 2011. Fetal and Neonatal Exposure to Nicotine Disrupts Postnatal Lung Development in Rats: Role of VEGF and Its Receptors: International Journal of Toxicology. doi:10.1177/1091581810395332. https://journals.sagepub.com/doi/10.1177/1091581810395332.

Pineles BL, Park E, Samet JM. 2014. Systematic Review and Meta-Analysis of Miscarriage and Maternal Exposure to Tobacco Smoke During Pregnancy. Am J Epidemiol. 179(7):807–823. doi:10.1093/aje/kwt334.

Pinheiro CR, Moura EG, Manhães AC, Fraga MC, Claudio-Neto S, Younes-Rapozo V, Santos-Silva AP, Lotufo BM, Oliveira E, Lisboa PC. 2015. Maternal nicotine exposure during lactation alters food preference, anxiety-like behavior and the brain dopaminergic reward system in the adult rat offspring. Physiology & Behavior. 149:131–141. doi:10.1016/j.physbeh.2015.05.040.

Polli FS, Scharff MB, Ipsen TH, Aznar S, Kohlmeier KA, Andreasen JT. 2020. Prenatal nicotine exposure in mice induces sex-dependent anxiety-like behavior, cognitive deficits, hyperactivity, and changes in the expression of glutamate receptor associated-genes in the prefrontal cortex. Pharmacology Biochemistry and Behavior. 195:172951. doi:10.1016/j.pbb.2020.172951.

Räisänen S, Sankilampi U, Gissler M, Kramer MR, Hakulinen-Viitanen T, Saari J, Heinonen S. 2014. Smoking cessation in the first trimester reduces most obstetric risks, but not the risks of major congenital anomalies and admission to neonatal care: a population-based cohort study of 1 164 953 singleton pregnancies in Finland. J Epidemiol Community Health. 68(2):159–164. doi:10.1136/jech-2013-202991.

Ramamurthi D, Gall PA, Ayoub N, Jackler RK. 2016. Leading-Brand Advertisement of Quitting Smoking Benefits for E-Cigarettes. Am J Public Health. 106(11):2057–2063. doi:10.2105/AJPH.2016.303437.

Ratsch A, Bogossian F. 2014. Smokeless tobacco use in pregnancy: an integrative review of the literature. Int J Public Health. 59(4):599–608. doi:10.1007/s00038-014-0558-6.

Rayfield S, Plugge E. 2017. Systematic review and meta-analysis of the association between maternal smoking in pregnancy and childhood overweight and obesity. J Epidemiol Community Health. 71(2):162–173. doi:10.1136/jech-2016-207376.

Rehan VK, Liu J, Naeem E, Tian J, Sakurai R, Kwong K, Akbari O, Torday JS. 2012. Perinatal nicotine exposure induces asthma in second generation offspring. BMC Med. 10(1):129. doi:10.1186/1741-7015-10-129.

Riaz M, Lewis S, Coleman T, Aveyard P, West R, Naughton F, Ussher M. 2016. Which measures of cigarette dependence are predictors of smoking cessation during pregnancy? Analysis of data from a randomized controlled trial. Addiction. 111(9):1656–1665. doi:10.1111/add.13395.

Rogers JM. 2019. Smoking and pregnancy: Epigenetics and developmental origins of the metabolic syndrome. Birth Defects Research. 111(17):1259–1269. doi:10.1002/bdr2.1550.

Roomans GM, Vanthanouvong V, Dragomir A, Kozlova I, Wróblewski R. 2002. Effects of nicotine on intestinal and respiratory epithelium. J Submicrosc Cytol Pathol. 34(4):381–388.

Rotroff DM, Joubert BR, Marvel SW, Håberg SE, Wu MC, Nilsen RM, Ueland PM, Nystad W, London SJ, Motsinger-Reif A. 2016. Maternal smoking impacts key

biological pathways in newborns through epigenetic modification in Utero. BMC Genomics. 17(1):976. doi:10.1186/s12864-016-3310-1.

