The Effects of Nicotine on Development

Sharon A. McGrath-Morrow, MD,[a,b] Julie Gorzkowski, MSW,[a] Judith A. Groner, MD,[a,c] Ana M. Rule, PhD,[a,d] Karen Wilson, MD, MPH,[a,e] Susanne E. Tanski, MD, MPH,[a,f] Joseph M. Collaco, MD, PhD,[a,b] Jonathan D. Klein, MD, MPH[a,g]

abstract

Recently, there has been a significant increase in the use of noncombustible nicotine–containing products, including electronic cigarettes (e-cigarettes). Of increasing popularity are e-cigarettes that can deliver high doses of nicotine over short periods of time. These devices have led to a rise in nicotine addiction in adolescent users who were nonsmokers. Use of noncombustible nicotine products by pregnant mothers is also increasing and can expose the developing fetus to nicotine, a known teratogen. In addition, young children are frequently exposed to secondhand and thirdhand nicotine aerosols generated by e-cigarettes, with little understanding of the effects these exposures can have on health. With the advent of these new nicotine-delivery systems, many concerns have arisen regarding the short- and long-term health effects of nicotine on childhood health during all stages of development. Although health studies on nicotine exposure alone are limited, educating policy makers and health care providers on the potential health effects of noncombustible nicotine is needed because public acceptance of these products has become so widespread. Most studies evaluating the effects of nicotine on health have been undertaken in the context of smoke exposure. Nevertheless, in vitro and in vivo preclinical studies strongly indicate that nicotine exposure alone can adversely affect the nervous, respiratory, immune, and cardiovascular systems, particularly when exposure occurs during critical developmental periods. In this review, we have included both preclinical and clinical studies to identify age-related health effects of nicotine exposure alone, examining the mechanisms underlying these effects.

In recent years, new nicotine-delivery systems and other noncombustible nicotine–containing products have become increasingly available for recreational purposes and for smoking cessation. Currently, nicotine-containing electronic cigarettes (e-cigarettes), smokeless tobacco (Swedish snuff, pituri, or mishri), and nicotine-replacement therapies (NRTs), such as transdermal patches or chewing gum, are commonly being used by the public.[1–4]

The use of these noncombustible nicotine products has raised significant concerns about the health effects of nicotine alone on children and vulnerable populations. Most recently, widespread adolescent use and addiction to nicotine has been recognized as a consequence of new e-cigarette technologies.[5,6] Among adolescents, the introduction of JUUL in particular has contributed to higher nicotine exposure and greater addiction potential compared with nonpod users.[7] The health effects of unintentional or secondhand and thirdhand nicotine exposure from noncombustible nicotine sources are

[a]Julius B. Richmond Center of Excellence, American Academy of Pediatrics, Itasca, Illinois; [b]Eudowood Division of Pediatric Respiratory Sciences, Department of Pediatrics, School of Medicine and [d]Department of Environmental Health and Engineering, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, Maryland; [c]Department of Pediatrics, Nationwide Children's Hospital, Columbus, Ohio; [e]Department of Pediatrics, Icahn School of Medicine at Mount Sinai and Kravis Children's Hospital, New York, New York; [f]Department of Pediatrics, Geisel School of Medicine, Dartmouth College, Lebanon, New Hampshire; and [g]Department of Pediatrics, University of Illinois at Chicago, Chicago, Illinois

To cite: McGrath-Morrow SA, Gorzkowski J, Groner JA, et al. The Effects of Nicotine on Development. *Pediatrics.* 2020;145(3):e20191346

STATE-OF-THE-ART REVIEW ARTICLE

less understood. It has been recognized, however, that use of these products can expose nonusers to detectable nicotine levels.[8] For instance, nicotine exposure can occur in offspring of mothers who use noncombustible nicotine products during pregnancy[9] and in children exposed to secondhand nicotine-containing aerosols.[10] Breast milk from users of Swedish snuff has been shown to contain high nicotine and cotinine levels,[11] and measurable levels of nicotine have been found in breast milk from mothers who use the nicotine patch for smoking cessation.[12] Elevated levels of nicotine from e-cigarette aerosols have also been detected by air sampling,[13] with measurable levels of nicotine found in nontobacco users attending an e-cigarette convention.[14] In addition, other studies have found that thirdhand nicotine exposure from e-cigarettes can also occur.[15,16]

Before the widespread acceptance of these noncombustible nicotine products, there has been little focus on the health effects of nicotine alone on childhood health and development, with most studies focused on tobacco smoke exposure.[17,18] Consequently, current knowledge of the health effects of nicotine alone on development come primarily from in vitro and in vivo preclinical studies, maternal in utero snuff exposure, and cross-sectional studies in e-cigarette users. Although several recent clinical studies support an association between nicotine aerosols and a higher likelihood of cardiovascular and respiratory disease in users, no long-term longitudinal studies exist that have addressed the health effects of noncombustible nicotine products on childhood development.[19–21]

Because of the recent popularity of noncombustible nicotine–containing products, there has emerged an urgent need to inform policy makers and health care providers about the potential health effects of nicotine exposure on childhood development. In this review, we aim to explore the age-related effects of nicotine exposure and the mechanisms underlying these effects using, when available, clinical studies focused on noncombustible nicotine use during development. Because there are few existing human studies examining the effects of pure nicotine exposure, we have included in vivo, in vitro, and human smoke exposure studies in this review to determine the likelihood of nicotine exposure alone in causing adverse health consequences during development.

NICOTINE AS A LIGAND FOR NICOTINIC ACETYLCHOLINE RECEPTORS

Nicotinic acetylcholine receptors (nAChRs) are located throughout the central and peripheral nervous system. These receptors are transmembrane pentameric neurotransmitter-gated ion channels that open with ligand binding, enabling fast synaptic transmission.[22] The neuronal nAChR subunits are composed of α-2 to α-10 subunits and β-2 to β-4 subunits.[23] Although acetylcholine is the endogenous ligand for nAChRs, these receptors can also bind with nicotine.[24] The α-4 and β-2 nAChRs bind nicotine with high affinity, whereas the α-7 nAChRs bind nicotine with less affinity. Animal modeling has revealed that nicotine exposure can cause inappropriate activation or deactivation of nAChRs during critical periods of brain development.[25]

Nicotine addiction causes upregulation of nAChRs.[26] When nicotine binds to nAChRs, the neurotransmitter dopamine is released, reinforcing drug use[27,28] and feelings of pleasure.[29] Chronic exposure to nicotine can decrease responsiveness of nAChRs in the brain, alter sensitivity to dopamine, and change brain circuits involved in learning, stress, and self-control; this can result in addiction and dependence, characterized by withdrawal symptoms when not using nicotine.[30,31] Nicotine can also activate the endogenous opioid system through α-7 nAChRs binding.[32]Preclinical studies in knock-out mice have revealed that both β-2 and α-7 subunits are important for nicotine addiction and withdrawal.[23] Other neurotransmitters can also be released when nicotine binds to nAChRs, including norepinephrine, acetylcholine, serotonin, γ-aminobutyric acid, and glutamate.[17]

NICOTINE METABOLISM

The development of health issues and propensity toward addiction are likely influenced by nicotine metabolism. Nicotine is primarily metabolized by CYP2A6 in the liver, and age, genetics, sex, and kidney function can contribute to the variability in rates of nicotine metabolism.[33–36] Nicotine exposure can occur during fetal and early postnatal life. Dempsey et al[37] reported detectable umbilical cord nicotine levels in newborns of smoking mothers. They also found that elimination of nicotine was prolonged in the newborns compared with adults.[37] Nordenstam et al[11] reported that users of snuff had higher levels and slower clearance of nicotine from their breast milk compared with smokers.

