Published in final edited form as:

Curr Opin Pediatr. 2017 April ; 29(2): 225–230. doi:10.1097/MOP.0000000000000456.

Tobacco, E-Cigarettes and Child Health

Lisa A. Peterson* and Stephen S. Hecht

Masonic Cancer Center, University of Minnesota, Minneapolis, MN 55455

Abstract

Purpose of the review—The availability of the Children’s Health Exposure Assessment Resource funded by the National Institute of Environmental Health Sciences provides new opportunities for exploring the role of tobacco smoke exposure in causing harm to children.

Findings—Children of smokers are exposed to nicotine and other harmful tobacco smoke chemicals in utero as well as in their environment. This passive exposure to tobacco smoke has a variety of negative effects on children. In utero exposure to tobacco smoke causes poor birth outcomes and influences lung, cardiovascular and brain development, placing children at increased risk of a number of adverse health outcomes later in life such as obesity, behavioral problems and cardiovascular disease. Furthermore, most smokers start in their adolescence, an age of increased nicotine addiction risk. Biomarkers of tobacco exposure helps clarify the role tobacco chemicals play in influencing health both in childhood and beyond. While e-cigarettes appear to be a nicotine delivery device of reduced harm, it appears to be a gateway to the use of combustible cigarette smoking in adolescents.

Summary—Pediatric researchers interested in elucidating the role of tobacco smoke exposure in adverse outcomes in children should incorporate biomarkers of tobacco exposure in their studies.

Keywords

children; tobacco smoke exposure; e-cigarettes; adverse health outcomes

Introduction

The negative health effects of tobacco use have been well documented since the first report of the U.S. Surgeon General, released in 1964 [1]. Over the ensuing 50 years, 31 U.S. Surgeon General’s reports described the damaging health consequences of tobacco use and involuntary exposure to tobacco smoke [2]. The 2014 Report, entitled “The Health Consequences of Smoking – 50 Years of Progress” summarizes the evidence linking cigarette smoking to more than 20 million premature deaths in the U.S. since 1964. Cigarette smoking causes diseases in nearly all organs of the body as well as diminished health status and harm to the fetus [2]. Since virtually all cigarette smoking begins before the age of 18 [2], the effects of tobacco use on children is clearly of utmost importance. Furthermore,

*To whom correspondence should be addressed: Lisa A. Peterson, PhD., Masonic Cancer Center, University of Minnesota, 2231 6th Street SE - 2-126 CCRB, Minneapolis, MN 55455, USA. phone: (612) 626-0164; fax: (612) 624-3869; peter431@umn.edu.

Conflicts of interest

The authors declare no conflicts of interest.

mother's smoking during pregnancy and secondhand cigarette smoke exposure are still important issues in children's health.

Biomarkers of exposure have been critical in validating and quantifying exposure of the fetus, newborns, and children to tobacco smoke toxicant and carcinogens. The most important biomarkers in this regard are tobacco-specific compounds: nicotine and its metabolites and the lung carcinogen metabolite 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) [3–10].

In this review, we highlight some of the most important research articles dealing with the effects of tobacco smoke, environmental tobacco smoke, and e-cigarettes on adverse health outcomes in children.

Exposure Scenarios

Mother's use of tobacco products during pregnancy and lactation

Smoking during pregnancy is relatively common in the United States, where an estimated 12.8% of women smoked during the last 3 months of pregnancy [11]. It is still an important cause of maternal, fetal, and infant morbidity and mortality [2]. One recent review concluded that any active maternal smoking was associated with increased risks of stillbirth, neonatal death, and perinatal death, and these increased with the amount smoked by the mother [12].