Rowe H, Baker T, Hale TW. 2015. Maternal Medication, Drug Use, and Breastfeeding. Child and Adolescent Psychiatric Clinics of North America. 24(1):1–20. doi:10.1016/j.chc.2014.09.005.

Ruszkiewicz JA, Zhang Z, Gonçalves FM, Tizabi Y, Zelikoff JT, Aschner M. 2020. Neurotoxicity of e-cigarettes. Food and Chemical Toxicology. 138:111245. doi:10.1016/j.fct.2020.111245.

Sailer S, Sebastiani G, Andreu-Férnández V, García-Algar O. 2019. Impact of Nicotine Replacement and Electronic Nicotine Delivery Systems on Fetal Brain Development. Int J Environ Res Public Health. 16(24). doi:10.3390/ijerph16245113.

Sanner T, Grimsrud TK. 2015. Nicotine: Carcinogenicity and Effects on Response to Cancer Treatment – A Review. Front Oncol. 5. doi:10.3389/fonc.2015.00196. [accessed 2020 May 11]. http://journal.frontiersin.org/Article/10.3389/fonc.2015.00196/abstract.

Sekhon HS, Jia Y, Raab R, Kuryatov A, Pankow JF, Whitsett JA, Lindstrom J, Spindel ER. 1999. Prenatal nicotine increases pulmonary α7 nicotinic receptor expression and alters fetal lung development in monkeys. J Clin Invest. 103(5):637–647. doi:10.1172/JCI5232.

Sekhon HS, Keller JA, Proskocil BJ, Martin EL, Spindel ER. 2002. Maternal Nicotine Exposure Upregulates Collagen Gene Expression in Fetal Monkey Lung: Association with α 7 Nicotinic Acetylcholine Receptors. Am J Respir Cell Mol Biol. 26(1):31–41. doi:10.1165/ajrcmb.26.1.4170.

Shah NR, Bracken MB. 2000. A systematic review and meta-analysis of prospective studies on the association between maternal cigarette smoking and preterm delivery. American Journal of Obstetrics & Gynecology. 182(2):465–472. doi:10.1016/S0002-9378(00)70240-7.

Shobeiri F, Jenabi E. 2017. Smoking and placenta previa: a meta-analysis. The Journal of Maternal-Fetal & Neonatal Medicine. 30(24):2985–2990. doi:10.1080/14767058.2016.1271405.

Shobeiri F, Masoumi SZ, Jenabi E. 2017. The association between maternal smoking and placenta abruption: a meta-analysis. The Journal of Maternal-Fetal & Neonatal Medicine. 30(16):1963–1967. doi:10.1080/14767058.2016.1235694.

Sifat AE, Nozohouri S, Villalba H, Al Shoyaib A, Vaidya B, Karamyan VT, Abbruscato T. 2020. Prenatal electronic cigarette exposure decreases brain glucose utilization and worsens outcome in offspring hypoxic-ischemic brain injury. J Neurochem. 153(1):63–79. doi:10.1111/jnc.14947.

Silvestri M, Franchi S, Pistorio A, Petecchia L, Rusconi F. 2015. Smoke exposure, wheezing, and asthma development: A systematic review and meta-analysis in unselected birth cohorts. Pediatric Pulmonology. 50(4):353–362. doi:10.1002/ppul.23037.

Slotkin TA, Ryde IT, Tate CA, Seidler FJ. 2007. Lasting effects of nicotine treatment and withdrawal on serotonergic systems and cell signaling in rat brain regions: separate or sequential exposure during fetal development and adulthood. Brain Res Bull. 73(4–6):259–272. doi:10.1016/j.brainresbull.2007.03.012.