Although adolescent use of alternative tobacco products is increasing,[38] most studies on nicotine metabolism have been done in smokers. Nevertheless, genetics likely influences the probability of nicotine addiction in both smokers and noncombustible nicotine users. A study in Mexican mestizo smokers revealed that the number of risk alleles in the *CYP2A6* gene correlated with earlier initiation of smoking and greater consumption.[39] Another study in adolescent smokers reported that fast metabolizers of nicotine had greater nicotine withdrawal symptoms.[40]

Nicotine pharmacokinetics can also vary by nicotine-delivery device and likely contributes to addiction potential. In one study, researchers compared plasma nicotine levels in users of cigarettes, snus, and nicotine gum. They found that loose snus had peak plasma nicotine levels at 1 hour, nicotine gum at 45 minutes, and cigarette users at 7 minutes.[41] A small study in adults using nicotine-containing e-cigarettes revealed peak plasma nicotine levels at 5 minutes, with nicotine levels similar to smokers.[42] Another study reported that experienced smokers and e-cigarette users can self-titrate to achieve optimal levels of nicotine.[43] Additional studies are needed to further understand age-related differences in metabolism of noncombustible nicotine in infants, children, and adolescents and how these differences can affect health outcomes.

NICOTINE AND PREGNANCY

Nicotine levels have been detected in offspring of mothers who smoke during pregnancy,[44,45] and in utero smoke exposure has been associated with some forms of birth defects. This relationships was highlighted in a live-birth cohort study in which smoking during the first trimester increased the likelihood of birth defects, including limb reduction, gastroschisis, and oral clefts.[46] However, determining the effects of nicotine alone on health outcomes is difficult because tobacco smoke contains >4800 different components.[47–49] Preclinical studies suggest that nicotine alone may interfere with normal development. A study in pregnant mice found that nicotine crosses the placenta into the fetal bloodstream and binds to fetal nAChRs.[50] Another study in pregnant rats revealed a transient reduction in uterine blood flow with nicotine aerosols that could be blocked by using a nAChR antagonist.[51] Of increasing concern is the perception that e-cigarette or noncombustible tobacco use is a safe alternative to smoking during pregnancy. The prevalence of e-cigarette use in pregnant women has been estimated to be between 0.6% and 15%.[52] However, to date, studies evaluating birth outcomes in mothers who use nicotine-containing e-cigarette during pregnancy are lacking. However, a study in the United Kingdom revealed a significant increase in respiratory anomalies (odds ratio [OR]: 4.65) in mothers using NRTs compared with controls.[53]

Cleft Palate

Fetal exposure to maternal smoking during pregnancy is related to the presence of orofacial clefts in the offspring.[54,55] A case-control study revealed[56] that offspring exposed to prenatal smoke were 1.6 to 2.0 times as likely to have a cleft lip or palate if these defects were not associated with other congenital abnormalities. Separating out the effect of nicotine on birth outcomes, however, can be difficult. Nevertheless, a preclinical study in mice found that persistent exposure to nicotine during pregnancy led to stillbirth, low birth weight, and abnormalities of the palate.[57] Gunnerbeck et al[58] also reported that mothers who used Swedish snuff during pregnancy had a higher adjusted OR (1.19) of delivering a child with an oral cleft compared with nontobacco users. These studies suggest that nicotine alone is associated with abnormal in utero palate development.

Preterm Birth

Maternal smoking during pregnancy is a known risk factor for prematurity. In a study from New Zealand, maternal smoking during pregnancy was related to an independent increase in preterm birth, and in a case-control study from Stockholm, preterm birth was increased in moderate to heavy smokers.[54,59] A study supporting a nicotine link to preterm birth revealed that mothers who used snuff during pregnancy had an increased OR of 1.58 for premature birth compared with mothers not using tobacco products.[60]

Stillbirth

In a preclinical study in mice, nicotine exposure during pregnancy caused a significant increase in fetal loss.[61] Noncombustible nicotine use and increased risk for stillbirth delivery is supported by several human studies. Mothers who used Swedish snuff during pregnancy had a higher likelihood of having a stillborn infant.[62,63] Another study revealed that the absolute risks of stillbirth were similar between mothers who smoked or used NRT (5 per 1000 live births) compared with controls (3.5 per 1000 live births); however, the adjusted OR in the NRT group was not significantly different from that of controls.[64]

Intrauterine Growth Restriction

Maternal smoking during pregnancy has been associated with intrauterine growth restriction.[54,65] Preclinical nicotine studies also support this relationship. A study in pregnant rats revealed fetal growth restriction and reduction in uterine and placental blood flow in nicotine-treated rats,[66] and Rowell and Clark[67] reported that nicotine-treated pregnant mice had decreased placental and fetal weights. The role of nicotine and altered fetal growth is also supported by a study in mothers who used snuff during pregnancy. They had an increased OR of 1.26 for a small-for-gestational-age infant, whereas offspring of mothers who smoked had an increased OR of 2.55.[68]

These preclinical and human studies of pregnant mothers who smoke or use smokeless tobacco support an association between nicotine exposure and adverse pregnancy outcomes.

NICOTINE AND SUDDEN INFANT DEATH SYNDROME

Maternal smoking during pregnancy is a known risk factor for sudden infant death syndrome (SIDS).[69] In a large national case-control study, Mitchell et al[70] found a relative risk of SIDS of 4.09 (95% confidence interval 3.28–5.11) among infants whose mothers smoked during pregnancy. Preclinical studies in animals support a relationship between nicotine exposure in utero and abnormal respiratory responses in mice.[71] Mouse pups exposed to in utero nicotine can develop abnormal respiratory responses to hypoxia and depressed arousal to intermittent hypoxia. Cohen et al[50] found that pups lacking functional β-2-containing nAChRs had similar respiratory responses as the nicotine-exposed pups. Slotkin et al[72] also found that catecholamine responses were impaired in rats exposed to in utero nicotine. Another study in pregnant baboons given nicotine infusions revealed that offspring developed altered serotonergic and nAChR binding in areas of the medulla that regulate cardiorespiratory control.[73] Although no studies were found linking SIDS and infants exposed to noncombustible tobacco products, Nordenstam et al[74] reported that infants of mothers who used Swedish snuff or smoked during pregnancy had higher low frequency and high frequency ratios at 1 to 2 months of age compared with controls, indicative of lower vagal activity. Taken together, the preclinical animal studies and observations in children exposed to prenatal smoke indicate a possible association between in utero nicotine exposure and increased risk of SIDS.

NICOTINE EXPOSURE AND BEHAVIORAL OUTCOMES

Neuronal nAChRs are expressed during different periods of fetal development and are involved in cell survival, synaptogenesis, and morphogenesis.[25] Inappropriate activation of nAChRs during fetal and early postnatal development by nicotine exposure can disrupt normal brain development.[25] In utero nicotine exposure may also have more long-term effects on behavior. In our murine model, adult mice exposed to nicotine-containing e-cigarette aerosols during late gestation and early postnatal life only demonstrated increased levels of activity in the zero maze and open-field tests compared with controls.[75] In other murine models, prenatal nicotine exposure was associated with behavioral analogs of anxiety and altered sensorimotor integration[76] and deficits in attention and working memory in male mice.[77] In rats, prenatal nicotine exposure was associated with developmental effects on the medial prefrontal cortex, decreased synaptic plasticity, and attention deficit–related deficits in cognitive behavior.[78] In contrast, one study found that adolescent rats had enhanced learning when exposed to nicotine in some settings.[79] Multiple studies in humans exposed to smoke support the preclinical findings. Behavioral and cognitive outcome studies in children with in utero smoke exposure revealed impaired executive function,[80] altered intelligence and auditory functioning,[81] and behavioral problems.[82] A meta-analysis found an association between prenatal smoke exposure and attention-deficit/hyperactivity disorder.[83] In a Finnish national birth cohort study, an association was found between in utero smoke exposure and higher rates of behavioral and emotional disorders.[84] The combination of preclinical and human studies in children exposed to prenatal smoke indicate that in utero nicotine exposure alone likely contributes to adverse behavioral and cognitive outcomes. However prospective observational studies will be needed to determine the extent by which noncombustible nicotine exposures can affect developmental and behavioral problems during childhood and adolescence.