Ip *et al* examined the relationship between prenatal tobacco exposure and telomere length in children [13*]. Telomeres are the regions of repetitive nucleotide sequences at each end of a chromosome; they protect the chromosome end from deterioration or fusion with neighboring chromosomes. Telomere shortening is associated with a number of adverse health outcomes including cancer, type 2 diabetes, cardiovascular diseases, Alzheimer's disease, and early mortality [13*]. Cigarette smoking is an established cause of telomere shortening [14]. The study by Ip *et al* involved 98 randomly selected nonsmoking children from the Hong Kong Child Health Study whose mother smoked during pregnancy compared to 98 age- and gender-matched children randomly selected from all nonsmoking children in the Hong Kong Child Health Study whose mothers never smoked during pregnancy. Information on the length and extent of mother's smoking during pregnancy was obtained. Telomere length was measured in buccal epithelial cells of the children. The results demonstrated that telomere length in children with prenatal tobacco exposure was significantly shorter than in those with no exposure (T/S ratio = 24.9 ± 8.58 in exposed vs. 28.97 ± 14.15 in controls, $P = 0.02$). A dose response relationship was observed whereby longer duration of smoking during pregnancy was associated with shorter telomere length. The relationship between telomere length in the children and prenatal tobacco exposure was still significant after taking into account family socioeconomic status and exposure to secondhand tobacco smoke during pregnancy and childhood. Thus, this study demonstrated telomere shortening due to prenatal tobacco smoke exposure, which could have important negative health consequences on the children of women who smoked during pregnancy. Furthermore, telomere length can be considered as a potential biomarker of biological effects.

Secondhand smoke exposure

Secondhand tobacco smoke exposure is an established cause of a number of negative health effects in children including asthma, cough, phlegm, wheeze, breathlessness, lower respiratory illnesses, lung function, middle ear disease, nasal irritation, and sudden infant death syndrome [2].

Agaku *et al*/have determined the prevalence and determinants of secondhand smoke exposure among middle and high school students (grades 6 – 12, United States) in homes and vehicles, and at school, work, and indoor/outdoor public areas [15**]. Their study depended on self-reported secondhand smoke exposure within the past 7 days, taken from the 2013 National Youth Tobacco Survey of 18,406 youths. The results demonstrated that 48.0% of never tobacco users reported exposure to secondhand smoke in one or more locations: 15.5% in the home; 14.7% in a vehicle; 16.8% at school; 27.1% at work, and 35.2% in indoor or outdoor public areas. They concluded that about half of United States students in grades 6 through 12 were exposed to secondhand smoke in 2013. Exposure in the home or vehicle was more than 9 times higher among those with no smoke-free rules than those with smoke-free rules. Thus, secondhand smoke exposure is still a significant problem, which can potentially be ameliorated by voluntary smoke-free rules. As noted above, nicotine metabolites and NNAL are excellent biomarkers for distinguishing active from passive smoking [6].

Use of tobacco products by children

It is estimated that, at current smoking rates, 5.6 million United States residents who are less than 18 years old will die prematurely from smoking-related disease. CDC and FDA determined the prevalence of tobacco use in the past 30 days, including the following tobacco types: cigarettes, cigars, smokeless tobacco, e-cigarettes, hookahs, pipe tobacco, and bidis among students in grades 6–8 and 9–12. During 2011–2015, the use of e-cigarettes and hookahs increased significantly, whereas use of conventional products decreased resulting in null overall change in tobacco product use. Overall, in 2015, there were an estimated 4.7 million middle and high school students who were current tobacco product users [16*]. Biomarkers are useful in distinguishing active smokers from passively exposed individuals, as the levels of nicotine metabolites will be significantly different. Biomarkers will also distinguish smokers from smokeless tobacco users because, while both have high concentrations of nicotine metabolites in their urine, only smokers will have high levels of biomarkers derived from volatiles such as acrolein, crotonaldehyde, and benzene [17].

Adverse Health Outcomes

Fetal growth and birth outcomes

It has long been recognized that smoking during pregnancy negatively impacts fetal growth and results in pre-term deliveries [1]. While studies indicate that smoking dose (active versus passive smoking) affects the extent to which fetal growth is restricted, studies in smokeless tobacco users suggest that nicotine makes a modest contribution to this effect and that combustion products enhance this effect [2]. Smokeless tobacco users are at increased risk of preterm delivery providing a role for nicotine in this adverse outcome. Investigations into

gene-environment interactions demonstrate that other tobacco chemicals may play a role in these negative birth outcomes; CYP1A1 variants and GSTT1 null genotypes are associated with more extreme effects on birth weight and preterm delivery [18–21]; variants of nicotine metabolism did not have any significant effect [18]. This is a situation where biomarkers studies might provide insight into the tobacco smoke chemicals that are contributing to the adverse birth outcomes. For example, GSTT1 null genotype influences the levels of urinary benzene and 1,3-butadiene metabolites in smokers [22,23]. CYP1A1 and GSTT1 variants affect metabolite levels of a model polycyclic aromatic hydrocarbon, phenanthrene [24,25].

