Published in final edited form as:

Curr Probl Pediatr Adolesc Health Care. 2014 September ; 44(8): 219–241. doi:10.1016/j.cppeds.

Physical, Behavioral, and Cognitive Effects of Prenatal Tobacco and Postnatal Secondhand Smoke Exposure

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Abstract

The purpose of this review is to examine the rapidly expanding literature regarding the effects of prenatal tobacco and postnatal secondhand smoke (SHS) exposure on child health and development. Mechanisms of SHS exposure are reviewed, including critical periods during which exposure to tobacco products appears to be particularly harmful to the developing fetus and child. The biological, biochemical, and neurologic effects of the small fraction of identified components of SHS are described. Research describing these adverse effects of both in utero and childhood exposure is reviewed, including findings from both animal models and humans. The following adverse physical outcomes are discussed: sudden infant death syndrome, low birth weight, decreased head circumference, respiratory infections, otitis media, asthma, childhood cancer, hearing loss, dental caries, and the metabolic syndrome. In addition, the association between the following adverse cognitive and behavioral outcomes and such exposures is described: conduct disorder, attention-deficit/hyperactivity disorder, poor academic achievement, and cognitive impairment. The evidence supporting the adverse effects of SHS exposure is extensive yet rapidly expanding due to improving technology and increased awareness of this profound public health problem. The growing use of alternative tobacco products, such as hookahs (a.k.a. waterpipes), and the scant literature on possible effects from prenatal and secondhand smoke exposure from these products are also discussed. A review of the current knowledge of this important subject has implications for future research as well as public policy and clinical practice.

Introduction

More than 1 billion people worldwide smoke tobacco products, and it is predicted that this remarkable number will reach 1.9 billion by 2025.¹ According to the World Health Organization (WHO), there are approximately 6 million deaths per year caused by tobacco, and the economic burden of increased tobacco-related morbidity and mortality runs in the hundreds of billions of dollars.² Many smokers, however, remain unaware of the harmful consequences of their tobacco use for themselves, their families, as well as for the larger

public. Many others, although knowing about these consequences to themselves and others, still have profound difficulty in quitting because of the addictive nature of nicotine.²

There are several ways children and adolescents can be exposed to tobacco. Prenatally, this occurs through maternal smoking or maternal secondhand smoke (SHS) exposure. During childhood or adolescence, active smoking, SHS and thirdhand smoke are all possible means of exposure.

The first evidence statistically linking tobacco smoking with lung cancer appeared in the German journal *Der Tabakgegner* (The Tobacco Opponent) in 1912.³ Doll and Hill⁴ confirmed this finding in 1950 using elegantly developed epidemiologic techniques. These and other findings linking tobacco smoking and adverse health consequences became widely recognized worldwide by the 1964 publication in the U.S. of the seminal report entitled *Smoking and Health: Report of the Advisory Committee to the Surgeon General of the Public Health Service*.⁵ It is now authoritatively recognized that there is no safe level of exposure to tobacco smoke. Despite dramatic decreases in rates of cigarette smoking, tobacco use continues to be the leading cause of preventable premature death worldwide.⁶

In addition to the widely recognized effects of tobacco use and exposure on adult health, literature regarding the prenatal and postnatal physical effects of tobacco exposure on children is extensive and continues to grow. Prenatal exposure to tobacco and postnatal exposure to secondhand smoke are the leading preventable causes of sudden infant death syndrome (SIDS),⁷⁻⁹ have been linked with intrauterine growth restriction and decreased head circumference among newborns, and are associated with numerous physical health problems during childhood including lower respiratory tract infections, asthma, otitis media, dental caries, hearing loss, and the metabolic syndrome.

Recently, research has examined the cognitive and behavioral effects of prenatal and postnatal SHS exposure. Animal models have elucidated that prenatal exposure to nicotine results in neurotoxic and neuro-modulatory effects on the brain that result in alterations of normal brain composition, causing impairments in learning, memory, hearing, and behavior. New studies are beginning to focus on dysregulation of specific genes and biochemical pathways by tobacco smoke exposure during the prenatal period, elucidating a novel mechanism that will be discussed in this article to explain the pathology.

In the words of Cuthbertson and Britton,¹⁰ failure to protect children exposed to SHS “is potentially catastrophic” for their future health. Our estimates are that every day of practice, each primary care physician seeing children for well child care will encounter on average 3 children who will die prematurely of tobacco-related exposure (unpublished data). Growing numbers of individuals and groups are actively calling for measures such as smoking bans in households and in public places to ensure the elimination of children’s exposure to SHS.¹¹

Components of Secondhand Smoke

Secondhand smoke, also known as “environmental tobacco smoke” (ETS), refers to the smoke discharged from the lit end of a burned tobacco product as well as the smoke exhaled during active smoking.¹² There are more than 4000 chemicals present in SHS, and more

than 250 of these are known to be carcinogenic or toxic in some other way.¹³ Some of the toxic agents in SHS are as follows: “hydrogen cyanide (used in chemical weapons), carbon monoxide (found in car exhaust), butane (used in lighter fluid), ammonia (used in household cleaners), and toluene (found in paint thinner), arsenic (used in pesticides), lead (formerly found in paint), chromium (used to make steel), and cadmium (used to make batteries).”¹⁴ There also are additional recognized carcinogens in SHS, including polycyclic aromatic hydrocarbons (PAHs), tobacco-specific *N*-nitrosamines (TSNA), and numerous other hydrocarbons, aldehydes, organic compounds, and metals, although these agents have been less rigorously studied.^{6,12}

Measurement of SHS Exposure

The ideal biomarker for SHS exposure has yet to be identified. Currently, the same markers used to measure active smoking are used to measure SHS exposure.¹⁵ Exposure to SHS is assessed indirectly by measuring the concentrations of carbon monoxide, thiocyanate, or nicotine metabolites such as cotinine.¹⁶ Although carbon monoxide and thiocyanate can reflect SHS exposure, they are not specific because they are found in multiple sources and can be produced from exposures to agents other than SHS.¹⁶

Cotinine is a direct metabolite of nicotine that has a longer half-life and a high specificity for SHS exposure.¹⁷ This chemical freely crosses the placenta and accumulates in fetal tissues.^{18,19} Cotinine can be measured in saliva, blood, or urine, and indicates the amount of nicotine exposure over the past 3 days.²⁰ It is currently unclear whether measurement of cotinine in meconium reflects exposures over a more extended period of time.²¹ After birth, breast milk is a potential source of nicotine exposure. Nicotine and cotinine can accumulate to concentrations two- to three-fold higher in breast milk than in plasma.²²

New methods of postnatal cotinine detection, such as liquid chromatography–tandem mass spectroscopy, are being developed to quantitatively estimate exposure to SHS.²³