NICOTINE AND ADDICTION

Nicotine addiction is characterized by mood or performance enhancement and avoidance of withdrawal symptoms, whereas nicotine withdrawal symptoms include irritability, depression, restlessness, anxiety, problems socializing, difficulty with concentrating, increased hunger, insomnia, and craving for tobacco. Preclinical studies suggest that behavioral differences and greater dopamine release in response to nicotine underlie the greater likelihood of addiction occurring in adolescents compared with adults.[85] Among never smokers, adolescents who tried nicotine-containing e-cigarettes were at significantly higher risk for daily use of e-cigarettes (adjusted OR: 2.92), whereas adolescents who tried nonnicotine-containing e-cigarettes were not.[86] In addition, pod products containing high levels of nicotine, such as JUUL, have resulted in widespread acceptance of e-cigarettes among adolescents. In a study of high school students who ever used e-cigarettes, JUUL was the preferred device among ever users of single devices and was associated with the highest nicotine use.[87] Another study revealed that adolescents who were pod e-cigarette users had greater nicotine dependence and higher urinary cotinine levels than nonpod e-cigarette users.[7] Another study emphasized the addictive potential of e-cigarettes in adolescents. Of the adolescents who only used e-cigarettes, 80.3% were still using 12 months later, daily use increased from 14.5% to 29.8%, and tobacco smoking initiation occurred in 28.8%.[5] These studies and others[88,89] suggest that the widespread use and acceptance of e-cigarettes, particularly the pod devices

containing high levels of nicotine, will likely increase the number of adolescents addicted to nicotine and increase tobacco smoking initiation in upcoming years.

NICOTINE AND THE CARDIOVASCULAR SYSTEM

Maternal smoking is associated with an increased risk of long-term pediatric cardiovascular morbidity in offspring.[90] There is little known, however, regarding the effects of nicotine alone on the development of cardiovascular disease in children and adolescents. Several clinical studies indicate that nicotine-containing e-cigarettes can cause short-term cardiovascular changes in adults.[91,92] Franzen et al[92] reported that users of nicotine-containing e-cigarettes or conventional cigarettes had greater arterial stiffness, higher systolic and diastolic blood pressure, and a higher heart rate compared with subjects not exposed to nicotine. In this study, the users of nicotine-containing e-cigarette sustained elevated blood pressure longer than those smoking conventional cigarettes. Although short-term cardiovascular abnormalities may predict long-term cardiovascular abnormalities in users of nicotine-containing e-cigarettes, there are currently no long-term studies. However, a preclinical study from Espinoza-Derout et al[93] strongly supports a link between nicotine alone and cardiovascular abnormalities. They reported that ApoE$^{-/-}$ mice exposed to 2.4%-nicotine e-cigarettes for 12 weeks had increased atherosclerotic lesions and decreased left ventricular fractional shortening and ejection fraction compared with mice exposed to 0%-nicotine e-cigarette aerosols. Another study using ApoE$^{-/-}$ mice revealed that nicotine promoted autophagy in blood vessels, increased migratory capacity of vascular smooth muscle cells (VSMCs), and promoted the development of atherosclerosis.[94] Nicotine was also shown to induce VSMC transformation toward a more atherosclerotic phenotype in human VSMCs.[95] Taken together, these studies support the biological plausibility for cardiovascular disease development with the use of nicotine alone.

NICOTINE AND THE LUNG

Lung development in utero begins with lung-bud development in the early first trimester and extends up until the late third trimester with the formation of alveoli and surfactant maturation. Subsequently, the majority of postnatal alveolar growth occurs by age 2 years,[96] with more recent evidence suggesting some additional growth into adolescence.[97] Thus, any environmental exposures occurring between conception and adolescence have the potential to affect lung growth. However, parsing the effects of nicotine from those of other constituents in smoke exposure or e-cigarette aerosols in the developing human lung is difficult because the respiratory epithelium is exposed to both.

In utero, nicotine is readily absorbed into the maternal bloodstream and crosses the placenta, with blood levels in the fetus thought to be similar to those in the mother.[98] Mechanisms by which nicotine may affect the developing lung include via nAChRs and through reduction of antioxidant enzyme activity.[99,100] Animal studies of prenatal nicotine exposure reveal multiple changes within the lung, including narrowing of airways and thickening of their walls, and dysynaptic lung growth with reduced surface area complexity.[98] The resultant effects in rodents include reduced forced expiratory flows in adulthood akin to obstructive lung disease in humans.[101] There are some data suggesting that the pulmonary effects of prenatal nicotine may be ameliorated by antioxidant therapy (vitamin C) in monkeys and melatonin in rats.[102,103]

The effects of postnatal nicotine exposure on lung development are less well elucidated than those of prenatal exposure. Nicotine and nicotine metabolites have been detected in children exposed to secondhand smoke.[104] There are causal links between smoke exposure and lower respiratory tract illnesses in infants and children, asthma in school-aged children, and reduced childhood lung function, suggesting effects on immune function, airway characteristics, and lung growth.[105] Several cross-sectional studies in adolescent users of e-cigarettes have revealed an association between e-cigarette use and chronic bronchitis symptoms, self-reported doctor diagnosis of asthma, higher rates of respiratory symptoms, and greater school absenteeism due to asthma.[106–109] In vitro and in vivo studies examining mucociliary clearance (MCC) in the lung have revealed that nicotine-containing e-cigarettes can impair MCC and decrease airway hydration.[110,111] Impairment of MCC can alter immune defenses in the lung and increase the likelihood of lower airway infections.

Nicotine exposure in utero or in early childhood may also have respiratory effects throughout the life span of the individual through epigenetic changes, which may be heritable. One study of nicotine-exposed pregnant rats revealed that the offspring of the exposed offspring had potentially epigenetic-induced increased airway resistance and contractility proteins.[112]

Although no long-term studies exist, preclinical and limited clinical studies support an association between exposure to nicotine alone and impaired lung development and altered MCC. Cross-sectional studies in adolescents also suggest an increased risk for respiratory symptoms in adolescent e-cigarette

TABLE 1 Influences of Nicotine Exposure on Health Outcomes During Development

	Age of Nicotine Exposure			
	Fetal Life	Infancy	Childhood	Adolescence
Gestational				
Orofacial clefts	X	—	—	—
Preterm birth	X	—	—	—
Stillbirth	X	—	—	—
Intrauterine growth restriction	X	—	—	—
Central nervous system				
SIDS	—	X	—	—
Neurocognitive and behavior	X	X	X	—
Addiction	—	—	—	X
Cardiovascular				
Cardiovascular changes	X	X	X	X
Respiratory				
Wheezing and airflow obstruction	X	X	X	X
Lung growth	X	X	X	—
Immune or malignancy	—	X	X	X

—, not applicable.

users with and without asthma. Prospective observational studies will be needed to fully delineate the effects of nicotine alone on lung function and respiratory outcomes.

