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Impact of prenatal exposure to smoking on child health

Michelle C. Maciag[1,2,3], **Aroub Yousuf**[4], **Marissa Hauptman**[3,5,6]

[1]Asthma & Allergy Affiliates, Salem, MA

[2]Boston Children's Hospital, Division of Allergy and Immunology, Boston, MA.

[3]Harvard Medical School, Boston, MA

[4]Boston College, Division of General Pediatrics, Pediatric Environmental Health Center, Boston, MA

[5]Boston Children's Hospital, Division of General Pediatrics, Pediatric Environmental Health Center, Boston, MA

[6]Region 1 New England Pediatric Environmental Health Specialty Unit, Boston, MA

Abstract

Prenatal exposure to tobacco smoke remains common, through active smoking and/or passive environmental exposure, and is linked to adverse childhood outcomes. Not only have high-quality studies and meta-analyses demonstrated increased risks of prenatal as well as postnatal complications, but adverse child outcomes are well described. In utero exposure to tobacco smoke has been associated with congenital anomalies, infant and teenager overweight and obesity, and neuropsychiatric sequelae. In addition, certain childhood malignancies have been linked to paternal smoking during pregnancy. In this chapter, adverse childhood outcomes related to intrauterine exposure to electronic cigarettes and marijuana are described.

Keywords

prenatal exposure; tobacco; electronic cigarette; nicotine; intrauterine exposure

INTRODUCTION

With both traditional tobacco products as well as electronic cigarettes available, there are many potential venues for exposure to the pregnant individual and thus the developing fetus. Globally, the prevalence of maternal smoking during pregnancy ranges from 5–40%, and results in exposure to tens of millions of developing fetuses.[1] In a European study evaluating five different cohorts, the prevalence was 12–20%.[2] In high- income countries, the number of pregnant people who smoke is waning, but in low-income countries, this number is on the rise. [3] Neonates and children have little control over their environment and are vulnerable

Address Correspondence to: Marissa Hauptman, MD, MPH, Boston Children's Hospital, Harvard Medical School, 300 Longwood Ave, Boston, MA 02115, Marissa.hauptman@childrens.harvard.edu.

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to the harmful effects of tobacco smoke. Exposure early in life, starting from exposure to maternal smoking during pregnancy, often continues into early childhood.[3]

Since Barker's publication of "The fetal and infant origins of adult disease" in 1990, significant emphasis has been placed on the intrauterine environment and its effect on chronic, noncommunicable diseases later in life. Historical events severe famine, as well as prior pandemics have provided organic data about the epigenetic changes that can result from intrauterine stress.[4] Because nicotine and tobacco products are transferred across the placenta, children in utero are harmed from exposure to tobacco products both from the pregnant individual's own use, as well as her environmental exposure (inhaled through the respiratory tract or even absorbed through the skin).[5] The effects of maternal smoke exposure on the developing fetus may impact the pregnancy itself, as well as cause pervasive impacts on the child's health after birth and throughout their lives (Figure I).

Despite efforts devoted to smoking cessation during pregnancy about half of smokers will continue to use tobacco products during pregnancy.[1] The effects of nicotine exposure while in utero may later increase risk for life threatening conditions that impact the child for their whole lives. Several meta-analyses have demonstrated increased risk for childhood cancer, namely acute lymphoblastic leukemia, in offspring of fathers who smoke around conception or through the pregnancy.[6, 7] Exposure to nicotine products while in utero can increase a child's risk for neurologic sequalae, like ADHD.[8] This exposure also elevates risk of psychiatric disorders in the offspring.[9, 10] Respiratory conditions such as asthma and allergic rhinitis are increased in offspring of pregnant individuals who smoke.[2] Intrauterine tobacco smoke exposure may predispose to overweight and obesity, which are also linked to a myriad of other health complications.[11] In this chapter, we explore the effects of prenatal tobacco smoke exposure on childhood health outcomes. We also review available data on childhood outcomes related to electronic cigarette exposures,[1, 12] and prenatal marijuana exposure. [11]

CONGENITAL HEART DEFECTS

Large studies have shown that maternal smoking, as well as paternal smoking increase the risk of congenital heart defects. A meta-analysis encompassing 125 studies and 137,574 cases of congenital heart defects in 8,770,873 study participants was conducted to determine the risk of congenital heart defects associated with active and passive maternal smoking, as well as paternal smoking.[13] Overall, maternal active (RR=1.25; 95% CI: 1.16–1.34; $p < 0.01$) and passive (RR=2.24, 95% CI: 1.81–2.77; $p<0.01$) smoking as well as paternal active smoking (RR:1.74, 95% CI: 1.48–2.06; $p < 0.01$) were significantly associated with CHD risk. For specific CHD subtypes, the study showed that maternal active smoking was significantly associated with risk of atrial septal defect (RR: 1.27, 95% CI: 1.02–1.59; p=0.03) and right ventricular outflow tract obstruction (RR:1.43, 95% CI: 1.04–1.97; p=0.03).[13]