Thirdhand Smoke

The term “thirdhand” smoke was coined in 2006, referring to residual matter from tobacco smoke that stays on surfaces and in dust.²⁴ While many components of thirdhand smoke are the same as those in SHS, there are additional biologically active chemicals formed from reactions between SHS particles with chemicals such as ozone and gaseous oxide.^{24,25} Of great concern is that exposure to thirdhand smoke can occur in household with no active smokers. In fact, thirdhand smoke particles in homes of former smokers can be measured in new occupant’s urine and blood samples for up to 2 months after evacuation and cleaning.²⁶ This study supports the 2006 statement from the Surgeon General of the U.S. Public Health Service that the most important environmental tobacco smoke exposure for children occurs in the home.²⁷

Similar to the deleterious effects of prenatal SHS exposure, studies have shown that chemicals present in thirdhand smoke can cause damage to the lungs in utero. For instance, pulmonary damage via disrupted homeostatic signaling, stimulation of surfactant production and protein synthesis, and breakdown of alveolar epithelial–mesenchymal cross-talk have all been associated with thirdhand smoke exposure.²⁵ Children are especially at increased risk

from accumulation of these harmful chemicals because environmental dust with thirdhand smoke particles is present in higher concentrations and lower to the ground, such as floors and carpet, where children play.²⁸

Mechanisms of Prenatal and Postnatal Tobacco Exposure

Critical Periods of Prenatal and Postnatal Exposure

A basic concept in child environmental health is that there are specific periods during development during which exposure to specific toxic chemicals, including those in tobacco smoke, is especially harmful. Almost every developing organ system, including the lungs, brain, heart, and ears, appears to be affected by prenatal exposure to tobacco^{15,29,30} (Figs 1 and 2).

Postnatally, infancy appears to be the period associated with the highest risk of respiratory, neurological, and immunological morbidity.^{30,31} For example, the risk of bronchitis and pneumonia from SHS exposure is highest in infancy,¹⁵ and early postnatal SHS exposure is associated both with increased rates of hospitalization for respiratory illness and bronchial hyper-responsiveness during the first 6 months of life.³² As children get older, rates of such complications decrease, perhaps because of diminished exposure as they spend less time in the presence of parents and so have decreased SHS exposure.³³

Biological Mechanisms

Prenatal tobacco exposure results in alterations in fetal blood flow and protein metabolism as well as the accumulation of certain chemicals both in the mother and the fetus. Each of these can contribute to or cause adverse consequences. Levels of maternal and fetal carboxyhemoglobin may be elevated, depending upon the intensity of maternal smoking or exposure to others who are smoking, leading to chronic fetal hypoxic stress.³⁴ Certain chemicals present in cigarette smoke cause vasospasm of vessels supplying the placenta, increasing placental vascular resistance and resulting in further reduction in blood flow to the fetus.^{35–39}

In animal models, nicotine has been shown to have teratogenic effects on neurodevelopment.^{40,41} Marked alterations in neurotransmitters alter neuronal pathways both before and after birth.¹⁵ A recent study suggested that the marked neurologic effects of fetal tobacco exposure are the result of alterations in the developmental trajectory of synaptic function rather than of a single neurotoxic injury.⁴² This results in synaptic dysregulation, with presynaptic neurons being juxtaposed to incorrect target cells, thereby resulting in impaired synaptic communication.^{42–47}

Nicotine exposure causes upregulation of the 5-HT (serotonin) transporter and receptor in male rats, whereas females experience a downregulation of the 5-HT-1A receptor subtype.⁴² In addition, the number of hippocampal muscarinic receptors is increased.^{48,49} These changes cause a high turnover of serotonin and dopamine, resulting in an overall deficit in these neurotransmitters.⁴² Consequences of these changes include impaired dopaminergic activity and reduced serotonin uptake in many areas of the brain, including the ventral tegmental area and nucleus accumbens.^{50,51}

Nicotine exposure increases the number of nicotinic acetylcholine receptors globally, but with certain regional preferences. The $\alpha 4\beta 2$ nicotinic acetylcholine receptor ($\alpha 4\beta 2$ nAChR) shows the greatest increase in the occipital cortex, followed by the frontal cortex and hippocampus, with lesser increases seen in the caudate. As a consequence, the caudate nucleus, a critical component of reward pathways involving nicotine, is actually less sensitive than other areas in the brain. It also has been shown that nicotine exposure decreases the total cell number and number of cell projections in specific areas of the brain, with the caudate affected most severely.⁴⁵ These alterations in the brain result in increased fetal susceptibility to cholinergic effects, including tachycardia and fetal hypoxia. Such changes may contribute to increased risk of SIDS and other fetal morbidities.^{45,52} There also is impaired development of noradrenergic presynaptic projections and postsynaptic beta-receptor binding capabilities. This results in an increase of noradrenergic receptor sites in the cerebral cortex.^{53–55}

While the negative effects of only a fraction of the chemicals in tobacco smoke have been studied, the full spectrum of adverse health consequences of the thousands of harmful substances in tobacco and tobacco smoke will likely never be fully appreciated.

Effects of Prenatal and Postnatal Tobacco Exposure

Physical Effects

Evidence From Animal Models—Animal models provide information about prenatal and postnatal tobacco smoke exposure that cannot be elucidated by human studies.

Feng et al.⁵⁶ reported that prenatal nicotine exposure increases the risk of fatal cardiac arrhythmias in rats aged 4–5 months. Fu et al.⁵⁷ also showed that prenatal nicotine exposure upregulates nicotinic acetylcholine receptors in bronchial epithelial cells, predisposing infants to bronchial hyper-responsiveness. Animal models also have documented a dose-dependent relationship^{58,59} between prenatal nicotine exposure and low birth weight.⁶⁰

Sudden Infant Death Syndrome—The World Health Organization and many other international groups have assiduously reviewed the evidence linking prenatal and childhood SHS exposure and SIDS, and it is now accepted by the scientific, public health, and pediatric communities that tobacco exposure is the *most common* preventable cause of SIDS.⁶¹

An extensive epidemiologic literature indicates a causal relationship between both prenatal tobacco and postnatal SHS exposure and SIDS, including a meta-analysis with 35 case–control studies world-wide.⁶² The authors found that prenatal maternal smoking was associated with significantly increased risk of SIDS (OR = 2.25, 95% CI: 2.03–2.50), and postnatal maternal smoking had a comparable effect (OR = 1.97, 95% CI: 1.77–2.19). Furthermore, smoking cessation during pregnancy is found to decrease the incidence of SIDS.⁶³

As the main neurotoxic component of cigarette smoke, nicotine is hypothesized to affect neuronal nicotinic acetylcholine receptors in brainstem nuclei in a manner that results in diminished respiration and arousal during sleep.⁶⁴ This leading hypothesis suggesting a

possible mechanism linking SHS exposure and SIDS is called the “brainstem hypothesis”⁶⁵ since the brainstem is responsible for controlling temperature control, breathing, blood pressure, chemosensitivity, and upper airway reflexes. This hypothesis suggests that SIDS may be due, at least in part, to impairment of these basal functions, which “impairs the infant’s response to life-threatening, but often occurring, stressors during sleep (e.g., hypoxia, hypercarbia, asphyxia, and hyperthermia) and leads to sudden death in a vulnerable developmental period.”⁶⁶

A recent study explored this hypothesis mechanistically by comparing the $\alpha 7$ and $\beta 2$ subunits of nicotinic acetylcholine receptors in 8 nuclei of the medulla and 7 nuclei of the pons among 46 SIDS and 14 non-SIDS infants.⁶⁷ The authors discovered that compared to non-SIDS infants, SIDS infant had significantly decreased $\alpha 7$ and $\beta 2$ subunits of nicotinic acetylcholine receptors, suggesting that SIDS infants responded differently to cigarette smoke exposure that likely predisposed them to the lethal consequences of cigarette smoke.