Sudden infant death syndrome (SIDS)

Roughly a quarter of SIDS deaths in 2009 were due to prenatal smoke exposure [26]. Epidemiology studies indicate the risk of SIDS associated with bed sharing was elevated for babies whose mothers smoked than for those whose mothers did not (combined OR = 6.3 versus associated OR = 1.7) [27*]. Prenatal exposure to nicotine or other tobacco chemicals likely results in dysfunctional and/or immature organs and/or arousal systems. While support for this proposal exists in animal models, data in humans are more limited [2].

Brain development and neurobehavioral disorders

Tobacco smoke alters brain development; many of these effects are associated with nicotine exposure. In the developing fetus, nicotine targets nicotinic acetylcholine receptors [2]. A number of epidemiological studies shown an association between intrauterine tobacco smoke exposure and an elevated risk of attention-deficit/hyperactivity disorder (ADHD) [2]. There is controversy as to whether these effects result from prenatal nicotine exposure or are related to other confounding factors that affect parental nicotine dependence [2,28*]. A study in a Danish population determined that maternal prenatal smoking or use of nicotine replacement therapy was more strongly associated to an increased risk of ADHD in children than paternal tobacco use [29*]. A recent study in overweight and obese children found an association between plasma cotinine levels and poorer cognitive scores [30**], suggesting that environmental tobacco smoke exposure during childhood can impact brain development.

Adolescence is another time when the brain is undergoing a wide variety of changes. The adolescent brain is more sensitive to the pharmacological properties of nicotine, causing teenagers to develop nicotine dependence more easily than adults [31]. Studies in laboratory animals along with limited data from adolescent and young adult smokers provide evidence that nicotine exposure during adolescence negatively impacts brain development, leading to impaired cognition and behavior issues [2]. Numerous reports indicate that adolescent smokers have an elevated risk of developing cognitive impairment and psychiatric disorders later in life [31].

Obesity and related effects

Prenatal exposure to tobacco smoke is a likely risk factor for childhood and adolescent obesity [32*]. Animal studies support a role for nicotine in this adverse health outcome [32*]. A study in adolescents demonstrated a link between intrauterine tobacco smoke exposure, increased adiposity, a smaller amygdala and increased fat intake [33**]. The individuals with the smaller amygdalas were also more likely to consume alcohol and

experiment with drugs. These data suggest that prenatal exposure to tobacco smoke may stimulate an increased preference for fat consumption and that changes in the amygdala may facilitate this outcome. Additionally, intrauterine exposure to cigarette smoke may affect the activity of the opioid receptor mu-1 through an epigenetic mechanism. Methylation of this gene is associated with increased fat consumption in prenatally exposed adolescents [34**].

Cardiovascular health

While cigarette smoking is well-established as a cause of cardiovascular disease in adults [2], the impact of childhood exposure to environmental tobacco smoke is more difficult to assess. The evidence for the negative impact of childhood tobacco smoke exposure on cardiovascular health has been summarized in a scientific statement from the American Heart Association [35**]. A study in a Finnish population demonstrates how biomarkers of tobacco smoke exposure, specifically cotinine, are valuable tools in providing strong evidence of linkage between childhood exposure to tobacco smoke and increased risk of cardiovascular disease [36**]. Use of serum cotinine levels instead of parental self-report of smoking increased the relative risk of developing carotid plaques in adulthood from 1.7 to 4.0. The reason for the difference is that some of the parents protected their children from tobacco smoke exposure as demonstrated by negligible urinary cotinine levels in these children. Tobacco smoke chemicals proposed to be responsible for the adverse cardiovascular effects of environmental tobacco smoke include nicotine, acrolein, crotonaldehyde, cadmium, lead and particulate matter [35**].