NICOTINE AND THE IMMUNE SYSTEM

The mechanisms underlying nicotine's effect on immune responses is complex. Tobacco smoke exposure can alter immune responses by inducing T helper 2 cytokine production[113] and attenuating interferon-γ responses in children.[114,115] Young children with mothers who smoked had a higher risk of lower respiratory tract infections, as did children exposed to secondhand smoke.[116–118] Preclinical studies have revealed that nicotine can alter immune function via nAChRs on lymphocytes[119] or by glucocorticoid hypersecretion.[120] In other animal studies, authors have attempted to parse out the effects of nicotine from tobacco smoke. The authors in a study in mice used nicotine e-cigarette aerosols and found that exposed mice had impaired bacterial clearance of *Streptococcus* pneumonia and increased viral titers of influenza A virus compared with controls.[121] Another study in mice revealed that nicotine-activated α-7 nAChRs increased recruitment of T regulatory cells.[122,123] Other mouse studies reported that nicotine can impede airway clearance by impairing MCC,[111] increasing mucus viscosity,[124] and inactivating α-7 nAChRs in the airways.[125]

Taken together, these preclinical and smoke studies indicate that nicotine can alter antimicrobial and inflammatory responses and impact MCC in the airways.

NICOTINE AND MALIGNANCY

It is well known that the use of combustible tobacco products increases the risk for a malignancy; however, nicotine alone may contribute to treatment resistance and cancer progression.[126,127] An in vitro study using human umbilical cord mesenchymal stem cells treated with nicotine revealed increased migration, enhanced stemness, and increased epithelial-mesenchymal transition (EMT),[128] consistent with cellular processes that promote tumor progression. In another study, nicotine induced EMT of breast cancer cells and activated fibroblasts, which enhanced EMT and cancer cell migration.[129] A study using human non–small cell lung cancer cells revealed that nicotine induced non–small cell lung cancer cell invasion, migration, and EMT, effects that were mediated by α-7 nAChRs.[130] No studies currently exist linking nicotine-containing e-cigarettes and tumor progression or development in any organ systems. Long-term observational studies will likely answer these questions. Nevertheless, current in vitro studies suggest a link between exposure to nicotine alone and tumor progression and cancer cell migration.

ACUTE NICOTINE INGESTION IN CHILDREN AND ADOLESCENTS

Nicotine is a water-soluble bioactive alkaloid with strong parasympathomimetic properties.[131,132] Mild acute nicotine intoxication can cause nausea, vomiting, respiratory symptoms, and cardiovascular instability, whereas high levels of systemic nicotine can lead to seizures and cardiorespiratory arrest.[131,133,134] The severity of nicotine intoxication depends on dose, duration, frequency of exposure, route of exposure, and formulation. Accidental ingestion of liquid nicotine has been responsible for the deaths of several young children.[135,136] As a result of these accidental nicotine ingestions in children, the Child Nicotine Poisoning Prevention Act was passed in 2016, resulting in a significant decline in accidental liquid nicotine exposures in the United States.[137]

In addition, suicide rates in adolescents and young adults have been increasing.[138] It has been recently recognized that adolescents who use e-cigarettes are at higher risk for mental health concerns[139,140] and that suicides and attempts by nicotine ingestion have occurred in teenagers and young adults.[134,141,142]

Therefore, health care providers need to be aware that adolescent e-cigarette users may represent a subset of children at increased risk for depression and suicide and that liquid nicotine can be used as a vehicle for suicide attempts.

GAPS IN KNOWLEDGE

This review supports biological plausibility for nicotine exposure alone to cause adverse health outcomes in children and adolescents (Table 1, Supplemental Table 2). With the emergence of new devices that deliver noncombustible nicotine and their increasing popularity to youth,[143] there is a growing need to understand the effects of nicotine alone on human health. In addition to preclinical studies, steps are needed to characterize users and their profiles (including trajectories) and to identify those at highest risk for nicotine addiction andnicotine-related health conditions. A morecomplete understanding of the health effects of nicotine exposure on offspring of pregnant women, on infants and children, on adolescents who vape, and on children with chronic health conditions is also needed. In addition, public health interventions that regulate the manufacture, sale, and use of these new nicotine-delivery systems should be implemented to reduce exposure to adolescents and young adults who are at an increased risk for long-term health issues.

CONCLUSIONS

Preclinical and clinical studies indicate that nicotine exposure alone has the potential to cause developmental abnormalities, harm childhood health, and addict a new generation of adolescents and young adults.[144,145] Additional education, studies, and policies are needed to protect children and to mitigate nicotine's adverse health effects in children and vulnerable populations.

ABBREVIATIONS

e-cigarette: electronic cigarette
EMT: epithelial-mesenchymal transition
MCC: mucociliary clearance
nAChR: nicotinic acetylcholine receptor
NRT: nicotine-replacement therapy
OR: odds ratio
SIDS: sudden infant death syndrome
VSMC: vascular smooth muscle cell

Dr McGrath-Morrow helped to conceptualize and draft the initial manuscript and reviewed and revised the manuscript; Ms Gorzkowski helped to conceptualize the manuscript and critically reviewed the manuscript; Drs Groner, Rule, Wilson, and Klein helped to draft the initial manuscript and reviewed and revised the manuscript; Dr Tanski helped to conceptualize the manuscript and reviewed the manuscript; Dr Collaco helped to conceptualize and draft the initial manuscript and revised the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

DOI: https://doi.org/10.1542/peds.2019-1346

Accepted for publication Aug 5, 2019

Address correspondence to Sharon A. McGrath-Morrow, MD, Eudowood Division of Pediatric Respiratory Sciences, Department of Pediatrics, School of Medicine, Johns Hopkins University, David M. Rubenstein Building, Suite 3075B, 200 N Wolfe St, Baltimore, MD 21287-2533. E-mail: smcgrath@jhmi.edu

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: Funded in part by R01 HL114800 to Dr McGrath-Morrow. Funded by the National Institutes of Health (NIH).

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

REFERENCES

1. Slotkin TA. If nicotine is a developmental neurotoxicant in animal studies, dare we recommend nicotine replacement therapy in pregnant women and adolescents? *Neurotoxicol Teratol*. 2008;30(1):1–19
2. Ganganahalli P, Pratinidhi A, Patil J, Kakade SV. Correlation of cotinine levels with use of smokeless tobacco (mishri) among pregnant women and anthropometry of newborn. *J Clin Diagn Res*. 2017;11(3):LC16-LC19
3. Gunnerbeck A, Raaschou P, Cnattingius S, Edstedt Bonamy AK, Wickström R. Maternal snuff use and cotinine in late pregnancy-a validation study. *Acta Obstet Gynecol Scand*. 2018;97(11):1373–1380
4. Ratsch A, Steadman KJ, Bogossian F. The pituri story: a review of the historical literature surrounding traditional Australian Aboriginal use of nicotine in Central Australia. *J Ethnobiol Ethnomed*. 2010;6:26
5. Vogel EA, Prochaska JJ, Ramo DE, Andres J, Rubinstein ML. Adolescents' e-cigarette use: increases in

frequency, dependence, and nicotine exposure over 12 months. *J Adolesc Health*. 2019;64(6):770–775