Another characteristic of SIDS is upregulation of serotonin receptors in the brain. It has been shown that prenatal tobacco exposure elicits hyperactivity of serotonin, dopamine, and norepinephrine pathways, resulting in consequent deficits of these neurotransmitters.⁶⁸ This in turn results in cardiac sympathetic innervation being decreased, increasing the vulnerability of the fetus and infant to hypoxia during times of stress.

Low Birth Weight—Tobacco smoke exposure is the most important determinant resulting in low birth weight after adjusting for gestational age at the time of birth.^{69,70}

Approximately twice as many mothers who smoke or are exposed to SHS experience term low-birth-weight deliveries (small for gestational age babies) compared to mothers who are not exposed.⁶⁹ Pregnant non-smokers who are exposed to SHS have an increased risk of giving birth to a child with low birth weight, although with less severity than prenatal maternal smokers.^{71–74} Birth weight has been shown to be improved by reducing or eliminating smoking during pregnancy.^{75,76} It is estimated that the hospital costs for preterm birth/low-birth-weight births, during the first year of life, totaled near \$6 billion in the U.S.⁷⁷

Reduced birth weight itself, irrespective of tobacco exposure, is independently associated with an increased risk for the behavioral and cognitive problems that are discussed throughout this review. These problems include hyperactivity, learning disabilities, anxiety, and decreased IQ.^{78–80}

Decreased Head Circumference—Numerous studies have found that prenatal tobacco exposure is inversely related to head circumference at birth, and that this decrease can persist throughout childhood.⁸¹ In utero brain weight has been shown to be a function of fetal head circumference.⁸² Studies have demonstrated a 0.13-mm⁸³ to 0.56-mm⁸⁴ reduction per week in fetal head circumference among children exposed to tobacco prenatally. Overall, prenatal tobacco use is associated with a 0.72–0.89-cm decrease in fetal head circumference.⁸⁵

The association between decreased head circumference and decreased brain volume is strongest in younger children.⁸⁶ The mean performance IQ in children with low brain volume has been found to be reduced by 15 points compared to individuals with medium

total brain volume.⁸⁶ In 4-year-olds, full scale IQ is increased by 2.41 points for each standard deviation increase in newborn head circumference and is increased by 1.97 points for each standard deviation increase after birth.⁸⁷ The majority of studies show that the head circumference of these children catches up to normal values as they age; one study, however, found that these decreases in head circumference persist throughout childhood.⁸⁸

Although the entire brain size is decreased by prenatal tobacco exposure, specific areas of the brain are preferentially affected. The decrease in head circumference appears to be related to reductions in cortical gray matter and total parenchymal volumes.⁸⁹ Other studies indicate that prenatal smoke exposure is related to fractional anisotropy in anterior cortical white matter and in the corticofugal fibers of the internal capsule of the brain,⁹⁰ reduction of the mass of the frontal lobe and cerebellum,⁹¹ and a deficit of nicotinic cholinergic receptors in the hippocampus and prefrontal cortex.³⁶

Impaired brain development and growth during fetal life, infancy, and early childhood is associated with decreased cognitive functions among the elderly.⁸⁷ Individuals with larger head circumferences between the ages of 66 and 75 years show less cognitive decline and score higher on intelligence tests compared to those with smaller head circumferences.⁸⁵

As the data have shown, the effect of SHS on head circumference is not limited to childhood, and the deficits caused by these neurological effects persist throughout life.

Upper Respiratory Tract Illnesses—Exposure to SHS is independently associated with an increased incidence of middle ear disease, adenoid hypertrophy, tonsillitis, pharyngitis, and snoring among infants.¹⁵ This results in an increased incidence of tonsillectomies, higher rates of antibiotic use, and a greater incidence of hospitalization for respiratory illness.¹⁵

Ear Infections. The research literature documenting the association between SHS exposure and otitis media is extensive and conclusive.^{2,14,92} The morbidity associated with the ear is not only limited to otitis media but also includes tympanic membrane perforation, cholesteatoma, and sensorineural hearing loss.⁹³

As early as 1998, a systematic review revealed a causal relationship between SHS exposure and otitis media, middle ear effusion, and surgery for these conditions.⁹⁴ In a subsequent meta-analysis of 61 studies from 1997 to 2010 on the association between SHS exposure and middle ear disease in children, the authors found that maternal postnatal smoking significantly increased the risk of middle ear disease in children (OR = 1.62, 95% CI: 1.33–1.97) as did living with a household smoker (OR = 1.37, 95% CI: 1.25–1.50). In contrast, paternal smoking was not associated with a significantly increased risk of childhood middle ear disease (OR = 1.24, 95% CI: 0.98–1.5). Additionally, this study identified that the main consequence of childhood exposure to SHS was the increased risk of having to have surgery for chronic middle ear diseases.⁹⁵ SHS exposure is, therefore, the leading preventable cause of children's middle ear infection, and as such is the leading cause of outpatient prescriptions for antibiotics.^{96–98}

Lower Respiratory Tract Illnesses—The association between SHS exposure and respiratory tract infections in children is very well-established.⁹⁹ Smoking during pregnancy actually confers an additional risk compared to postnatal exposure alone, and maternal smoking during pregnancy is independently associated with an almost 4-fold increase in respiratory disease in infants.¹⁵ The impaired immunologic effects of SHS exposure predisposes children not only to respiratory infection but also to allergy and bronchial hyper-responsiveness.¹⁰⁰

Both prenatal and postnatal exposure to tobacco is associated with decreased pulmonary function.^{101,102} Adverse lung effects begin as early as pregnancy demonstrated by one study that found a reduction in fetal lung growth by 33 weeks of gestation.¹⁰³ A meta-analysis in 1996 found that children exposed to SHS experienced a 1.4% reduction in forced expiratory volume in 1 s, a 5% decrease in mid-expiratory flow rate, and a 4.3% decrease in end-expiratory flow rate,¹⁰⁴ yet the mechanism of damage has not been elucidated.¹⁰¹

An updated meta-analysis in 2011 extensively examined the evidence of passive smoke exposure and risk of lower respiratory tract infection in infants.⁹⁵ Among the 60 studies identified, smoking by either parent significantly increased the risk of lower respiratory tract infection (OR = 1.22, 95% CI: 1.10–1.35). The odds ratio increased to 1.62 (95% CI: 1.38–1.89) if both parents smoked and was 1.54 (95% CI: 1.40–1.69) if any household member smoked. Overall, postnatal smoking had a stronger effect than prenatal in causing lower respiratory tract infections, especially bronchiolitis.