Respiratory health

Prenatal and postnatal exposure to tobacco smoke results in disrupted lung development, resulting in reduced lung function in children [37*]. Epidemiological studies indicate an inverse dose response relationship between the number of cigarettes smoked/day by the mother and a variety of measures of lung functionality in newborns [38]. Studies in men with previous prenatal exposure to tobacco smoke demonstrated that the impact on lung function continues into adulthood [39]. Prenatal and childhood exposure to tobacco smoke also increases the incidence of wheezing, asthma and the susceptibility to lower respiratory tract infections in children [40].

Nicotine is thought to play a role in the adverse effects of tobacco smoke on lung development [37*]. Furthermore, there is some evidence that prenatal tobacco smoke exposure alters the immune profile of children, causing them to be more susceptible to infections [37*]. Genetic variations in GST proteins modify the adverse effects of in utero exposure to tobacco smoke on respiratory health, indicating that other tobacco smoke chemicals may also contribute to this adverse outcome. Tobacco smoke exposed GSTM1 and GSTT1 null children are at increased risk of wheezing and/or asthma as compared to similarly exposed children with the functional gene [41,42].

Cancer

A major health effect of long term tobacco use is cancer in many organ sites including lung, mouth, throat, esophagus, larynx, kidney, bladder, liver, colon, rectum, cervix and acute myeloid leukemia [2,38,43]. Epidemiological data suggest that prenatal and postnatal

exposure to tobacco smoke increases the risk of childhood leukemia and lymphomas as well as brain tumors [40].

e-Cigarettes and Children

What are e-cigarettes?

An e-cigarette consists of several components: a battery, a microprocessor, an activating button, a heating element, and a reservoir which contains a mixture of propylene glycol, nicotine, and flavorants. Sometimes there are other additives and glycerol in the reservoir as well. More than 7,000 flavorants are being used and, as of this writing, are totally unregulated. When the user puffs, an air flow sensor causes electricity to flow through the heating element, which results in the production of an aerosol of the e-liquid. The aerosol resembles cigarette smoke to some extent and is inhaled. There are multiple e-cigarette designs, most of which no longer resemble cigarettes but rather are “tank systems” which have relatively large reservoirs. Users of e-cigarettes can adjust the voltage to modify the amount of nicotine in each puff [44].

Known health effects and impact on teen smoking behavior

In contrast to tobacco cigarettes, e-cigarettes contain no tobacco and there is no combustion of its constituents. Thus, the “smoke” of an e-cigarette has considerably lower amounts of virtually all toxicants and carcinogens than tobacco cigarette smoke, which contains over 7000 constituents and at least 72 carcinogens [45,46]. The exception to this is nicotine, which is delivered in comparable quantities to smokers of e-cigarettes and tobacco cigarettes. The e-cigarette user is also exposed to considerable amounts of propylene glycol and relatively small quantities of a vast variety of flavorants. There may be relatively high levels of exposure to formaldehyde under certain conditions of e-cigarette use [47]. There are no clinical studies on the relationship of e-cigarette use to disease because e-cigarettes have not been used for a long enough period of time. However, urinary biomarker studies indicate that the profile of toxicants and carcinogen metabolites in e-cigarette users is far more favorable than in cigarette smokers [48].

One concern regarding e-cigarettes is nicotine poisoning. Thus, Kamboj *et al* carried out an analysis of exposures associated with nicotine and tobacco products among children less than 6 years of age [49*]. From 2012–2015, the National Poison Data System received more than 29,000 calls for nicotine and tobacco product exposures among children. Cigarettes accounted for 60.1% of exposures and e-cigarettes 14.2%. Children less than 2 years old accounted for 44.1% of e-cigarette exposures. They concluded that the frequency of exposures to e-cigarettes and nicotine liquid among young children is rapidly increasing and needs to be prevented.

Another concern about e-cigarettes is that they may be a gateway to tobacco product use. A review of the longitudinal effects of e-cigarette use on onset of smoking among adolescents and young adults concluded that e-cigarette use does lead to a higher incidence of combustible cigarette smoking [50].