NEUROPSYCHIATRIC CONSEQUENCES

Meta-analyses demonstrate that prenatal smoke exposure is associated with schizophrenia, mood disorders, and ADHD.[10,14,9,8] Four cohort and three case-control studies analyzed the

relationship between prenatal tobacco smoke exposure and the likelihood of the onset of schizophrenia. 2,444,910 participants were included from seven studies published between 1995 and 2017.[10] A pooled analysis demonstrated a 29% increased risk of developing schizophrenia as a consequence of maternal prenatal smoke exposure.[10]

Additionally, 17 studies investigated levels of prenatal smoke exposure on neonatal neurologic parameters using either a questionnaire method (n=7), biological measures such as cotinine levels through saliva (n=2), or both methods.[14] Cumulatively, data from 19,162 infants established a medium pooled effect size for negative affect, attention, excitability, irritability, and orientation, as a result of prenatal cigarette exposure. The effect size for muscle tone, regulation, and difficult temperament was small, with lethargy and stress failing to demonstrate significant pooled effects.[14]

To investigate the correlation between prenatal tobacco use and mood disorders in offspring, data from eight cohort studies and two case-control studies was analyzed. Although significant heterogeneity was found in bipolar disorder (RR=1.44; $I2$ = 70.72%; Q = 10.25; P value = 0.02) and depressive disorder (RR=1.44; $I2$ = 86.03%; Q = 42.96; P value < 0.01), a positive association between prenatal tobacco use and risk of mood disorders in offspring was established (RR=1.43; 95% CI 1.27–1.60).[9]

Furthermore, a meta-analysis performed with 27 articles, including 3,076,173 participants, found a significant association between maternal smoking during pregnancy (MSDP) and childhood attention-deficit/ hyperactivity disorder (ADHD) (OR 1.78, 95% CI 1.32–2.38). The results also indicated that smoking cessation during the first trimester of pregnancy is an effective means to reduce the risk of childhood ADHD, while smoking cessation before pregnancy is less effective, though recommended.[8]

Further investigation is needed to determine with certainty the mechanisms underlying the association between prenatal tobacco exposure and neurologic sequelae in offspring.[5]

It is suggested that as nicotine and other chemicals present in tobacco smoke can cross the placenta, and that excessive stimulation of serotonergic and dopaminergic receptors may alter nerve sensitivity, and directly impair neural growth and circuit formation.[5]

RESPIRATORY COMPLICATIONS

Maternal smoking during pregnancy has been linked with an elevated risk of developing asthma and rhinitis in young children, and a dose–response relationship has been suggested.[2] Studying five ongoing European birth cohorts, the Mechanisms of the Development of Allergy project attempted to elucidate the complicated associations between tobacco smoke exposure and asthma and allergic rhinoconjunctivitis.[2] These cohorts collected relevant data regarding smoke exposure during pregnancy or the first year of life, follow up between 14–16 years of age and interval follow up between ages 4–6, and 8–10. Maternal smoking during pregnancy was defined as smoking ≥1 cigarette per day during any trimester of pregnancy. Asthma was defined as fulfilling at least two of the following three criteria: a) a physician’s diagnosis of asthma; b) asthma medication in the past 12 months; and c) wheezing in the past 12 months. Models were adjusted for other potential confounders,

including the sex of the child, parental allergic history, parental education, and breastfeeding status. Children with any exposure to maternal smoking during pregnancy were more likely to have asthma between ages 4–6 [OR = 1:71 (95% CI: 1.21, 2.41)], compared with children who were not exposed to maternal smoking during pregnancy. A non-significantly increased odds ratio was observed for persistent asthma (asthma at age 14–16) [OR = 1:22 (95% CI: 0.87, 1.71)].[2] In the same study, maternal smoking during pregnancy was also associated with persistent rhinoconjunctivitis [OR = 1:77 (95% CI: 1.20, 2.59)]. However, after adjusting for continued second hand smoke exposure during the child's life, the association with persistent rhinoconjunctivitis was no longer significant [OR = 1:79 (95% CI: 0.92, 3.48)].[2]

