


## CONTEMPORARY REVIEW

# Early Life Exposure to Nicotine: Postnatal Metabolic, Neurobehavioral and Respiratory Outcomes and the Development of Childhood Cancers

Laiba Jamshed, Genevieve A. Perono, Shanza Jamshed, and  
Alison C. Holloway <sup>1</sup>

Department of Obstetrics and Gynecology, McMaster University, Hamilton, Ontario L8N 3Z5, Canada

<sup>1</sup>To whom correspondence should be addressed. Fax: +1-905-524-2911, E-mail: 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 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 nicotine replacement therapy 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.

**Key words:** nicotine; pregnancy; fetal programming of adult disease; nicotine replacement therapy (NRT); electronic nicotine delivery system (e-cigarettes); dysmetabolism; lung development; neurotoxicity; childhood cancer.

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 (Dahlin *et al.*, 2016; Moore *et al.*, 2016; Shah and Bracken, 2000), stillbirth (Bjørnholt *et al.*, 2016; Marufu *et al.*, 2015), impaired fetal growth (Abraham *et al.*, 2017; Blatt *et al.*, 2015; Pereira *et al.*, 2017), and sudden infant death syndrome (Anderson *et al.*, 2019; Zhang and Wang, 2013). 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 suggest 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). Although approximately 75% of pregnant smokers want to quit, studies indicate that only half of women successfully abstain completely from smoking during pregnancy (Gilbert *et al.*, 2015; Greaves *et al.*, 2011; Orton *et al.*, 2014; Tong *et al.*, 2013). Nicotine dependence is a significant element of most women's smoking behavior and a significant negative predictor of smoking abstinence during pregnancy (Baraona *et al.*, 2017; Benowitz, 2010;

Riaz et al., 2016). Consequently, nicotine replacement therapy (NRT; eg, 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 (Bar-Zeev et al., 2018; Behrakis et al., 2017; Ordean et al., 2017; Zwar et al., 2011). Recently, electronic nicotine delivery systems (e-cigarettes) have become available and marketed as effective smoking cessation tools (Collins et al., 2019; Farsalinos, 2018; Patel et al., 2016; Ramamurthi et al., 2016). 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; Napierala et al., 2016; Rowe et al., 2015). 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 nonpharmacologic means (Canadian Action Network for the Advancement, Dissemination and Adoption of Practice-informed Tobacco Treatment, 2011; National Institute for Health and Care Excellence, 2010; The Royal Australian and New Zealand College of Obstetricians and Gynaecologists, 2017; Zwar et al., 2011). Although NRT is highly effective for smoking cessation in nonpregnant 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 (relative risk [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 <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 et al. (2019) published a small cohort study using self-reports and noninvasive smoking biomarkers in 232 pregnant women and found that 6.8% of pregnant women were e-cigarette users, with most being concurrent smokers (75%).

#### **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 (eg, 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 with nontobacco users (adjusted odds ratio [aOR] 1.48, 95% CI 1.00–2.21). Similarly, using data from the Danish National Birth Cohort (1997–2003), Morales-Suárez-Varela et al. (2006) showed an increased prevalence of congenital malformations in pregnant NRT users compared with nonsmokers. 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 with 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; Hossain et al., 2018; Suliankatchi and Sinha, 2016). Moreover, while smoking is clearly associated with preterm birth and intrauterine growth restriction (Pereira et al., 2017; Shah and Bracken, 2000), 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 approximately 2-fold increased risk of low birthweight and preterm birth compared with nonsmokers (Gaither et al., 2009). Similarly, maternal snuff and smokeless tobacco use have also been associated with preterm birth and low birthweight (Dahlin et al., 2016; Ratsch and Bogossian, 2014; 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.,

2018), 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 with traditional tobacco cigarette use (Etter, 2014; Jarvis et al., 1984; St Helen et al., 2016). Although some studies have reported that amongst pregnant women there is a perception that e-cigarettes are less harmful than traditional cigarettes (Breland et al., 2019; Mark et al., 2015), 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., 2018). 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; England et al., 2017; Holbrook, 2016). 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 e cigarette use during fetal and neonatal development in human populations.