Role of flavorants

In contrast to the use of flavor compounds in human food, there is currently no organized toxicological investigation of flavor compounds in e-cigarettes. This is a massively complex area which is begging for regulation. One recent study among English children aged 11–16 years addressed the concerns regarding the appeal of e-cigarettes [51]. It concluded that exposure to advertisements for e-cigarettes does not increase the appeal of tobacco smoking to children. However, e-cigarette advertisements featuring flavored, compared with non-flavored products, did elicit greater appeal and interest in buying and trying e-cigarettes.

Conclusions

Tobacco smoke is harmful to children. In utero as well as passive exposure to tobacco smoke leads to a host of adverse health effects in children both in childhood and later on in life. The use of biomarkers of tobacco exposure helps clarify the role tobacco chemicals play in influencing health both in childhood and beyond. While e-cigarettes appear to be a nicotine delivery device of reduced harm, they appear to be a gateway to combustible cigarette smoking in adolescents.

Acknowledgments

We would like to thank Bob Carlson for editorial assistance.

Financial support and sponsorship

The authors are Co-Principal Investigators of the Minnesota CHEAR Exposure Assessment Hub funded by a contract from the National Institute of Environmental Health Sciences (U2CES026533).

Reference List

1. United States Surgeon General. Smoking and Health: Report of the Advisory Committee to the Surgeon General of the Public Health Service. Washington, D.C: U.S. Department of Health, Education, and Welfare, Public Health Service; 1964. Public Health Service Publication No. 1103
2. U.S. Department of Health and Human Services. A Report of the Surgeon General. Atlanta, GA: U.S. Dept. of Health and Human Services, Centers for Disease Control and Prevention, Coordinating Center for Health Promotion, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2014. The Health Consequences of Smoking: 50 Years of Progress.
3. Llaquet H, Pichini S, Joya X, et al. Biological matrices for the evaluation of exposure to environmental tobacco smoke during prenatal life and childhood. *Anal Bioanal Chem.* 2010; 396:379–99. [PubMed: 19466395]
4. Spector LG, Murphy SE, Wickham KM, et al. Prenatal tobacco exposure and cotinine in newborn dried blood spots. *Pediatrics.* 2014; 133:e1632–e1638. [PubMed: 24819573]
5. Murphy SE, Wickham KM, Lindgren BR, et al. Cotinine and trans 3'-hydroxycotinine in dried blood spots as biomarkers of tobacco exposure and nicotine metabolism. *J Expo Sci Environ Epidemiol.* 2013; 23:513–18. [PubMed: 23443235]
6. Vogel RI, Carmella SG, Stepanov I, et al. The ratio of a urinary tobacco-specific lung carcinogen metabolite to cotinine is significantly higher in passive than in active smokers. *Biomarkers.* 2011; 16:491–97. [PubMed: 21812592]
7. Milunsky A, Carmella SG, Ye M, et al. A tobacco-specific carcinogen in the fetus. *Prenat Diagn.* 2000; 20:307–10. [PubMed: 10740203]