The authors, Thacher and colleagues, noted that the amount of exposure to the fetus during pregnancy was an important factor.[2] In dose–response analyses, children exposed to ≥10 cigarettes/day during pregnancy had significantly increased odds of early transient and persistent asthma as well as persistent rhinoconjunctivitis. These results remained significant after additional adjustment for second hand smoke exposure through childhood.[2]

Another study evaluated 21,000 children across eight birth cohorts.[15] This analysis showed maternal smoking during pregnancy is associated with an increased likelihood of wheeze with an OR of 1.39 (95% CI 1.08–1.77) and an increased likelihood of asthma with an OR of 1.65 (95% CI 1.18–2.31) at 4–6 years of age.[15]

There are several possible mechanisms suggested for how early exposure to tobacco smoke may predispose to development of respiratory disease, namely asthma and rhinitis. Perinatal tobacco smoke exposure may heighten airway hyperresponsiveness and impair the immune response to viral pathogens.[16] Further, perinatal exposure to maternal smoking during pregnancy may alter epigenetics. [17, 18] These modifications are known to occur in enhancer regions controlling the activity of genes involved in airway inflammatory processes. This likely underscores the development of asthma symptoms among young children.[17, 18] The pathogenesis of how maternal smoking increases risk for allergic rhinoconjunctivitis is less clear, however, studies demonstrate that maternal smoking during pregnancy may impact the adaptive and innate immune systems of newborns, causing nasal obstruction, modifications in mucociliary clearance in the airways, and changes the number and function of T lymphocytes.[19]

OVERWEIGHT

A large meta-analysis of 229,158 families from 28 European birth cohorts evaluated the associations of parental smoking during pregnancy on childhood overweight and obesity.[20] Compared with nonsmoking individuals, first trimester smoking was associated with increased risk of childhood overweight (OR 1.17 [95% CI 1.02–1.35], p =0.030). The risk was higher for children born to individuals continued to smoke during the pregnancy (OR 1.42 [95% CI 1.35–1.48], p<0.001). Additionally, among nonsmoking pregnant individuals exposed to paternal smoking, there was also an increased risk of childhood overweight (OR 1.21 [95% CI 1.16–1.27.[20]

Data was collected from The Danish National Birth Cohort (DNBC) which included 101,042 pregnant individuals who gave birth to a child between 1996 and 2002.[11] The subjects were interviewed by telephone twice during pregnancy, and postnatally when the child was 6–18 months of age. When the child was around age 7, they were mailed a follow up questionnaire inquiring on the child's height and weight was sent, to which 53,888 participants responded. Final study population included 32,747 dyads. Age and sex-specific cut offs for BMI were used and overweight was recorded as a dichotomous variable with obese children in the overweight group. 23.4% of the pregnant individuals reported smoking during pregnancy and/or postnatally. Maternal smokers had higher gestational weight gain overall ($p<0.001$), and were of lower socio-occupational status ($p<0.001$). Birth weight was lower ($p<0.001$) in their children, and they also were less likely to breastfeed, or more likely to have shorter duration of breast feeding ($p<0.001$). Overweight at age 7 was the primary outcome variable. Exposure to smoking only during pregnancy or both during pregnancy and postnatally were significantly associated with childhood overweight at age 7 years (OR: 1.31, 95% CI: 1.15– 1.48, and OR: 1.76, 95% CI: 1.58–1.97, respectively). In addition, a significantly higher risk of overweight was observed with exposure to smoking both during pregnancy and postnatally than exposure to smoking only during pregnancy (OR: 1.35, 95% CI: 1.16–1.56). Results were adjusted for confounders (maternal age, maternal pre-pregnancy BMI, gestational weight gain, paternal smoking, socio-occupational status, parity, gestational age, child sex and child's birth weight). None altered the result notably when tested separately, except for paternal smoking. In the model adjusted for paternal smoking, this increased the OR of overweight (OR: 1.27, 95% CI: 1.17–1.39).[11]

The authors concluded that children born at term to maternal smokers who had low birth weight had a much higher risk of childhood overweight if they were exposed to maternal smoking during pregnancy than children with low birth weight not exposed to smoking during pregnancy.[11] There was a dose-response relationship noted: Increasing number of cigarettes smoked daily during pregnancy was significantly associated with increased risk of childhood overweight at age 7 years. Significantly, even increasing the amount smoked by 1 cigarette daily increased the risk of childhood overweight.[11]