Asthma: The relationship between SHS exposure and childhood asthma is widely believed to be causal in nature.^{30,105,106} A meta-analysis in 1998 by Strachan and Cook¹⁰⁷ based on 6 studies of asthma incidence, 7 of prognosis, 22 case–controls, and 10 case series found that if either parent smoked cigarettes, the odds ratio of developing childhood asthma was 1.37. Additionally, maternal smoking was associated with an increased incidence of wheezing illness up to the age of 6 years (pooled odds ratio = 1.31, 95% CI: 1.22–1.41), but less strongly thereafter (OR = 1.13, 95% CI: 1.04–1.22).^{106–109}

Since 1998, a plethora of studies have emerged on the health effects of exposure to prenatal and postnatal smoking on childhood incidence of wheeze and asthma. Consequently, a more updated meta-analysis in 2012 by Burke et al.¹¹⁰ identified 79 prospective studies and found that exposure to prenatal or postnatal SHS was associated with as much as 70% increased risk of incident wheezing with strongest effect from postnatal maternal smoking on wheeze in children aged 2 years (OR = 1.70, 95% CI: 1.24–2.35). Moreover, incident asthma was increased between 21% and 85% with strongest effect from prenatal maternal smoking on asthma in children aged 2 years (OR = 1.85, 95% CI: 1.35–2.53).

Both asthma prevalence and severity are increased in children exposed to SHS,¹¹¹ and affected children have a greater number of visits to the emergency department,¹¹² hospitalization, and a greater risk of intubation.¹¹³ Although the mechanisms by which SHS exposure causes these effects have not clearly been elucidated, children's higher blood cotinine levels are associated with increased bronchial hyper-responsiveness.¹⁰³ When child and adolescent exposure to SHS is reduced, the severity of asthma is decreased.¹¹⁴

Third-Generation Effects of In Utero Smoking on Asthma. Although abundant evidence suggests that in utero exposure to maternal smoking increases asthma risk, exacerbates preexisting asthma, and adversely affects postnatal lung function,^{104,115–120} research continues to explore other novel associations of smoking during pregnancy with asthma risk. One study reported that grandmaternal smoking during the mother's fetal period was linked to increased asthma risk in her grandchildren,¹²¹ suggesting the burden of maternal smoking was possibly underestimated and that the inheritance of asthma susceptibility could very well be through epigenetic mechanisms. To study this possibility, Rehan et al.¹²² used a well-established rat model and found that first-generation offspring of nicotine-treated pregnant rats not only exhibited asthma-like changes in lung function but also epigenetic changes to DNA and histones in both lungs and gonads. They reported, for the first time, that transgenerational transmission of the asthma phenotype was observed in third-generation offspring following perinatal nicotine exposure of the first generation. Therefore, epigenetic as well as genetic mechanisms appear to play an important role in SHS and asthma in children.

Increased Risk of Respiratory and Nonrespiratory Infections—Although it is well-established that maternal smoking is associated with infant respiratory infections, such as pneumonia, bronchitis, bronchiolitis,^{95,123–128} and pulmonary tuberculosis,^{129,130} growing literature suggests that it is also linked to infectious diseases, such as otitis media,^{2,14,92,124,131,132} bacterial meningitis,^{128,133–135} necrotizing enterocolitis,¹³⁶ and increased risk of vertical HIV transmission,^{137,138} all of which greatly jeopardize infant health. A study by Metzger et al.¹³⁹ found that infants who were hospitalized or died due to infection during the first year of life were 50% more likely to have had mothers who smoked than those who did not. In subgroup analyses, the authors found that maternal smoking was associated with infant hospitalization due to both respiratory and nonrespiratory infectious diseases.

Effects of Maternal Smoking on Delayed Immune Development—Research has illustrated the complex interactions between antenatal environment and the maturation of fetal immune system. Cytokines are an important part of the immune system and contribute to the development of various allergic diseases, such as atopy and asthma.^{140–142} In a prospective cohort study, Macaubas et al.¹⁴³ found an inverse relationship between cord blood concentrations of cytokines, such as IL4, IL- γ , and TNF α and the risk of asthma, atopy, or both in children at the age of 6 years. More importantly, these investigators found that maternal smoking was associated with lower concentrations of IL4, IL- γ , and TNF α in cord blood, suggesting a higher likelihood for the child to develop allergic diseases later in life. Moreover, the authors found that infants born to ex-smoking mothers had cord blood concentrations of IL4 and IL- γ intermediate between those of nonsmokers and current smokers, suggesting that the adverse pregnancy outcomes due to maternal smoking may not be entirely preventable by smoking cessation during pregnancy.

SHS and Epigenetic Changes—As noted earlier, it is well-known that tobacco use adversely modifies pregnancy outcomes, resulting in higher perinatal and obstetric complications, such as premature birth, low-birth-weight infants, and impaired lung

function,^{144,145} the mechanism has yet to be elucidated. Some proposed hypotheses include fetal hypoxia,¹⁴⁵ carbon monoxide,¹⁴⁶ and nicotine exposure.¹⁴⁷ More recently, research has focused on the role of epigenetics in maternal tobacco smoke exposure's effects on fetal growth. Exposure to tobacco smoke can alter gene expression through epigenetic changes, such as DNA methylation. In general, aberration of DNA methylation is a typical mechanism of epigenetic change.¹⁴⁸ Studies have shown that maternal smoking during pregnancy can alter DNA methylation patterns in myriad locations. For example, it has been found that maternal tobacco use is associated with placental DNA methylation in genes crucial for the proper growth and development of the fetus.^{146,149} Guerrero-Preston et al.¹⁵⁰ found that global DNA methylation was most reduced in cord blood from newborns whose mothers smoked during pregnancy. In addition to the methylation pattern alterations in placental and cord blood, maternal smoking is also associated with methylation changes in leukocytes¹⁵¹ and neurons of the central and peripheral nervous systems associated with cognitive performance, executive function, behaviors, and mental health.^{152–155}

Associations of Exposure to Paternal Smoking and Risk of Developing Childhood Cancer

—The relationship between prenatal and postnatal exposure to secondhand smoke and subsequent risk of childhood cancer has been studied in multiple epidemiological studies in the past 2 decades. A meta-analysis by Boffetta et al.¹⁵⁶ reviewed over 30 epidemiologic studies of exposure to secondhand smoke and development of childhood neoplasms and lung cancer. Their results, based on 12 studies, suggested a small (approximately 10%) increase in risk of all neoplasms, except leukemia and CNS tumors (RR = 1.10, CI: 1.03–1.19), among children exposed to prenatal maternal tobacco smoke. Interestingly, the authors found that there was an association between *paternal* smoking with brain tumors based on 10 studies (RR = 1.22, CI: 1.05–1.40) and lymphomas based on 4 studies (RR = 2.08, CI: 2.08–3.98). However, more data are needed to confirm that parental tobacco smoke, especially paternal, is a risk factor for developing childhood cancer.