Smith A, Dwoskin L, Pauly J. 2016. Early exposure to nicotine during critical periods of brain development: Mechanisms and consequences. J Pediatr Biochem. 01(02):125–141. doi:10.1055/s-0036-1586367.

de Smith AJ, Kaur M, Gonseth S, Endicott A, Selvin S, Zhang L, Roy R, Shao X, Hansen HM, Kang AY, et al. 2017. Correlates of Prenatal and Early-Life Tobacco Smoke Exposure and Frequency of Common Gene Deletions in Childhood Acute Lymphoblastic Leukemia. Cancer Res. 77(7):1674–1683. doi:10.1158/0008-5472.CAN-16-2571.

Somm E, Schwitzgebel VM, Vauthay DM, Camm EJ, Chen CY, Giacobino J-P, Sizonenko SV, Aubert ML, Hüppi PS. 2008. Prenatal Nicotine Exposure Alters Early Pancreatic Islet and Adipose Tissue Development with Consequences on the Control of Body Weight and Glucose Metabolism Later in Life. Endocrinology. 149(12):6289–6299. doi:10.1210/en.2008-0361.

Soneji S, Beltrán-Sánchez H. 2019. Association of Maternal Cigarette Smoking and Smoking Cessation With Preterm Birth. JAMA Netw Open. 2(4):e192514–e192514. doi:10.1001/jamanetworkopen.2019.2514.

Spindel ER, McEvoy CT. 2016. The Role of Nicotine in the Effects of Maternal Smoking during Pregnancy on Lung Development and Childhood Respiratory Disease. Implications for Dangers of E-Cigarettes. Am J Respir Crit Care Med. 193(5):486–494. doi:10.1164/rccm.201510-2013PP.

St Helen G, Havel C, Dempsey DA, Jacob P, Benowitz NL. 2016. Nicotine delivery, retention and pharmacokinetics from various electronic cigarettes. Addiction. 111(3):535–544. doi:10.1111/add.13183.

Stocks J, Hislop A, Sonnappa S. 2013. Early lung development: lifelong effect on respiratory health and disease. The Lancet Respiratory Medicine. 1(9):728–742. doi:10.1016/S2213-2600(13)70118-8.

Strandberg-Larsen K, Tinggaard M, Andersen A-MN, Olsen J, Grønbæk M. 2008. Use of nicotine replacement therapy during pregnancy and stillbirth: a cohort study. BJOG: An International Journal of Obstetrics & Gynaecology. 115(11):1405–1410. doi:10.1111/j.1471-0528.2008.01867.x.

Suliankatchi RA, Sinha DN. 2016. The Human Cost of Tobacco Chewing Among Pregnant Women in India: A Systematic Review and Meta-analysis. J Obstet Gynecol India. 66(1):161–166. doi:10.1007/s13224-015-0821-7.

Suter M, Abramovici A, Showalter L, Hu M, Shope CD, Varner M, Aagaard-Tillery K. 2010. In utero tobacco exposure epigenetically modifies placental CYP1A1 expression. Metabolism. 59(10):1481–1490. doi:10.1016/j.metabol.2010.01.013.

Suter MA, Abramovici AR, Griffin E, Branch DW, Lane RH, Mastrobattista J, Rehan VK, Aagaard K. 2015. In utero nicotine exposure epigenetically alters fetal chromatin structure and differentially regulates transcription of the glucocorticoid receptor in a rat model. Birth Defects Res Part A Clin Mol Teratol. 103(7):583–588. doi:10.1002/bdra.23395.

Tarantal AF, Chen H, Shi TT, Lu C-H, Fang AB, Buckley S, Kolb M, Gauldie J, Warburton D, Shi W. 2010. Overexpression of transforming growth factor- 1 in fetal monkey lung results in prenatal pulmonary fibrosis. European Respiratory Journal. 36(4):907–914. doi:10.1183/09031936.00011810.

Taskar VS, Coultas DB. 2006. Is Idiopathic Pulmonary Fibrosis an Environmental Disease? Proceedings of the American Thoracic Society. 3(4):293–298. doi:10.1513/pats.200512-131TK.