6. McKelvey K, Baiocchi M, Halpern-Felsher B. Adolescents' and young adults' use and perceptions of pod-based electronic cigarettes. *JAMA Netw Open*. 2018;1(6):e183535
7. Boykan R, Goniewicz ML, Messina CR. Evidence of nicotine dependence in adolescents who use Juul and similar pod devices. *Int J Environ Res Public Health*. 2019;16(12):E2135
8. Logue JM, Sleiman M, Montesinos VN, et al. Emissions from electronic cigarettes: assessing vapers' intake of toxic compounds, secondhand exposures, and the associated health impacts. *Environ Sci Technol*. 2017; 51(16):9271–9279
9. Hurt RD, Renner CC, Patten CA, et al. Iqmik–a form of smokeless tobacco used by pregnant Alaska natives: nicotine exposure in their neonates. *J Matern Fetal Neonatal Med*. 2005; 17(4):281–289
10. Quintana PJE, Hoh E, Dodder NG, et al. Nicotine levels in silicone wristband samplers worn by children exposed to secondhand smoke and electronic cigarette vapor are highly correlated with child's urinary cotinine. *J Expo Sci Environ Epidemiol*. 2019;29(6):733–741
11. Nordenstam F, Lundell B, Edstedt Bonamy AK, Raaschou P, Wickström R. Snus users had high levels of nicotine, cotinine and 3-hydroxycotinine in their breastmilk, and the clearance was slower than in smoking mothers. *Acta Paediatr*. 2019;108(7):1250–1255
12. Nicotine. In: *Drugs and Lactation Database (LactMed)*. Bethesda, MD: National Library of Medicine (US); 2006
13. Johnson JM, Naeher LP, Yu X, Rathbun SL, Muilenburg JL, Wang JS. Air monitoring at large public electronic cigarette events. *Int J Hyg Environ Health*. 2018;221(3):541–547
14. Johnson JM, Naeher LP, Yu X, et al. A biomonitoring assessment of secondhand exposures to electronic cigarette emissions. *Int J Hyg Environ Health*. 2019;222(5):816–823
15. Khachatoorian C, Jacob Iii P, Benowitz NL, Talbot P. Electronic cigarette chemicals transfer from a vape shop to a nearby business in a multiple-tenant retail building. *Tob Control*. 2019;28(5): 519–525
16. Khachatoorian C, Jacob P III, Sen A, Zhu Y, Benowitz NL, Talbot P. Identification and quantification of electronic cigarette exhaled aerosol residue chemicals in field sites. *Environ Res*. 2019;170:351–358
17. Vizi ES, Lendvai B. Modulatory role of presynaptic nicotinic receptors in synaptic and non-synaptic chemical communication in the central nervous system. *Brain Res Brain Res Rev*. 1999; 30(3):219–235
18. Raghuveer G, White DA, Hayman LL, et al; American Heart Association Committee on Atherosclerosis, Hypertension, and Obesity in the Young of the Council on Cardiovascular Disease in the Young; Behavior Change for Improving Health Factors Committee of the Council on Lifestyle and Cardiometabolic Health and Council on Epidemiology and Prevention; and Stroke Council. Cardiovascular consequences of childhood secondhand tobacco smoke exposure: prevailing evidence, burden, and racial and socioeconomic disparities: a scientific statement from the American Heart Association [published correction appears in Circulation. 2016;134(16): e366]. *Circulation*. 2016;134(16): e336–e359
19. National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Population Health and Public Health Practice; Committee on the Review of the Health Effects of Electronic Nicotine Delivery Systems. In: Eaton DL, Kwan LY, Stratton K, eds. *Public Health Consequences of E-Cigarettes*. Washington, DC: National Academies Press (US); 2018
20. Rubinstein ML, Delucchi K, Benowitz NL, Ramo DE. Adolescent exposure to toxic volatile organic chemicals from e-cigarettes. *Pediatrics*. 2018;141(4): e20173557
21. Olmedo P, Goessler W, Tanda S, et al. Metal concentrations in e-cigarette liquid and aerosol samples: the contribution of metallic coils. *Environ Health Perspect*. 2018;126(2):27010
22. Karlin A, Akabas MH. Toward a structural basis for the function of nicotinic acetylcholine receptors and their cousins. *Neuron*. 1995;15(6): 1231–1244
23. Brunzell DH, Stafford AM, Dixon CI. Nicotinic receptor contributions to smoking: insights from human studies and animal models. *Curr Addict Rep*. 2015;2(1):33–46
24. Gotti C, Clementi F. Neuronal nicotinic receptors: from structure to pathology. *Prog Neurobiol*. 2004;74(6):363–396
25. Dwyer JB, Broide RS, Leslie FM. Nicotine and brain development. *Birth Defects Res C Embryo Today*. 2008;84(1):30–44
26. Govind AP, Vezina P, Green WN. Nicotine-induced upregulation of nicotinic receptors: underlying mechanisms and relevance to nicotine addiction. *Biochem Pharmacol*. 2009;78(7): 756–765
27. Faure P, Tolu S, Valverde S, Naudé J. Role of nicotinic acetylcholine receptors in regulating dopamine neuron activity. *Neuroscience*. 2014;282: 86–100
28. Gueorguiev VD, Zeman RJ, Meyer EM, Sabban EL. Involvement of alpha7 nicotinic acetylcholine receptors in activation of tyrosine hydroxylase and dopamine beta-hydroxylase gene expression in PC12 cells. *J Neurochem*. 2000;75(5):1997–2005
29. Wei C, Han X, Weng D, et al. Response dynamics of midbrain dopamine neurons and serotonin neurons to heroin, nicotine, cocaine, and MDMA. *Cell Discov*. 2018;4:60
30. DiFranza JR. A 2015 update on the natural history and diagnosis of nicotine addiction. *Curr Pediatr Rev*. 2015;11(1):43–55
31. Benowitz NL. Nicotine addiction. *N Engl J Med*. 2010;362(24):2295–2303
32. Kishioka S, Kiguchi N, Kobayashi Y, Saika F. Nicotine effects and the endogenous opioid system. *J Pharmacol Sci*. 2014; 125(2):117–124
33. Benowitz NL, Hukkanen J, Jacob P III. Nicotine chemistry, metabolism, kinetics and biomarkers. *Handb Exp Pharmacol*. 2009;(192):29–60
34. Liakoni E, Edwards KC, St Helen G, et al. Effects of nicotine metabolic rate on withdrawal symptoms and response to