SHS Exposure and Hearing Loss—Recently, studies have begun to investigate the association between exposure to SHS and hearing loss.¹⁵⁷ Cigarette smoke damages the entire cochlea, causing hearing loss across the entire frequency spectrum.¹⁵⁸ Smokers are up to twice as likely to experience hearing loss as compared to nonsmokers after adjusting for multiple potential confounders.¹⁵⁹ Prenatal tobacco smoke exposure has been found to be independently associated with higher pure-tone hearing thresholds and a nearly three-fold increase in unilateral low-frequency hearing loss among adolescents.^{157,160}

Prenatal smoke exposure is associated with decreased performance on auditory tasks as early as the neonatal period^{161–163} and a dose-dependent relationship between SHS exposure and decreased auditory-related tasks.^{164,165} In utero exposure, even if the mother quits smoking during the first trimester of pregnancy, may be injurious to the developing auditory system, which also develops during the first trimester.¹⁶⁶ These hearing deficits may contribute to the cognitive and behavioral deficits that persist throughout life.¹⁶⁵

Although no mechanism has been established to explain the association between hearing loss and SHS exposure,¹⁵⁷ proposed mechanisms include fetal malnourishment due to altered placental architecture,¹⁶⁷ fetal hypoxia due to vasoconstriction,¹⁶⁸ or direct damage

by nicotine or other chemicals present in cigarette smoke.¹⁶⁰ Very similar findings have recently been published concerning prenatal tobacco exposure and sensorineural hearing loss.¹⁶⁹

SHS Exposure and Dental Caries—Exposure to SHS has been found to be independently associated with an almost doubled risk of dental caries.¹⁷⁰ Three major mechanisms are proposed to explain this phenomenon.¹⁷¹ The first involves the direct exposure of the developing teeth to the chemicals present in SHS. Nicotine and heavy metals such as cadmium may impair mineralization of tooth, and smoking during pregnancy may be related to delayed tooth formation.^{172–174} The chemicals in SHS also result in injury to the salivary glands, which decreases buffering capacity and salivary flow rate.¹⁷⁵ Third, SHS increases colonization of the oral mucosa by cariogenic bacteria including *Streptococcus mutans*,¹⁷¹ and impairs immune function and blood levels of vitamin C, which have been implicated in the formation of dental caries.^{176,177}

SHS Exposure and the Metabolic Syndrome—The metabolic syndrome is a combination of glucose intolerance, dyslipidemia, obesity, and hypertension.¹⁷⁸ The association between metabolic syndrome and SHS exposure has been well-studied and validated in a number of countries.^{179–181} One recent study found that SHS exposure both before and after birth increases the risk of obesity in children at 6 years of age up to 4.4-fold.¹⁸¹

While it is difficult to explain the exact mechanism underlying this phenomenon due to the numerous behavioral, social, and genetic influences on child growth, a number of hypotheses have been developed. The “thrifty phenotype hypothesis,” also known as Barker’s hypothesis, explains that “early-life metabolic adaptations promote survival, with the developing organism responding to cues of environmental quality by selecting an appropriate trajectory of growth.”¹⁸² Proponents of this idea argue that a fetus exposed to SHS, while small for gestational age in utero, would adopt metabolic characteristics to survive in a nutrition-poor environment. Postnatally, the risk of the metabolic syndrome and other associated morbidities would be exacerbated if the infant is exposed to conditions discordant to those in utero, such as the “toxic” diet of western society.¹⁸²

Another theory postulates that because children born to smokers are more likely to be small, metabolic syndrome is the result of the postnatal growth “catch-up.”¹⁸³ Others propose that neuroendocrine imbalances caused by SHS exposure contribute to metabolic syndrome.¹⁸⁴ Another theory points toward behavioral differences observed between smoking and non-smoking mothers such as breastfeeding frequency,^{185,186} physical activity, and overall nutrition.¹⁸⁷

In addition to the thoroughly studied association between the metabolic syndrome and SHS exposure in children, a study by Cutler et al. found that children living with smokers are twice as likely to experience food insecurity, or the inability to access food in a socially acceptable way every day of the year, than children not living with smokers.¹⁸⁸ Food insecurity is associated with poor physical health, neuropsychological development, and poor academic achievement in children.¹⁸⁸

Behavioral and Cognitive Effects

Evidence From Animal Models—Nicotine interferes with neurodevelopment, “altering the formation, survival, and differentiation of brain cells, eliciting deficits in structure, synaptic function, and behavioral performance.”¹⁸⁹ Nicotine exposure causes premature neuronal differentiation, increasing the cholinergic effects on neurological processes such as mitosis, cellular communication, and neuronal path finding during differentiation.¹⁹⁰ Both prenatal and postnatal nicotine exposure cause sex-selective cholinergic hypoactivity in male rats, which can explain the observed effects in humans of “affective, appetitive and sleep disorders in the offspring of women who smoke during pregnancy as well as in adolescent smokers.”^{43,191–196} In addition, a study using rats showed that the concentration of brain DNA was decreased in rats exposed to nicotine.^{197,198}

Animal studies have shown that prenatal exposure to nicotine causes increased motor activity, hyperactivity, and problems with attention, memory, and learning.^{199,200} One such study found a dose-dependent relationship between levels of nicotine exposure and “stimulation of locomotor activity in offspring,” reporting “involvement of both mesolimbic and nigrostriatal dopaminergic pathways.”²⁰⁰ SHS exposure in the perinatal period is sufficient to raise levels of nicotine to concentrations great enough to alter normal neurodevelopment.²⁰¹ It has been shown that the amount of brain damage is equally severe in terms of magnitude and regional selectivity between perinatally and postnatally exposed groups. The nature of the neuromodulation includes cell loss, cell hypertrophy, and neurite formation, a marker of potential damage to neuronal projections.¹⁸⁹

Adverse Behavioral Outcomes in Human Studies

Although the nature of human research is fundamentally different from that using animal models, the evidence provided by human studies also strongly suggests that exposure to tobacco smoke, both prenatally and postnatally, increases the risk of poor behavioral and cognitive outcomes in children.