The Royal Australian and New Zealand College of Obstetricians and Gynaecologists. 2017. Pre-pregnancy Counselling. https://ranzcog.edu.au/RANZCOG_SITE/media/RANZCOG-MEDIA/Women%27s%20Health/Statement%20and%20guidelines/Clinical-Obstetrics/Pre-pregnancy-Counselling-(C-Obs-3a)-review-July-2017_1.pdf?ext=.pdf.

Thomas JD, Garrison ME, Slawecki CJ, Ehlers CL, Riley EP. 2000. Nicotine exposure during the neonatal brain growth spurt produces hyperactivity in preweanling rats. Neurotoxicol Teratol. 22(5):695–701. doi:10.1016/s0892-0362(00)00096-9.

Tiesler CMT, Heinrich J. 2014. Prenatal nicotine exposure and child behavioural problems. Eur Child Adolesc Psychiatry. 23(10):913–929. doi:10.1007/s00787-014-0615-y.

Tiniakos DG, Vos MB, Brunt EM. 2010. Nonalcoholic Fatty Liver Disease: Pathology and Pathogenesis. Annu Rev Pathol Mech Dis. 5(1):145–171. doi:10.1146/annurev-pathol-121808-102132.

Tong VT, Dietz PM, Morrow B, D'Angelo DV, Farr SL, Rockhill KM, England LJ, Centers for Disease Control and Prevention (CDC). 2013. Trends in smoking before, during, and after pregnancy--Pregnancy Risk Assessment Monitoring System, United States, 40 sites, 2000-2010. MMWR Surveill Summ. 62(6):1–19.

Veisani Y, Jenabi E, Delpisheh A, Khazaei S. 2019. Effect of prenatal smoking cessation interventions on birth weight: meta-analysis. The Journal of Maternal-Fetal & Neonatal Medicine. 32(2):332–338. doi:10.1080/14767058.2017.1378335.

Vicary GW, Ritzenthaler JD, Panchabhai TS, Torres-González E, Roman J. 2017. Nicotine stimulates collagen type I expression in lung via α7 nicotinic acetylcholine receptors. Respir Res. 18(1):115. doi:10.1186/s12931-017-0596-8.

Villarroya F, Cereijo R, Gavaldà-Navarro A, Villarroya J, Giralt M. 2018. Inflammation of brown/beige adipose tissues in obesity and metabolic disease. J Intern Med. 284(5):492–504. doi:10.1111/joim.12803.

Wang B, Chen H, Chan YL, Wang G, Oliver BG. 2020. Why Do Intrauterine Exposure to Air Pollution and Cigarette Smoke Increase the Risk of Asthma? Front Cell Dev Biol. 8:38. doi:10.3389/fcell.2020.00038.

Wang Z, Ouyang Q, Huang Z, Lin L, Yu E, Ferrari MW. 2015. Prenatal nicotine exposure induces gender-associated left ventricular-arterial uncoupling in adult offspring. Molecular Medicine Reports. 12(1):410–418. doi:10.3892/mmr.2015.3364.

Ward AM, Yaman R, Ebbert JO. 2020. Electronic nicotine delivery system design and aerosol toxicants: A systematic review. PLOS ONE. 15(6):e0234189. doi:10.1371/journal.pone.0234189.

Wawryk-Gawda E, Chłapek K, Zarobkiewicz MK, Lis-Sochocka M, Chylińska-Wrzos P, Boguszewska-Czubara A, Sławiński MA, Franczak A, Jodłowska-Jędrych B, Biała G. 2018. CB2R agonist prevents nicotine induced lung fibrosis. Experimental Lung Research. 44(7):344–351. doi:10.1080/01902148.2018.1543368.