8. Hecht SS, Ye M, Carmella SG, et al. Metabolites of a tobacco-specific lung carcinogen in the urine of elementary school-aged children. *Cancer Epidemiol Biomarkers Prev.* 2001; 10:1109–16. [PubMed: 11700257]
9. Hecht SS, Carmella SG, Le K, et al. 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanol and its glucuronides in the urine of infants exposed to environmental tobacco smoke. *Cancer Epidemiol Biomarkers Prev.* 2006; 15:988–92. [PubMed: 16702381]
10. Lackmann GM, Salzberger U, Tollner U, et al. Metabolites of a tobacco-specific carcinogen in the urine of newborns. *J Natl Cancer Inst.* 1999; 91:459–65. [PubMed: 10070946]
11. CDC. PRAMS and Smoking Data Tables. Division of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion; <http://www.cdc.gov/prams/data-tobaccotables.htm> [accessed 10-19-2016]
12. Pineles BL, Hsu S, Park E, et al. Systematic review and meta-analyses of perinatal death and maternal exposure to tobacco smoke during pregnancy. *Am J Epidemiol.* 2016; 184:87–97. [PubMed: 27370789]
- *13. Ip P, Chung BH, Ho FK, et al. Prenatal tobacco exposure shortens telomere length in children. *Nicotine Tob Res.* 2016 pii: ntw139. [Epub ahead of print] The results demonstrated that telomere length in children with prenatal tobacco exposure was significantly shorter than in those with no exposure. A dose response relationship was observed whereby longer duration of smoking during pregnancy was associated with shorter telomere length. Telomere shortening is associated with a number of adverse health outcomes including cancer, type 2 diabetes, cardiovascular diseases, Alzheimer's disease, and early mortality.
14. Valdes AM, Andrew T, Gardner JP, et al. Obesity, cigarette smoking, and telomere length in women. *Lancet.* 2005; 366:662–64. [PubMed: 16112303]
- **15. Agaku IT, Singh T, Rolle I, et al. Prevalence and determinants of secondhand smoke exposure among middle and high school students. *Pediatrics.* 2016; 137:e20151985. This study demonstrated that about half of United States students in grades 6 through 12 were exposed to secondhand smoke in 2013. Exposure in the home or vehicle was more than 9 times higher among those with no smoke-free rules than those with smoke-free rules. [PubMed: 26755696]
- *16. Singh T, Arrazola RA, Corey CG, et al. Tobacco use among middle and high school students--United States, 2011–2015. *MMWR Morb Mortal Wkly Rep.* 2016; 65:361–67. This study determined the prevalence of tobacco use in the past 30 days, among students in grades 6–8 and 9–12. During 2011–2015, the use of e-cigarettes and hookahs increased significantly, whereas use of conventional products decreased. Overall, in 2015, there were an estimated 4.7 million middle and high school students who were current tobacco product users. [PubMed: 27077789]
17. Carmella SG, Chen M, Han S, et al. Effects of smoking cessation on eight urinary tobacco carcinogen and toxicant biomarkers. *Chem Res Toxicol.* 2009; 22:734–41. [PubMed: 19317515]
18. Aagaard-Tillery K, Spong CY, Thom E, et al. Pharmacogenomics of maternal tobacco use: metabolic gene polymorphisms and risk of adverse pregnancy outcomes. *Obstet Gynecol.* 2010; 115:568–77. [PubMed: 20177288]
19. Wang X, Zuckerman B, Pearson C, et al. Maternal cigarette smoking, metabolic gene polymorphism, and infant birth weight. *JAMA.* 2002; 287:195–202. [PubMed: 11779261]
20. Nukui T, Day RD, Sims CS, et al. Maternal/newborn GSTT1 null genotype contributes to risk of preterm, low birthweight infants. *Pharmacogenetics.* 2004; 14:569–76. [PubMed: 15475730]
21. Grazuleviciene R, Danileviciute A, Nadisauskiene R, et al. Maternal smoking, GSTM1 and GSTT1 polymorphism and susceptibility to adverse pregnancy outcomes. *Int J Environ Res Public Health.* 2009; 6:1282–97. [PubMed: 19440446]
22. Haiman CA, Patel YM, Stram DO, et al. Benzene Uptake and Glutathione S-transferase T1 Status as Determinants of S-Phenylmercapturic Acid in Cigarette Smokers in the Multiethnic Cohort. *PLoS One.* 2016; 11:e0150641. [PubMed: 26959369]
23. Park SL, Kotapati S, Wilkens LR, et al. 1,3-Butadiene exposure and metabolism among Japanese American, Native Hawaiian, and White smokers. *Cancer Epidemiol Biomarkers Prev.* 2014; 23:2240–49. [PubMed: 25368399]