Multiple studies have found children exposed prenatally to tobacco smoke to have increased rates of behavior problems. An early longitudinal study found that such children exhibit overall worse behavior and that they also had increased rates of specific problems like hyperactivity, oppositional defiant disorder, delinquency, and both internalizing and externalizing behaviors.²⁰² A cross-sectional study reported a dose-dependent response between children with prenatal exposure and “hyperactivity/inattention” and “conduct problems,”²⁰² and others have directly linked prenatal tobacco smoke exposure to conduct disorder and ADHD, adjusting for multiple potential confounders and covariates such as income, parental antisocial tendencies, prematurity, birth weight, and poor parenting practices.²⁰³

Among children exposed to tobacco smoke either prenatally or postnatally, increased rates of behavioral problems are seen very early in life. Newborns exposed in utero have heightened startle responses, tremors, hypertonicity,¹⁶⁴ and have more severe reactions to bowel movements and diapering, and tend to cry more and be more fussy.²⁰⁴ By 18 months,

children exposed to SHS in utero manifest increased externalizing behaviors, including defiance, not responding to punishment, inability to pay attention, and hyperactivity.²⁰⁵

During pre-school years, children prenatally or postnatally exposed show more externalizing behavioral problems than unexposed children.^{206,207} Some of the more common problems include demanding attention, changes in mood, emotional instability, arguing, aggression, and destructive behavior.^{207,208} The adverse effects seen in early childhood tend to persist into adolescence.^{209–214} Children exposed prenatally to SHS are more likely to exhibit aggression, break rules, and display still other behavioral problems.²¹⁵

Studies have attempted to separate the effects of prenatal and postnatal maternal smoking and child behavior, although this presents very difficult methodologic problems. The 2006 Surgeon General's Report points out that this is a daunting challenge, since most women who smoke during pregnancy continue to do so after the birth of the child.¹⁴ A study by Weitzman et al.²¹⁶ showed that postnatal smoking alone and prenatal and postnatal smoking together were each independently associated with behavioral problems in children in a dose-dependent fashion. Findings from still another study show that while both prenatal and postnatal exposures are associated with increased likelihoods of having abnormal behavior, those exposed during the prenatal period were 90% more likely to be classified as abnormal, whereas children exclusively exposed only postnatally were 30% more likely.²¹⁷

The effect of controlling for potential confounders on examining associations between maternal smoking and behavioral problems in their offspring is a significant hurdle in elucidating meaningful conclusions from the data. Studies have been conducted suggesting that maternal smoking is either marginally associated or not independently associated with behavioral problems, and the link could be completely accounted for by confounding factors.²¹⁸ Contrary to this finding in select studies, Weitzman et al.²¹⁹ explained in a review article that the vast majority of studies that take these confounders into account report a positive correlation between maternal smoking and behavior problems even though there may exist differences between non-smoking and smoking mothers. Furthermore, animal studies contradict the notion that confounders alone (rather than tobacco smoke) are the cause of the behavioral problems seen in exposed children.²¹⁹

Conduct Disorder—Studies have found that children born to mothers who smoke more than a half pack of cigarettes per day during pregnancy are approximately 4 times more likely to have conduct disorders, and that they experience increased rates of oppositional defiant disorder and delinquency.^{220–222} Another study reported that this relationship between tobacco smoke exposure and conduct disorder may be confounded by multiple factors, including an increased prevalence of smoking among young people, poorer education of mothers of lower socioeconomic status, higher prevalence of smoking among women with depressive or antisocial traits, and the idea that prenatal smoking could be a marker of genetic risk for antisocial behavior.²²³ Clearly, further research needs to be done on this topic to account for all of these confounders.

Attention-Deficit/Hyperactivity Disorder—The association between ADHD and SHS exposure was reported as early as 1975 in a study that found that mothers who smoked were

3 times more likely to have “hyperkinetic” children.²²⁴ Review articles examining almost 40 years of research show that in utero exposure to tobacco smoke is a risk factor for ADHD and similar behavioral disorders,²²⁵ and the risk of developing ADHD has been reported from 2.4 to 3.4 times higher than among children not exposed.^{226,227} Of all of the factors implicated in causing ADHD, maternal smoking during pregnancy has been found to be the most important risk factor identified to date.²²⁷

The majority of studies relating prenatal and postnatal SHS exposure to ADHD show a positive and dose-dependent correlation, but some do not take into account important confounders such as familial ADHD, making the ability to establish a causal relationship more difficult. More recent studies have accounted for these confounders.²²⁸ A twin cohort study showed that prenatal substance abuse beyond the first trimester is associated with a 3.8-fold increased risk of ADHD after adjustment for maternal genetics.²²⁹ Thapar et al.²³⁰ found that when confounders such as genetic factors, shared and non-shared environmental influences, birth weight, social adversity, and antisocial symptom scores were considered, maternal smoking was still found to be significant.

Using data from the 1992–2002 National Health and Nutrition Examination Surveys (NHANES), Braun et al. examined the link between tobacco exposure, lead exposure, and ADHD. Adjusting for confounders, prenatal lead exposure and tobacco exposure were each significantly associated with ADHD with odds ratios of 4.1 and 2.5, respectively. The investigators reported that 32.2% of ADHD cases among children between the ages of 4 and 15 years can be attributed either to prenatal smoke exposure or increased blood lead levels ($>2 \mu\text{g/dL}$); the investigators could not, however, control for prenatal exposure to other substances or family history of mental health and ADHD.²³¹ Another study suggested that up to 38.2% of ADHD cases among children aged 8–15 years could be attributed to either prenatal smoke exposure, blood lead concentrations above $1.3 \mu\text{g/dL}$, or both; the population attributable fraction for prenatal tobacco exposure alone was reported as 21.7% and for blood lead concentrations above $1.3 \mu\text{g/dL}$ was 25.4%.²³²

Several studies have examined the interaction between dopaminergic genes and SHS exposure in the etiology of childhood ADHD. One study showed that children with 2 copies of a dopamine transporter gene polymorphism are more likely to develop ADHD in the presence of maternal smoking.^{233,234} Children with the DAT1 440 allele, or DRD4 7-repeat allele, and a history of prenatal tobacco smoke exposure were found to be 1.8 and 2.1 times more likely, respectively, to be diagnosed with DSM-IV combined subtype ADHD.²³⁵ Children with prenatal tobacco smoke exposure plus one such allele were found to be 3 times more likely to have an ADHD diagnosis, and children with both alleles plus maternal prenatal smoke exposure were 9 times more likely to have “population-defined” ADHD diagnosis than children with neither risk factor.²³⁵ In contrast, a recent study found no gene–environment interaction between children with the DRD4 7-repeat allele, prenatal SHS exposure, and the diagnosis of ADHD.²³⁶ Still another study found that only males containing the DAT1 genotype showed a gene–environment interaction with prenatal smoke exposure and ADHD; no such correlation was found in females.²³⁷ Although further research is needed to clarify these discrepancies, the studies represent a new frontier for

discerning the relationship between behavioral problems such as ADHD and prenatal tobacco smoke exposure.