## LONG-TERM EFFECTS OF FETAL AND NEONATAL EXPOSURE TO NICOTINE

### 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 (Kazemi et al., 2020; Mahar et al., 2012; Muhammad et al., 2012; Sailer et al., 2019; Slotkin et al., 2007; Thomas et al., 2000; Zhu et al., 2012). 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; Holbrook, 2016; Liao et al., 2012; 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 (Church et al., 2020; Nguyen et al., 2018; Ruskiewicz 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 (El Marroun et al., 2014; Polli et al., 2020; Zhu et al., 2012, 2017).

Although 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 Smoking, Nicotine And Pregnancy 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). Although 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.

### Metabolic Outcomes

Maternal smoking during pregnancy is consistently linked to an increased risk of obesity and dysmetabolism (ie, 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 (ie, type 2 diabetes mellitus, hypertension, nonalcoholic fatty liver disease [NAFLD], and dyslipidemia), lower health-related quality of life indicators and increased health care utilization and costs ([Buttitta et al., 2014](#); [Pelone et al., 2012](#); [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 United States 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 (ie, increased weight gain/adiposity, aberrant glucose homeostasis and cardiovascular disease) in postnatal life.

*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, an important orexigenic neuropeptide ([Chen et al., 2012](#); [Huang and Winzer-Serhan, 2007](#); [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 ([Pinheiro et al., 2015](#); [Somm et al., 2008](#); [Younes-Rapozo et al., 2013](#)). 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](#); [Lee et al., 2015a](#)). 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 (ie, whitening of BAT) along with decreased expression of thermogenesis-specific genes and sympathetic nervous system activity (ie, reduced BAT activity) ([Fan et al., 2016a](#); [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 ([Behl et al., 2013](#); [Fan et al., 2016b](#); [Somm et al., 2008](#)). 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-L1 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 ([Cameron et al., 2018](#); [Moschonis et al., 2017](#)). 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](#)).



**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 (Gao *et al.*, 2008; Pausová *et al.*, 2003; 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 (Barra *et al.*, 2017; Wang *et al.*, 2015). 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.

### Respiratory Outcomes

**Lung function and development.** The developing lung is sensitive to exogenous compounds such as those found in maternal tobacco smoke (Dasgupta *et al.*, 2012; Gibbs *et al.*, 2016; Stocks *et al.*, 2013). 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 (den Dekker *et al.*, 2015; Kalliola *et al.*, 2013; 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 Kuniyoshi and Rehan, 2019; Maritz and Harding, 2011; McEvoy and Spindel, 2017; Spindel and McEvoy, 2016).

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 (England *et al.*, 2017; Krebs *et al.*, 2010; Lavezzi *et al.*, 2014; Maritz, 2013; Petre *et al.*, 2011; Sekhon *et al.*, 1999, 2002).

Collectively, these outcomes compromise the primary role of the respiratory system to mediate optimal blood-gas exchange (Spindel and McEvoy, 2016; Wongtrakool *et al.*, 2012). *In vitro* and *in vivo* studies reveal that the effects of nicotine on airway remodeling can be attributed to its activity at the  $\alpha 7$  nAChR (reviewed in Gibbs *et al.*, 2016; Spindel and McEvoy, 2016). Maternal nicotine exposure upregulates  $\alpha 7$  nAChR expression in fetal lung macrophages and epithelial cells and fibroblasts (England *et al.*, 2017; Sekhon *et al.*, 1999, 2002) and it has been suggested that nicotine activity at  $\alpha 7$  nAChR may play a role in altering lung development, morphogenesis and airway plasticity (Maritz and Harding, 2011; Sekhon *et al.*, 1999). In support of this hypothesis, perinatal nicotine exposure did not cause impaired lung function (as measured by forced expiratory flows) in  $\alpha 7$  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). Although 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). Although 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.

**Fibrosis.** To date, several epidemiologic studies have reported an association between adult cigarette smoking and idiopathic pulmonary fibrosis (Ebrahimpour *et al.*, 2019; Jensen *et al.*, 2012; Kärkkäinen *et al.*, 2017; Taskar and Coultas, 2006). There is some evidence that nicotine may accelerate pathogenesis; *in vitro* and *in vivo* studies have shown that nicotine plays a role in key profibrotic 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 remodeling 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  $\beta$ 1 signaling (Dasgupta et al., 2012). In fact, in multiple species (rat, mouse, and monkey) prenatal nicotine-induced overexpression of transforming growth factor  $\beta$ 1, 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 (Dasgupta et al., 2012; Gauldie et al., 2003; Sekhon et al., 2002; Tarantal et al., 2010; 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 knockout models of  $\alpha$ 7-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 histone deacetylase 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  $\alpha$  (Chen et al., 2015). Although 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).