24. Hecht SS, Carmella SG, Yoder A, et al. Comparison of polymorphisms in genes involved in polycyclic aromatic hydrocarbon metabolism with urinary phenanthrene metabolite ratios in smokers. *Cancer Epidemiol Biomarkers Prev.* 2006; 15:1805–11. [PubMed: 17035385]
25. Patel YM, Park SL, Carmella SG, et al. Metabolites of the Polycyclic Aromatic Hydrocarbon Phenanthrene in the Urine of Cigarette Smokers from Five Ethnic Groups with Differing Risks for Lung Cancer. *PLoS One.* 2016; 11:e0156203. [PubMed: 27275760]
26. Dietz PM, England LJ, Shapiro-Mendoza CK, et al. Infant morbidity and mortality attributable to prenatal smoking in the U. S. *Am J Prev Med.* 2010; 39:45–52. [PubMed: 20547278]
- *27. Vennemann MM, Hense HW, Bajanowski T, et al. Bed sharing and the risk of sudden infant death syndrome: can we resolve the debate? *J Pediatr.* 2012; 160:44–48. This study demonstrated that the risk of SIDS associated with bed sharing was elevated for babies whose mothers smoked than for those whose mothers did not. [PubMed: 21868032]
- *28. Kuja-Halkola R, D’Onofrio BM, Larsson H, et al. Maternal smoking during pregnancy and adverse outcomes in offspring: genetic and environmental sources of covariance. *Behav Genet.* 2014; 44:456–67. This article reviews the controversy as to whether the elevated risk of ADHD in prenatally exposed children is due to effects of tobacco smoke constituents on brain development or is related to other confounding factors. [PubMed: 25117564]
- *29. Zhu JL, Olsen J, Liew Z, et al. Parental smoking during pregnancy and ADHD in children: the Danish national birth cohort. *Pediatrics.* 2014; 134:e382–e388. This study in a Danish population determined that maternal prenatal smoking or use of nicotine replacement therapy was more strongly associated to an increased risk of ADHD in children than paternal tobacco use. [PubMed: 25049343]
- **30. Davis CL, Tingen MS, Jia J, et al. Passive Smoke Exposure and Its Effects on Cognition, Sleep, and Health Outcomes in Overweight and Obese Children. *Child Obes.* 2016; 12:119–25. This study in overweight and obese children found an association between plasma cotinine levels and poorer cognitive scores, suggesting that environmental tobacco smoke exposure during childhood can impact brain development. [PubMed: 26812049]
31. 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:a012120. [PubMed: 22983224]
- *32. Behl M, Rao D, Aagaard K, et al. Evaluation of the association between maternal smoking, childhood obesity, and metabolic disorders: a national toxicology program workshop review. *Environ Health Perspect.* 2013; 121:170–80. This report reviews the evidence linking maternal smoking with childhood obesity and metabolic disorders. [PubMed: 23232494]
- **33. Haghighi A, Schwartz DH, Abrahamowicz M, et al. Prenatal exposure to maternal cigarette smoking, amygdala volume, and fat intake in adolescence. *JAMA Psychiatry.* 2013; 70:98–105. This study in adolescents demonstrated a link between intrauterine tobacco smoke exposure, increased adiposity, a smaller amygdala and increased fat intake. [PubMed: 22945562]
- **34. Lee KW, Abrahamowicz M, Leonard GT, et al. Prenatal exposure to cigarette smoke interacts with OPRM1 to modulate dietary preference for fat. *J Psychiatry Neurosci.* 2015; 40:38–45. This study demonstrates that methylation of the opioid receptor mu-1 gene is associated with increased fat consumption in prenatally exposed adolescents. [PubMed: 25266401]
- **35. Raghuvver G, White DA, Hayman LL, et al. Cardiovascular Consequences of Childhood Secondhand Tobacco Smoke Exposure: Prevailing Evidence, Burden, and Racial and Socioeconomic Disparities: A Scientific Statement From the American Heart Association. *Circulation.* 2016; 134:e336–e359. This article provides an extensive review of the evidence that childhood exposure to environmental tobacco smoke affects cardiovascular disease in childhood and beyond. [PubMed: 27619923]
- **36. West HW, Juonala M, Gall SL, et al. Exposure to parental smoking in childhood is associated with increased risk of carotid atherosclerotic plaque in adulthood: the Cardiovascular Risk in Young Finns Study. *Circulation.* 2015; 131:1239–46. This study in a Finnish population demonstrates how biomarkers of tobacco smoke exposure, specifically cotinine, are valuable tools in providing strong evidence of linkage between childhood exposure to tobacco smoke and increased risk of cardiovascular disease. [PubMed: 25802269]