cigarette smoking after abstinence. *Clin Pharmacol Ther*. 2019;105(3):641–651

35. Claw KG, Beans JA, Lee SB, et al. Pharmacogenomics of nicotine metabolism: novel CYP2A6 and CYP2B6 genetic variation patterns in Alaska Native and American Indian populations [published online ahead of print June 25, 2019]. *Nicotine Tob Res*. 2019. doi: 10.1093/ntr/ntz105
36. López-Flores LA, Pérez-Rubio G, Falfán-Valencia R. Distribution of polymorphic variants of CYP2A6 and their involvement in nicotine addiction. *EXCLI J*. 2017;16:174–196
37. Dempsey D, Jacob P III, Benowitz NL. Nicotine metabolism and elimination kinetics in newborns. *Clin Pharmacol Ther*. 2000;67(5):458–465
38. Abdel Magid HS, Bradshaw PT, Ling PM, Halpern-Felsher B. Association of alternative tobacco product initiation with ownership of tobacco promotional materials among adolescents and young adults. *JAMA Netw Open*. 2019; 2(5):e194006
39. Pérez-Rubio G, López-Flores LA, Ramírez-Venegas A, et al. Genetic polymorphisms in CYP2A6 are associated with a risk of cigarette smoking and predispose to smoking at younger ages. *Gene*. 2017;628:205–210
40. Rubinstein ML, Benowitz NL, Auerback GM, Moscicki AB. Rate of nicotine metabolism and withdrawal symptoms in adolescent light smokers. *Pediatrics*. 2008;122(3). Available at: www.pediatrics.org/cgi/content/full/122/3/e643
41. Digard H, Proctor C, Kulasekaran A, Malmqvist U, Richter A. Determination of nicotine absorption from multiple tobacco products and nicotine gum. *Nicotine Tob Res*. 2013;15(1):255–261
42. Lopez AA, Hiler MM, Soule EK, et al. Effects of electronic cigarette liquid nicotine concentration on plasma nicotine and puff topography in tobacco cigarette smokers: a preliminary report. *Nicotine Tob Res*. 2016;18(5): 720–723
43. Dawkins LE, Kimber CF, Doig M, Feyerabend C, Corcoran O. Self-titration by experienced e-cigarette users: blood nicotine delivery and subjective effects. *Psychopharmacology (Berl)*. 2016; 233(15–16):2933–2941
44. Yang BC, Wang F, Yang X, et al. Medical swab touch spray-mass spectrometry for newborn screening of nicotine and cotinine in meconium. *J Mass Spectrom*. 2016;51(12):1237–1242
45. Spector LG, Murphy SE, Wickham KM, Lindgren B, Joseph AM. Prenatal tobacco exposure and cotinine in newborn dried blood spots. *Pediatrics*. 2014;133(6). Available at: www.pediatrics.org/cgi/content/full/133/6/e1632
46. Perry MF, Mulcahy H, DeFranco EA. Influence of periconception smoking behavior on birth defect risk. *Am J Obstet Gynecol*. 2019;220(6):588.e1-588.e7
47. Rodgman A, Smith CJ, Perfetti TA. The composition of cigarette smoke: a retrospective, with emphasis on polycyclic components. *Hum Exp Toxicol*. 2000;19(10):573–595
48. Faber T, Kumar A, Mackenbach JP, et al. Effect of tobacco control policies on perinatal and child health: a systematic review and meta-analysis. *Lancet Public Health*. 2017;2(9):e420–e437
49. Vanker A, Gie RP, Zar HJ. The association between environmental tobacco smoke exposure and childhood respiratory disease: a review. *Expert Rev Respir Med*. 2017;11(8):661–673
50. Cohen G, Roux JC, Grailhe R, Malcolm G, Changeux JP, Lagercrantz H. Perinatal exposure to nicotine causes deficits associated with a loss of nicotinic receptor function. *Proc Natl Acad Sci U S A*. 2005;102(10):3817–3821
51. Shao XM, López-Valdés HE, Liang J, Feldman JL. Inhaled nicotine equivalent to cigarette smoking disrupts systemic and uterine hemodynamics and induces cardiac arrhythmia in pregnant rats. *Sci Rep*. 2017;7(1):16974
52. Whittington JR, Simmons PM, Phillips AM, et al. The use of electronic cigarettes in pregnancy: a review of the literature. *Obstet Gynecol Surv*. 2018; 73(9):544–549
53. Dhalwani NN, Szatkowski L, Coleman T, Fiaschi L, Tata LJ. Nicotine replacement therapy in pregnancy and major congenital anomalies in offspring. *Pediatrics*. 2015;135(5):859–867
54. Cnattingius S. The epidemiology of smoking during pregnancy: smoking prevalence, maternal characteristics, and pregnancy outcomes. *Nicotine Tob Res*. 2004;6(suppl 2):S125–S140
55. Meyer KA, Williams P, Hernandez-Diaz S, Cnattingius S. Smoking and the risk of oral clefts: exploring the impact of study designs. *Epidemiology*. 2004;15(6): 671–678
56. Khoury MJ, Gomez-Farias M, Mulinare J. Does maternal cigarette smoking during pregnancy cause cleft lip and palate in offspring? *Am J Dis Child*. 1989;143(3):333–337
57. Ozturk F, Sheldon E, Sharma J, Canturk KM, Otu HH, Nawshad A. Nicotine exposure during pregnancy results in persistent midline epithelial seam with improper palatal fusion. *Nicotine Tob Res*. 2016;18(5):604–612
58. Gunnerbeck A, Edstedt Bonamy AK, Wikström AK, Granath F, Wickström R, Cnattingius S. Maternal snuff use and smoking and the risk of oral cleft malformations–a population-based cohort study. *PLoS One*. 2014;9(1): e84715
59. Kyrklund-Blomberg NB, Granath F, Cnattingius S. Maternal smoking and causes of very preterm birth. *Acta Obstet Gynecol Scand*. 2005;84(6): 572–577
60. Dahlin S, Gunnerbeck A, Wikström AK, Cnattingius S, Edstedt Bonamy AK. Maternal tobacco use and extremely premature birth - a population-based cohort study. *BJOG*. 2016;123(12): 1938–1946
61. Paulson R, Shanfeld J, Sachs L, Price T, Paulson J. Effect of smokeless tobacco on the development of the CD-1 mouse fetus. *Teratology*. 1989;40(5):483–494
62. Wikström AK, Cnattingius S, Stephansson O. Maternal use of Swedish snuff (snus) and risk of stillbirth. *Epidemiology*. 2010;21(6): 772–778
63. Baba S, Wikstrom AK, Stephansson O, Cnattingius S. Influence of snuff and smoking habits in early pregnancy on risks for stillbirth and early neonatal mortality. *Nicotine Tob Res*. 2014;16(1): 78–83
64. Dhalwani NN, Szatkowski L, Coleman T, Fiaschi L, Tata LJ. Stillbirth among

women prescribed nicotine replacement therapy in pregnancy: analysis of a large UK pregnancy cohort. *Nicotine Tob Res*. 2019;21(4): 409–415

65. Bernstein IM, Mongeon JA, Badger GJ, Solomon L, Heil SH, Higgins ST. Maternal smoking and its association with birth weight. *Obstet Gynecol*. 2005;106(5, pt 1):986–991

66. Birnbaum SC, Kien N, Martucci RW, et al. Nicotine- or epinephrine-induced uteroplacental vasoconstriction and fetal growth in the rat. *Toxicology*. 1994; 94(1–3):69–80

67. Rowell PP, Clark MJ. The effect of chronic oral nicotine administration on fetal weight and placental amino acid accumulation in mice. *Toxicol Appl Pharmacol*. 1982;66(1):30–38

68. Baba S, Wikström AK, Stephansson O, Cnattingius S. Changes in snuff and smoking habits in Swedish pregnant women and risk for small for gestational age births. *BJOG*. 2013; 120(4):456–462

69. Anderson TM, Lavista Ferres JM, Ren SY, et al. Maternal smoking before and during pregnancy and the risk of sudden unexpected infant death. *Pediatrics*. 2019;143(4):e20183325

70. Mitchell EA, Ford RP, Stewart AW, et al. Smoking and the sudden infant death syndrome. *Pediatrics*. 1993;91(5): 893–896

71. Ton AT, Biet M, Delabre JF, Morin N, Dumaine R. In-utero exposure to nicotine alters the development of the rabbit cardiac conduction system and provides a potential mechanism for sudden infant death syndrome. *Arch Toxicol*. 2017;91(12):3947–3960

72. Slotkin TA, Lappi SE, McCook EC, Lorber BA, Seidler FJ. Loss of neonatal hypoxia tolerance after prenatal nicotine exposure: implications for sudden infant death syndrome. *Brain Res Bull*. 1995;38(1):69–75

73. Duncan JR, Garland M, Myers MM, et al. Prenatal nicotine-exposure alters fetal autonomic activity and medullary neurotransmitter receptors: implications for sudden infant death syndrome. *J Appl Physiol (1985)*. 2009; 107(5):1579–1590

74. Nordenstam F, Lundell B, Cohen G, Tessma MK, Raaschou P, Wickstrom R. Prenatal exposure to snus alters heart rate variability in the infant. *Nicotine Tob Res*. 2017;19(7):797–803

75. Smith D, Aherrera A, Lopez A, et al. Adult behavior in male mice exposed to e-cigarette nicotine vapors during late prenatal and early postnatal life. *PLoS One*. 2015;10(9):e0137953