Weng SF, Redsell SA, Swift JA, Yang M, Glazebrook CP. 2012. Systematic review and meta-analyses of risk factors for childhood overweight identifiable during infancy. Archives of Disease in Childhood. 97(12):1019–1026. doi:10.1136/archdischild-2012-302263.

Willoughby MT, Kollins SH, McClernon FJ, The Family Life Investigative Group. 2009. Association between smoking and retrospectively reported attention-deficit/hyperactivity disorder symptoms in a large sample of new mothers. Nicotine & Tobacco Research. 11(3):313–322. doi:10.1093/ntr/ntp001.

Wongtrakool C, Wang N, Hyde DM, Roman J, Spindel ER. 2012. Prenatal nicotine exposure alters lung function and airway geometry through α7 nicotinic receptors. Am J Respir Cell Mol Biol. 46(5):695–702. doi:10.1165/rcmb.2011-0028OC.

World Health Organization. 2013. WHO | WHO recommendations for the prevention and management of tobacco use and second-hand smoke exposure in pregnancy. WHO. http://www.who.int/tobacco/publications/pregnancy/guidelinestobaccosmokeexposure/en/.

Wu C-C, Hsu T-Y, Chang J-C, Ou C-Y, Kuo H-C, Liu C-A, Wang C-L, Chuang H, Chen C-P, Yang KD. 2019. Paternal Tobacco Smoke Correlated to Offspring Asthma and Prenatal Epigenetic Programming. Front Genet. 10. doi:10.3389/fgene.2019.00471. https://www.frontiersin.org/articles/10.3389/fgene.2019.00471/full.

Xiao D, Dasgupta C, Li Y, Huang X, Zhang L. 2014. Perinatal nicotine exposure increases angiotensin II receptor-mediated vascular contractility in adult offspring. PLoS ONE. 9(9):e108161. doi:10.1371/journal.pone.0108161.

Xiao D, Huang X, Li Y, Dasgupta C, Wang L, Zhang L. 2015. Antenatal Antioxidant Prevents Nicotine-Mediated Hypertensive Response in Rat Adult Offspring. Biol Reprod. 93(3). doi:10.1095/biolreprod.115.132381. https://academic.oup.com/biolreprod/article/93/3/66, 1-8/2434396.

Younes-Rapozo V, Moura EG, Manhães AC, Pinheiro CR, Santos-Silva AP, Oliveira E de, Lisboa PC. 2013. Maternal nicotine exposure during lactation alters hypothalamic neuropeptides expression in the adult rat progeny. Food and Chemical Toxicology. 58:158–168. doi:10.1016/j.fct.2013.04.036.

Zhang K, Wang X. 2013. Maternal smoking and increased risk of sudden infant death syndrome: A meta-analysis. Legal Medicine. 15(3):115–121. doi:10.1016/j.legalmed.2012.10.007.

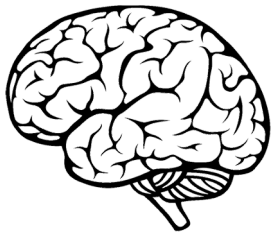
Zhang L, Spencer TJ, Biederman J, Bhide PG. 2018. Attention and working memory deficits in a perinatal nicotine exposure mouse model. Rosenfeld CS, editor. PLoS ONE. 13(5):e0198064. doi:10.1371/journal.pone.0198064.

Zhang W, Chen H, Fan J, Li G, Sun A, Lan L, Zhang L, Yan Y. 2020. The association between maternal nicotine exposure and adipose angiogenesis in female rat offspring: A mechanism of adipose tissue function changes. Toxicology Letters. 318:12–21. doi:10.1016/j.toxlet.2019.10.007.

Zhu J, Fan F, McCarthy DM, Zhang L, Cannon EN, Spencer TJ, Biederman J, Bhide PG. 2017. A prenatal nicotine exposure mouse model of methylphenidate responsive ADHD-associated cognitive phenotypes. Int j dev neurosci. 58(1):26–34. doi:10.1016/j.ijdevneu.2017.01.014.