- *37. Gibbs K, Collaco JM, McGrath-Morrow SA. Impact of Tobacco Smoke and Nicotine Exposure on Lung Development. *Chest*. 2016; 149:552–61. This article reviews the evidence that pre- and postnatal tobacco smoke and nicotine exposure influences lung development. [PubMed: 26502117]
38. U.S. Department of Health and Human Services. The Health Consequences of Smoking: A Report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2004.
39. Hayatbakhsh MR, Sadasivam S, Mamun AA, et al. Maternal smoking during and after pregnancy and lung function in early adulthood: a prospective study. *Thorax*. 2009; 64:810–14. [PubMed: 19525264]
40. U.S. Department of Health and Human Services. The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General. Atlanta, GA: U.S. Dept. of Health and Human Services, Centers for Disease Control and Prevention, Coordinating Center for Health Promotion, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2006.
41. Gilliland FD, Li YF, Dubeau L, et al. Effects of glutathione S-transferase M1, maternal smoking during pregnancy, and environmental tobacco smoke on asthma and wheezing in children. *Am J Respir Crit Care Med*. 2002; 166:457–63. [PubMed: 12186820]
42. Kabesch M, Hoefler C, Carr D, et al. Glutathione S transferase deficiency and passive smoking increase childhood asthma. *Thorax*. 2004; 59:569–73. [PubMed: 15223862]
43. United States Surgeon General. A Report of the Surgeon General. Rockville, MD: Dept. of Health and Human Services, Public Health Service, Office of Surgeon General; 2010. How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease.
44. Walton KM, Abrams DB, Bailey WC, et al. NIH electronic cigarette workshop: developing a research agenda. *Nicotine Tob Res*. 2015; 17:259–69. [PubMed: 25335949]
45. Rodgman, A., Perfetti, T. The Chemical Components of Tobacco and Tobacco Smoke. Boca Raton, FL: CRC Press; 2009. p. 1483-1784.
46. Hecht SS. Research opportunities related to establishing standards for tobacco products under the Family Smoking Prevention and Tobacco Control Act. *Nicotine Tob Res*. 2012; 14:18–28. [PubMed: 21324834]
47. Kosmider L, Sobczak A, Fik M, et al. Carbonyl compounds in electronic cigarette vapors-effects of nicotine solvent and battery output voltage. *Nicotine Tob Res*. 2014; 16:1319–26. [PubMed: 24832759]
48. Hecht SS, Carmella SG, Kotandeniya D, et al. Evaluation of toxicant and carcinogen metabolites in the urine of e-cigarette users versus cigarette smokers. *Nicotine Tob Res*. 2015; 17:704–09. [PubMed: 25335945]
- *49. Kamboj A, Spiller HA, Casavant MJ, et al. Pediatric exposure to e-cigarettes, nicotine, and tobacco products in the United States. *Pediatrics*. 2016; 137:e20160041. This study demonstrated that the frequency of exposures to e-cigarettes and nicotine liquid among young children is rapidly increasing and needs to be prevented. [PubMed: 27244861]
50. Chatterjee K, Alzghoul B, Innabi A, et al. Is vaping a gateway to smoking: a review of the longitudinal studies. *Int J Adolesc Med Health*. 2016; [Epub ahead of print]. doi: 10.1515/ijamh-2016-0033
51. Vasiljevic M, Petrescu DC, Marteau TM. Impact of advertisements promoting candy-like flavoured e-cigarettes on appeal of tobacco smoking among children: an experimental study. *Tob Control*. 2016; [Epub ahead of print]. doi: 10.1136/tobaccocontrol-2015-052593

Key points

- Significant numbers of children are exposed to tobacco smoke in utero and in their environment.
- Nicotine and tobacco smoke exposure during critical times of development results in a variety of adverse health outcomes in children.
- Biomarkers of tobacco smoke exposure clarify the role tobacco chemicals play in influencing health in childhood and beyond.
- While e-cigarettes appear to be less harmful than traditional cigarettes, they appear to be a gateway to combustible cigarette smoking in adolescents.