Cognitive Impairments and School Performance—Impaired cognitive function appears to be still another consequence of prenatal tobacco or childhood SHS exposure, manifesting as lower scores on intelligence tests and achievement tests, and in poor school performance. In New York City alone, it has been estimated that the annual cost of interventional services as a result of exposure to tobacco smoke is approximately \$100 million.²³⁸ Despite the many studies showing an association between tobacco smoke exposure and cognitive impairments, some suggest that confounders and certain methodological limitations negatively affect the validity of these conclusions.^{239,240} One study found that, after accounting for maternal education, there was no correlation between tobacco smoke exposure and children's impairments of cognitive abilities.²⁴⁰ Breslau et al.²⁴¹ reported that although children aged 6–11 years exposed prenatally to tobacco smoke scored lower on the Weschler Intelligence Scale for Children Revised and on the Weschler Adult Intelligence Scale Third Edition (for those aged 17 years), these results could be fully attributed to maternal IQ and education. Another recent study showed that after comparing smoking habits across 2 pregnancies, the cognitive impairments seen among children with smoking mothers were also seen in a successive pregnancy in which the mother did not smoke, thus suggesting that the association between cognitive impairments and prenatal tobacco smoke exposure could be explained by parental education, as well as other confounders.^{242,243} Multiple studies that have found a significant inverse relationship between prenatal tobacco and childhood SHS exposure and child intelligence scores failed to account for parental intelligence, which is believed to be the most important factor in child intelligence.^{244–246}

Despite these problems, other studies have attempted to account for many of the common potential confounders. One such study examined prenatal maternal smoking and offspring intelligence, finding that children born to smoking mothers have a 6-point decrease in IQ at 18 years of age compared to children born to non-smoking mothers. Confounders such as parental social status, parental education, single mother status, mother's height and age, number of pregnancies, and gestational age were taken into account.²⁴⁷ Another examined the learning outcomes in adolescents prenatally exposed to tobacco smoke, finding that academic achievement suffered in children exposed to SHS even after adjusting for confounders.²⁴⁸

A recent hypothesis attempting to explain the link between children's exposure to tobacco smoke and cognitive impairments suggests that sleep fragmentation is often seen in children exposed to SHS, which might explain the decrease in IQ seen in these children.²⁴⁹ An increase in arousal frequency of snoring infants, as well as a inverse relationship between respiratory arousal index (central apnea, desaturation, and snoring) and Mental Developmental Index of the Bayley Scales of Infant Development has been found in households with smokers.²⁴⁹ Others have confirmed these findings, demonstrating that after accounting for potential confounding variables such as socioeconomic status, marital status, physical abuse, prenatal medical care, and postnatal cigarette smoke exposure, there remains an independent association between prenatal nicotine exposure and children's sleep

problems persisting throughout the first 12 years of life,²⁵⁰ including longer sleep-onset delay, sleep-disordered breathing, parasomnias, daytime sleepiness, and overall sleep disturbance.²⁴⁶

Numerous studies have documented the association between child tobacco exposure and poorer school performance. One reported that children exposed to parental SHS are 50% more likely to repeat kindergarten or first grade.²⁵¹ Another found lower scores on mathematics and spelling tests (but not reading tests) associated with maternal smoking. Although this study accounted for maternal education and child behavioral problems, it did not control for parental IQ.²⁵² Still another found children prenatally exposed to tobacco to be at a higher risk for failing to regulate physical aggression.²⁵³ Many questions remain about the validity of findings of the relationship between maternal prenatal smoking and cognitive impairments among children.

Prenatal SHS Effects of Alternative Tobacco Products

While cigarette use has dramatically decreased in recent years, there has been a marked upsurge in adolescent and young adult use of new, non-cigarette tobacco products, commonly referred to as alternative tobacco products. Although the total consumption of cigarettes in the U.S. has decreased 33% between 2000 and 2011,²⁵⁴ the consumption of alternative tobacco products such as hookahs (waterpipes), cigarillos, cigars, bidis, kreteks, and smokeless tobacco (snuff, dip, snus, and chewing tobacco) has increased an alarming 123% over the same time period. Many alternative tobacco products are from regions of the world where their use is culturally rooted and widely diffused into mainstream U.S. culture. Such regions include South Asia, the Middle East, and Latin America, regions with great numbers of immigrants to the U.S. In contrast to the extensive literature on the serious effects of both mainstream and secondhand cigarette smoke, research on the health consequences of alternative tobacco products is in its infancy. Additionally, there is an even more marked paucity of data about the effect of child health and development of prenatal and postnatal secondhand exposure to alternative tobacco products.

One of the few published prevalence studies of alternative tobacco product use among pregnant women, a multicenter, cross-sectional study of a convenience sample of 7961 pregnant women in 9 developing nations showed a very wide variation in the prevalence of current use of non-cigarette tobacco products. For example, rates of usage varied from 6% in the Democratic Republic of Congo, 33.5% in Orissa, India, and 4.9% in Karnataka, India.²⁵⁵ These data did not, unfortunately, allow for detailed investigation of basic sociodemographic characteristics of users versus nonusers or the type of alternative tobacco product used. More important for public policy and clinical practice in the U.S., there are no comparable data about the prevalence of use of any alternative tobacco products among pregnant women.

Hookahs—Hookahs (also called waterpipes, nargiles, or hubble-bubble) originated in India in the 15th century, and their use then expanded into the Middle East and all of South Asia.²⁵⁶ The U.S. Centers for Disease Control and Prevention characterizes them as devices used to smoke specially made tobacco and non-tobacco herbal shisha available in a variety of flavors.²⁵⁷ In most hookahs, charcoal is placed on top of punctured aluminum foil.^{258,259}

When the user sucks in air from a mouthpiece, heat from the charcoal warms the tobacco creating smoke, which is then passed through water in the pipe before inhalation.^{258,259} Hookah users tend to perceive hookah as a safer and less addictive alternative to cigarettes although evidence suggests that hookah use may actually be more harmful and addictive than cigarettes.^{260,261} A single waterpipe session can equate to smoking up to 100 cigarettes and yield greater levels of nicotine, tar, and carbon monoxide than cigarettes.^{262,263}

Hookah use is extremely popular among women in many non-Western societies, especially in the Middle East as well as South Asia (Bangladesh, Bhutan, India, the Maldives, Nepal, Pakistan, and Sri Lanka).^{264,265} Studies in Lebanon have found that 5.4–6.1% of pregnant women use hookah.^{266,267} Another Lebanese study found that while smokers of either hookah or cigarettes were partially knowledgeable about the health risks of cigarette smoking, they knew virtually nothing about the harmful ingredients of hookah smoking and had many misconceptions regarding how hookah worked or how it could produce harm.²⁶⁸ These studies emphasized the importance of more rigorous research to begin to better inform the public and develop other public health and clinical policies to prevent uptake and encourage the cessation of use.