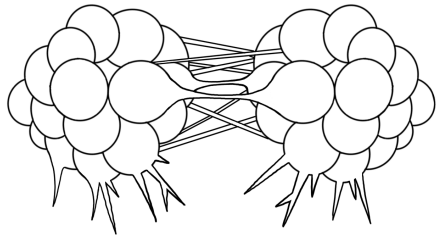
Zhu J, Zhang X, Xu Y, Spencer TJ, Biederman J, Bhide PG. 2012. Prenatal Nicotine Exposure Mouse Model Showing Hyperactivity, Reduced Cingulate Cortex Volume, Reduced Dopamine Turnover, and Responsiveness to Oral Methylphenidate Treatment. Journal of Neuroscience. 32(27):9410–9418. doi:10.1523/JNEUROSCI.1041-12.2012.

Zwar N, Richmond R, Borland R, Peters M, Litt J, Bell J, Caldwell B, Ferretter I. 2011. Supporting smoking cessation: A guide for health professionals. https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/supporting-smoking-cessation.



Neurodevelopment and Behavior

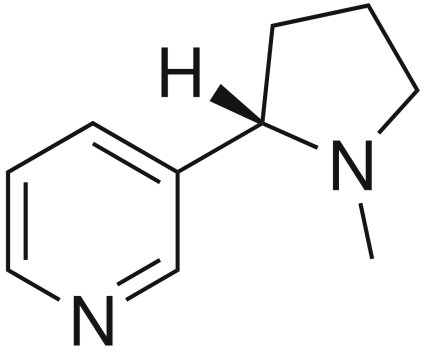
- Disrupted neurodevelopment and synaptic plasticity, ↓ neuronal viability, changes in brain volume
- ↑ risk of cognitive impairments, ADHD, depression, anxiety and somatosensory deficits in offspring
- Adverse neurobehavioral phenotypes and outcomes may persist into adulthood



Childhood Cancer

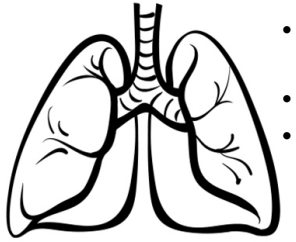
- ↑ risk of childhood cancer (mediated by genetic and epigenetic changes)
- ↑ chromosomal aberration and DNA double-strand breaks
- ↑ signal transduction pathways related to cancer pathogenesis (i.e. p53, ErbB, hedgehog, WNT)

Nicotine



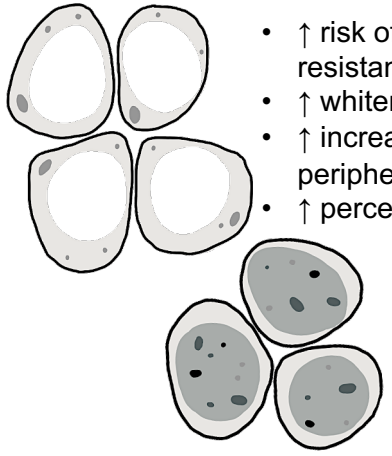
Hypertension

- ↑ blood pressure in adult life
- May induce vasoconstriction and facilitate hypertensive phenotype in adulthood via epigenetic mechanisms
- May be related to ↑ fat mass, glucose abnormalities or ↑ circulating triglyceride levels



Lung and Fibrosis

- ↓ lung size and volume capacity; thickening of airway walls and pulmonary vessels
- ↓ alveolar surface area
- ↑ TGFβ1 may inhibit alveolar development and ↑ risk of idiopathic pulmonary fibrosis



Adipose and Growth

- ↑ risk of obesity, dysmetabolism and insulin resistance
- ↑ whitening of BAT and ↓ BAT activity
- ↑ increased storage of lipids in WAT and peripheral tissues
- ↑ percent body fat and fat mass in offspring