76. Santiago SE, Huffman KJ. Prenatal nicotine exposure increases anxiety and modifies sensorimotor integration behaviors in adult female mice. *Neurosci Res*. 2014;79:41–51

77. Zhang L, Spencer TJ, Biederman J, Bhide PG. Attention and working memory deficits in a perinatal nicotine exposure mouse model. *PLoS One*. 2018; 13(5):e0198064

78. Goriounova NA, Mansvelder HD. Short- and long-term consequences of nicotine exposure during adolescence for prefrontal cortex neuronal network function. *Cold Spring Harb Perspect Med*. 2012;2(12):a012120

79. Meyer HC, Chodakewitz MI, Bucci DJ. Nicotine administration enhances negative occasion setting in adolescent rats. *Behav Brain Res*. 2016;302:69–72

80. Rose-Jacobs R, Richardson MA, Buchanan-Howland K, et al. Intrauterine exposure to tobacco and executive functioning in high school. *Drug Alcohol Depend*. 2017;176:169–175

81. Fried PA, Watkinson B, Gray R. Differential effects on cognitive functioning in 13- to 16-year-olds prenatally exposed to cigarettes and marihuana. *Neurotoxicol Teratol*. 2003; 25(4):427–436

82. Tiesler CM, Heinrich J. Prenatal nicotine exposure and child behavioural problems. *Eur Child Adolesc Psychiatry*. 2014;23(10):913–929

83. Dong T, Hu W, Zhou X, et al. Prenatal exposure to maternal smoking during pregnancy and attention-deficit/ hyperactivity disorder in offspring: a meta-analysis. *Reprod Toxicol*. 2018; 76:63–70

84. Ekblad M, Gissler M, Lehtonen L, Korkeila J. Prenatal smoking exposure and the risk of psychiatric morbidity into young adulthood. *Arch Gen Psychiatry*. 2010;67(8):841–849

85. Holliday E, Gould TJ. Nicotine, adolescence, and stress: a review of how stress can modulate the negative consequences of adolescent nicotine abuse. *Neurosci Biobehav Rev*. 2016;65: 173–184

86. Kinnunen JM, Ollila H, Minkkinen J, Lindfors PL, Timberlake DS, Rimpelä AH. Nicotine matters in predicting subsequent smoking after e-cigarette experimentation: a longitudinal study among Finnish adolescents. *Drug Alcohol Depend*. 2019;201:182–187

87. Krishnan-Sarin S, Jackson A, Morean M, et al. E-cigarette devices used by high-school youth. *Drug Alcohol Depend*. 2019;194:395–400

88. Vogel EA, Prochaska JJ, Rubinstein ML. Measuring e-cigarette addiction among adolescents [published online ahead of print May 11, 2019]. *Tob Control*. 2019. doi:10.1136/tobaccocontrol-2018-054900

89. Morean ME, Krishnan-Sarin S, S O'Malley S. Assessing nicotine dependence in adolescent e-cigarette users: the 4-item Patient-Reported Outcomes Measurement Information System (PROMIS) nicotine dependence item bank for electronic cigarettes. *Drug Alcohol Depend*. 2018;188:60–63

90. Leybovitz-Haleluya N, Wainstock T, Landau D, Sheiner E. Maternal smoking during pregnancy and the risk of pediatric cardiovascular diseases of the offspring: a population-based cohort study with up to 18-years of follow up. *Reprod Toxicol*. 2018;78:69–74

91. Chaumont M, de Becker B, Zaher W, et al. Differential effects of e-cigarette on microvascular endothelial function, arterial stiffness and oxidative stress: a randomized crossover trial. *Sci Rep*. 2018;8(1):10378

92. Franzen KF, Willig J, Cayo Talavera S, et al. E-cigarettes and cigarettes worsen peripheral and central hemodynamics as well as arterial stiffness: a randomized, double-blinded pilot study. *Vasc Med*. 2018;23(5): 419–425

93. Espinoza-Derout J, Hasan KM, Shao XM, et al. Chronic intermittent electronic cigarette exposure induces cardiac dysfunction and atherosclerosis in apolipoprotein-E knockout mice. *Am J Physiol Heart Circ Physiol*. 2019; 317(2):H445–H459

94. Wang Z, Liu B, Zhu J, Wang D, Wang Y. Nicotine-mediated autophagy of vascular smooth muscle cell accelerates atherosclerosis via nAChRs/ROS/NF-κB signaling pathway. *Atherosclerosis*. 2019;284:1–10

95. Yoshiyama S, Chen Z, Okagaki T, et al. Nicotine exposure alters human vascular smooth muscle cell phenotype from a contractile to a synthetic type. *Atherosclerosis*. 2014;237(2):464–470

96. Thurlbeck WM. Postnatal human lung growth. *Thorax*. 1982;37(8):564–571

97. Herring MJ, Putney LF, Wyatt G, Finkbeiner WE, Hyde DM. Growth of alveoli during postnatal development in humans based on stereological estimation. *Am J Physiol Lung Cell Mol Physiol*. 2014;307(4):L338–L344

98. Maritz GS. Perinatal exposure to nicotine and implications for subsequent obstructive lung disease. *Paediatr Respir Rev*. 2013;14(1):3–8

99. Zaken V, Kohen R, Ornoy A. Vitamins C and E improve rat embryonic antioxidant defense mechanism in diabetic culture medium. *Teratology*. 2001;64(1):33–44

100. Sekhon HS, Jia Y, Raab R, et al. Prenatal nicotine increases pulmonary alpha7 nicotinic receptor expression and alters fetal lung development in monkeys. *J Clin Invest*. 1999;103(5):637–647

101. Wongtrakool C, Wang N, Hyde DM, Roman J, Spindel ER. Prenatal nicotine exposure alters lung function and airway geometry through α7 nicotinic receptors. *Am J Respir Cell Mol Biol*. 2012;46(5):695–702

102. Proskocil BJ, Sekhon HS, Clark JA, et al. Vitamin C prevents the effects of prenatal nicotine on pulmonary function in newborn monkeys. *Am J Respir Crit Care Med*. 2005;171(9):1032–1039

103. Yildiz A, Vardi N, Karaaslan MG, Ates B, Taslidere E, Esrefoglu M. The protective effect of melatonin in lungs of newborn rats exposed to maternal nicotine. *Biotech Histochem*. 2018;93(6):442–452

104. Chao MR, Cooke MS, Kuo CY, et al. Children are particularly vulnerable to environmental tobacco smoke exposure: evidence from biomarkers of tobacco-specific nitrosamines, and oxidative stress. *Environ Int*. 2018;120:238–245

105. Moritsugu KP. The 2006 report of the Surgeon General: the health consequences of involuntary exposure to tobacco smoke. *Am J Prev Med*. 2007;32(6):542–543

106. McConnell R, Barrington-Trimis JL, Wang K, et al. Electronic cigarette use and respiratory symptoms in adolescents. *Am J Respir Crit Care Med*. 2017;195(8):1043–1049

107. Cho JH, Paik SY. Association between electronic cigarette use and asthma among high school students in South Korea. *PLoS One*. 2016;11(3):e0151022

108. Wang MP, Ho SY, Leung LT, Lam TH. Electronic cigarette use and respiratory symptoms in Chinese adolescents in Hong Kong. *JAMA Pediatr*. 2016;170(1):89–91

109. Choi K, Bernat D. E-cigarette use among Florida youth with and without asthma. *Am J Prev Med*. 2016;51(4):446–453

110. Chung S, Baumlin N, Dennis JS, et al. Electronic cigarette vapor with nicotine causes airway mucociliary dysfunction preferentially via TRPA1 receptors. *Am J Respir Crit Care Med*. 2019;200(9):1134–1145