#### 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 Fucic et al., 2017; Pattemore, 2013). 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, epidermal growth factor receptor, hedgehog, and wingless-related integration site 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

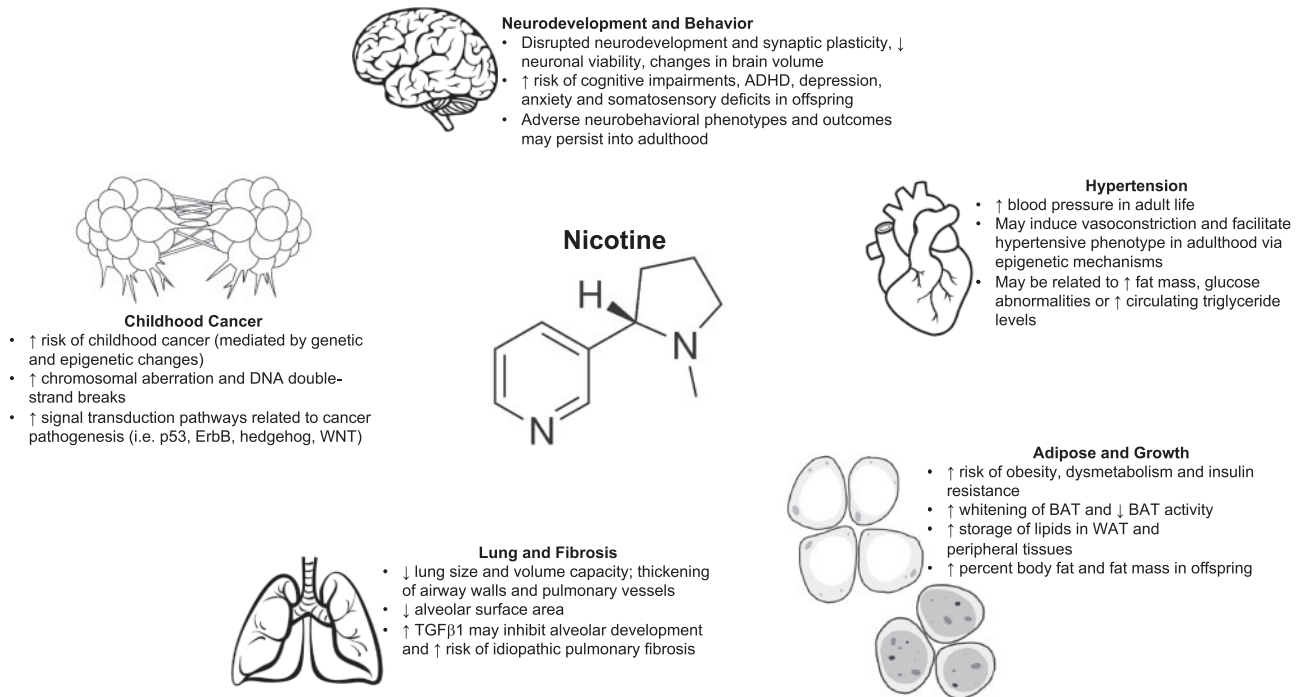
in newborns impacted by maternal smoking were related to cancer (Rotroff et al., 2016). Importantly, altered DNA methylation patterns associated with these pathways have been found to persist in exposed offspring into adolescence (Lee et al., 2015b; Rotroff et al., 2016). Taken together, these data suggest 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 (ie, 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). Although 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 antiapoptotic), 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 Grando, 2014; Hausmann and Fariss, 2016; Improgo et al., 2011; Mishra et al., 2015; Sanner and Grimsrud, 2015). 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). Although 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.

## 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 (Buttitta et al., 2014; Liang et al., 2020; Lobstein and Jackson-Leach, 2016; Pelone et al., 2012), pulmonary (Gibbs et al., 2016; Kuniyoshi and Rehan, 2019; Maritz and Harding, 2011; McEvoy and Spindel, 2017) 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; Figure 1). However, the contribution of nicotine to these same outcomes in humans remains unclear.

Although 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 are 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.,



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

2018; 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.

## DECLARATION OF CONFLICTING INTERESTS

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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