In a study of 106 pregnant hookah users and 512 nonusers in Lebanon, no significant reduction in infant birth weight was found among babies of hookah users. Infants born to hookah smokers in this study, however, had an increased risk of having low Apgar scores, malformations (e.g., cardiac and hip anomalies and hydrocephalus), perinatal complications (e.g., jaundice, respiratory difficulties, and prolapse of the cord) as well as significant increases in infant respiratory distress.²⁶⁹ A more extensive retrospective cohort study of 8592 women in 6 major hospitals in Beirut, Lebanon, from 2000 to 2003 found that 4.4% of pregnant women were exclusive hookah smokers and that mothers smoking hookah more than once per day were at a 2.4 increased odds of having low-birth-weight infants compared with nonsmokers.²⁶⁶ The association of hookah use during pregnancy was also examined in a study in Southern Iran, where it was found that hookah smoking during pregnancy is a risk factor for low-birth-weight babies, and that mothers who started smoking during the first trimester had lower-birth-weight babies compared to those who started during their second or third trimesters.²⁷⁰

Smokeless Tobacco—Smokeless tobacco is tobacco consumed orally, not smoked. The main types of smokeless tobacco in Western countries are chewing tobacco, mostly used in the U.S., and oral snuff, mostly used in Sweden. In developing countries, tobacco is mostly chewed with other ingredients.²⁷¹ Most reviews conclude that smokeless tobacco use has substantial negative health implications, including oral leukoplakias, gingival recession, cancer, cardiovascular disease, peripheral vascular disease, hypertension, peptic ulcers, and increased rates of fetal morbidity and mortality.²⁷²

Despite the myriad adverse health consequences, smokeless tobacco use among women is still widespread. Data from the Special Supplemental Nutrition Program for Women, Infants, and Children in the U.S. show that 50% of Alaska Native women use chewing tobacco.^{273,274} A cohort study in South Africa reported that 7.5% of women reported using snuff

during pregnancy.²⁷⁵ Another study of 1217 pregnant women in eight selected areas in Mumbai, India, revealed that 16.9% reported using smokeless tobacco.²⁷⁶

In South Africa, another study among a cohort of 1593 pregnant women found that snuff users had a significantly shorter gestational length compared to both cigarette smokers and nonsmokers, although no significant differences in infant birth weight were observed.²⁷⁵ In Sweden, a study examining birth weight, preterm delivery, and preeclampsia in snuff users, cigarette smokers, and nonsmokers found that compared with nonusers, adjusted mean birth weight was reduced in snuff users by 39 g and in cigarette smokers by 190 g. Not surprisingly, preterm delivery was increased among both snuff users and smokers, and while preeclampsia was reduced among smokers, it was increased among snuff users.²⁷⁷ In Mumbai, India, it was shown that smokeless tobacco use was associated with an average reduction of 105 g in birth weight and a reduction in gestational age of 6.2 days with an adjusted odds ratio of 1.4 for preterm delivery (<37 weeks).²⁷⁶ Also in Mumbai, India, the incidence of stillbirth was significantly higher among smokeless tobacco users than nonusers with an adjusted proportional hazard ratio of 2.6 in a cohort of 1217 pregnant women.²⁷⁸ In Jabalpur, India, a study of 70 pregnant smokeless tobacco users found that infants of smokeless tobacco users had a significant reduction in birth weight (395 g) and height (0.5 cm) compared to infants born to nonusers.²⁷⁹ In Pakistan, snuff users were found to have evidence of degenerative placental changes, such as a higher number of chorionic villi with excessive collagen compared with nonusers.²⁸⁰

There is no available study to date on the effects of cigars, cigarillos, bidis, or kreteks on pregnancy outcomes. Nor is there study on the long-term neuro-behavioral outcomes of prenatal SHS exposure to any alternative tobacco product. Therefore, the SHS effect of alternative tobacco products is a markedly under-studied public health threat. More information is urgently needed to inform health care providers and women about the risks of using alternative tobacco products during pregnancy.

Conclusion

Extensive research documents the numerous health-related consequences to children exposed to tobacco prenatally or to SHS postnatally despite the fact that only a small percentage of the harmful chemicals in SHS have been studied. The rapidly growing body of evidence concerning the aftermath of prenatal tobacco and childhood SHS exposure is compelling from the molecular level to the adverse outcomes in childhood that persist into and throughout adult life.

Abbreviations:

ADHD	attention-deficit/hyperactivity disorder
DNA	deoxyribonucleic acid
ETS	environmental tobacco smoke
5-HT	5-hydroxytryptamine (serotonin)

IQ	intelligence quotient
PAH	polycyclic aromatic hydrocarbon
SHS	secondhand smoke
SIDS	sudden infant death syndrome
TSNA	tobacco-specific <i>N</i> -nitrosamines

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Fig 1.

Prevalence of smoking before pregnancy, during pregnancy, and after delivery, ^aBy year—Pregnancy Risk Assessment Monitoring System, United States, 10 sites, ^b2000–2010.¹ Abbreviation: PRAMS = Pregnancy Risk Assessment Monitoring System. ^aSmoking before pregnancy was defined as smoking 3 months before pregnancy on the basis of the PRAMS survey. Smoking during pregnancy was defined as smoking during the last 3 months of pregnancy on the basis of the PRAMS survey. Smoking after delivery was defined as smoking approximately 4 months after delivery on the basis of the PRAMS survey. ^bData aggregated for 10 PRAMS sites (Alaska, Arkansas, Colorado, Hawaii, Maine, Nebraska, Oklahoma, Utah, Washington, and West Virginia) with data available for all years.

[§]Significant linear trend ($p < 0.05$).

Fig 2. Prevalence of smoking during pregnancy^a—Pregnancy Risk Assessment Monitoring System, United States, 27 sites, ^b2010.¹ Abbreviation: PRAMS = Pregnancy Risk Assessment Monitoring System. ^aSmoking during pregnancy was defined as smoking during the last 3 months of pregnancy on the basis of the PRAMS survey. ^bData aggregated for 27 PRAMS sites (Alaska, Arkansas, Colorado, Delaware, Georgia, Hawaii, Maine, Maryland, Massachusetts, Michigan, Minnesota, Missouri, Nebraska, New Jersey, New York, New York City, Ohio, Oklahoma, Oregon, Pennsylvania, Rhode Island, Texas, Utah, Vermont, Washington, West Virginia, and Wyoming) with data available for 2010. Births for New York City are reported separate. Tong VT, Dietz PM, Morrow B, et al. Trends in smoking before, during, and after pregnancy—pregnancy risk assessment monitoring system, United States, 40 sites, 2000–2010. *MMWR Surveill Summ.* 2013;62(6):1–19.