111. Laube BL, Afshar-Mohajer N, Koehler K, et al. Acute and chronic in vivo effects of exposure to nicotine and propylene glycol from an e-cigarette on mucociliary clearance in a murine model. *Inhal Toxicol*. 2017;29(5):197–205

112. Rehan VK, Liu J, Naeem E, et al. Perinatal nicotine exposure induces asthma in second generation offspring. *BMC Med*. 2012;10:129

113. Klingbeil EC, Hew KM, Nygaard UC, Nadeau KC. Polycyclic aromatic hydrocarbons, tobacco smoke, and epigenetic remodeling in asthma. *Immunol Res*. 2014;58(2–3):369–373

114. Wilson KM, Wesgate SC, Pier J, et al. Secondhand smoke exposure and serum cytokine levels in healthy children. *Cytokine*. 2012;60(1):34–37

115. Tebow G, Sherrill DL, Lohman IC, et al. Effects of parental smoking on interferon gamma production in children. *Pediatrics*. 2008;121(6). Available at: www.pediatrics.org/cgi/content/full/121/6/e1563

116. le Roux DM, Nicol MP, Myer L, et al. Lower respiratory tract infections in children in a well-vaccinated South African birth cohort: spectrum of disease and risk factors. *Clin Infect Dis*. 2019;69(9):1588–1596

117. Snodgrass AM, Tan PT, Soh SE, et al; GUSTO Study Group. Tobacco smoke exposure and respiratory morbidity in young children. *Tob Control*. 2016;25(e2):e75–e82

118. DiFranza JR, Masaquel A, Barrett AM, Colosia AD, Mahadevia PJ. Systematic literature review assessing tobacco smoke exposure as a risk factor for serious respiratory syncytial virus disease among infants and young children. *BMC Pediatr*. 2012;12:81

119. Maśliński W. Cholinergic receptors of lymphocytes. *Brain Behav Immun*. 1989;3(1):1–14

120. Fuxe K, Andersson K, Eneroth P, Härfstrand A, Agnati LF. Neuroendocrine actions of nicotine and of exposure to cigarette smoke: medical implications. *Psychoneuroendocrinology*. 1989;14(1–2):19–41

121. Sussan TE, Gajghate S, Thimmulappa RK, et al. Exposure to electronic cigarettes impairs pulmonary anti-bacterial and anti-viral defenses in a mouse model. *PLoS One*. 2015;10(2):e0116861

122. Gomes JP, Watad A, Shoenfeld Y. Nicotine and autoimmunity: the lotus' flower in tobacco. *Pharmacol Res*. 2018;128:101–109

123. Hao J, Simard AR, Turner GH, et al. Attenuation of CNS inflammatory responses by nicotine involves α7 and non-α7 nicotinic receptors. *Exp Neurol*. 2011;227(1):110–119

124. Chen EY, Sun A, Chen CS, Mintz AJ, Chin WC. Nicotine alters mucin rheological properties. *Am J Physiol Lung Cell Mol Physiol*. 2014;307(2):L149–L157

125. Maouche K, Medjber K, Zahm JM, et al. Contribution of α7 nicotinic receptor to airway epithelium dysfunction under nicotine exposure. *Proc Natl Acad Sci U S A*. 2013;110(10):4099–4104

126. McConnell DD, Carr SB, Litofsky NS. Potential effects of nicotine on glioblastoma and chemoradiotherapy: a review. *Expert Rev Neurother*. 2019;19(6):545–555

127. Li H, Ma N, Wang J, et al. Nicotine induces progressive properties of lung adenocarcinoma A549 cells by inhibiting cystic fibrosis transmembrane conductance regulator (CFTR) expression and plasma membrane localization. *Technol Cancer Res Treat*. 2018;17:1533033818809984

128. Li T, Zhang J, Zhang J, et al. Nicotine-enhanced stemness and epithelial-mesenchymal transition of human umbilical cord mesenchymal stem cells promote tumor formation and growth in nude mice. *Oncotarget*. 2017;9(1): 591–606

129. Chen PC, Lee WY, Ling HH, Cheng CH, Chen KC, Lin CW. Activation of fibroblasts by nicotine promotes the epithelial-mesenchymal transition and motility of breast cancer cells. *J Cell Physiol*. 2018;233(6):4972–4980

130. Zhang C, Ding XP, Zhao QN, et al. Role of α7-nicotinic acetylcholine receptor in nicotine-induced invasion and epithelial-to-mesenchymal transition in human non-small cell lung cancer cells. *Oncotarget*. 2016;7(37):59199–59208

131. Alkam T, Nabeshima T. Molecular mechanisms for nicotine intoxication. *Neurochem Int*. 2019;125:117–126

132. Nicotine and health. *Drug Ther Bull*. 2014;52(7):78–81

133. Kamboj A, Spiller HA, Casavant MJ, Chounthirath T, Smith GA. Pediatric exposure to e-cigarettes, nicotine, and tobacco products in the United States. *Pediatrics*. 2016;137(6):e20160041

134. Chen BC, Bright SB, Trivedi AR, Valento M. Death following intentional ingestion of e-liquid. *Clin Toxicol (Phila)*. 2015; 53(9):914–916

135. Eggleston W, Nacca N, Stork CM, Marraffa JM. Pediatric death after unintentional exposure to liquid nicotine for an electronic cigarette. *Clin Toxicol (Phila)*. 2016;54(9):890–891

136. Seo AD, Kim DC, Yu HJ, Kang MJ. Accidental ingestion of e-cigarette liquid nicotine in a 15-month-old child: an infant mortality case of nicotine intoxication. *Korean J Pediatr*. 2016; 59(12):490–493

137. Govindarajan P, Spiller HA, Casavant MJ, Chounthirath T, Smith GA. E-cigarette and liquid nicotine exposures among young children. *Pediatrics*. 2018;141(5): e20173361

138. Miron O, Yu KH, Wilf-Miron R, Kohane IS. Suicide rates among adolescents and young adults in the United States, 2000-2017. *JAMA*. 2019;321(23):2362–2364

139. Riehm KE, Young AS, Feder KA, et al. Mental health problems and initiation of e-cigarette and combustible cigarette use. *Pediatrics*. 2019;144(1): e20182935

140. Lee Y, Lee KS. Association of depression and suicidality with electronic and conventional cigarette use in South Korean adolescents. *Subst Use Misuse*. 2019;54(6):934–943

141. Park EJ, Min YG. The emerging method of suicide by electronic cigarette liquid: a case report. *J Korean Med Sci*. 2018; 33(11):e52

142. Jalkanen V, Värelä V, Kalliomäki J. Case report: two severe cases of suicide attempts using nicotine containing e-cigarette liquid. *Duodecim*. 2016; 132(16):1480–1483

143. Fadus MC, Smith TT, Squeglia LM. The rise of e-cigarettes, pod mod devices, and JUUL among youth: factors influencing use, health implications, and downstream effects. *Drug Alcohol Depend*. 2019;201:85–93

144. Leavens ELS, Stevens EM, Brett EI, et al. JUUL electronic cigarette use patterns, other tobacco product use, and reasons for use among ever users: results from a convenience sample. *Addict Behav*. 2019;95:178–183

145. Hammond D, Wackowski OA, Reid JL, O'Connor RJ; International Tobacco Control Policy Evaluation Project (ITC) Team. Use of Juul e-cigarettes among youth in the United States [published online ahead of print October 27, 2018]. *Nicotine Tob Res*. 2018. doi:10.1093/ntr/nty237