The authors of this study postulated that the increased rates of overweight and obesity in low birth weight infants born to maternal smokers could be due to chance, or be related to currently undefined susceptibility of lower birth weight infants to smoking-induced epigenetic changes.[11] It is possible that programming effects in the offspring that may affect fat storage and metabolism. Overall, risk estimates for overweight remained unchanged when low birth weight children were excluded from analyses.[11]

CHILDHOOD CANCER

Paternal smoking around the time of conception and through the pregnancy appears to be a risk factor for childhood acute lymphoblastic leukemia (ALL). [6,7] An Australian population-based case-control study evaluated 388 cases of ALL and 868 controls, recruited between 2003–2006. [6] There was no association found between maternal prenatal smoking and risk of childhood ALL, but the odds ratio for paternal smoking of 15 cigarettes per day or more around the time of the child's conception was 1.35 (95% confidence interval: 0.98, 1.86).

The same study reported that a history of paternal smoking of 15 cigarettes or more per day during the pregnancy year was associated with an increased risk of childhood ALL, with an OR of 1.46 (95% CI: 1.05–2.01). Results did not change when adjusted for other factors, like maternal smoking.[6]

The authors of the study, Milne and colleagues, also identified 9 prior studies that investigated the effect of paternal smoking around the time of conception and during pregnancy on rates of childhood ALL.[6] This produced summary odds ratios of 1.15 (95% confidence interval: 1.06, 1.24) for any paternal smoking around the time of the child's conception and 1.44 (95% confidence interval: 1.24, 1.68) for smoking 20 cigarettes or more per day at that time for childhood ALL.[6]

A more recent meta-analysis by Cao and colleagues, completed in 2020, including 17 case-control studies, also links paternal smoking both before conception and during pregnancy with an increased risk of childhood ALL.[7] Studies were completed with populations from North and Central America, Asia, Europe, and Australia and encompassed data from 1977–2011, with a total of 9,127 childhood ALL cases. Eight of the studies evaluated risk of ALL based on paternal smoking prior to conception and the RR for smoking before conception was 1.15 (95% confidence interval [CI]: 1.04–1.27). Nine studies evaluated the risk based on paternal smoking during the pregnancy and a statistically significant synthesized effect measure (RR=1.20, 95% CI: 1.12–1.28) was obtained as well.[7] Cao and colleagues determined that the amount of paternal smoking was critical: Paternal smoking prior to conception became a significant factor when the father smoked more than 16 cigarettes per day. Relative risk doubled for childhood ALL at about 35 cigarettes/day. During pregnancy, a significant effect measure was observed when paternal consumption of cigarettes surpassed 11 cigarettes per day, and it reached 1.4 at 20 cigarettes per day.[7]

ELECTRONIC CIGARETTES

Many studies evaluating the impact of e-cigarettes on progeny have been completed in murine models. A report on pregnant mice demonstrated abnormal neurodevelopment in the offspring as a result of exposure to e-cigarette vapor both with and without nicotine.[12] A positive relationship has been established between e-vapor exposure and embryonic oxidative stress, which can induce adverse development effects.[12]

While many in the lay community incorrectly deem e-cigarettes the "safer alternative" to tobacco-derived products, the potential persistent harmful effects on child health require further investigation. More research is needed to determine the differential effects of other components of e-cigarette aerosol. (Figure II)

MARIJUANA EXPOSURE

There is a shifting landscape in the use of cannabis and its derivative products as more states legalize marijuana for medicinal and recreational use. The 2017 Substance Abuse and Mental Health Services Administration's National Survey on Drug Use and Health found marijuana is the most widely used illicit (by federal standards) drug during pregnancy, and the percentage of pregnant people who reported using marijuana in the past month increased overall from 3.4% in 2002 to 7% in 2017 and 5.4% in 2019.[21] In the first trimester, past-

month marijuana use increased from 5.7% in 2002 to 12.1% in 2017.[22] Pregnant individuals consistently reported more medical marijuana use in the first trimester than in the second or third trimesters, potentially due to its antiemetic properties.[22] Marijuana can contain nearly 500 chemicals, including tetrahydrocannabinol (THC) which can pass through the placenta.[22]

Studies reviewed in Gunn et al. in a systematic review reported increased risk of neonatal intensive care unit (NICU) admission for infants exposed to prenatal cannabis (pOR, 2.02; 95% CI = 1.27–3.21).[23] This review was heavily leaned on as the highest quality systematic review in the NASEM report.[23] Although there are individual studies assessing the association between maternal cannabis use and later outcomes for the offspring, a systematic review is limited. In primary literature, there are some preliminary findings of the association between prenatal cannabis exposure and delinquency at age 14 years, OR, 1.84; 95% CI = 1.05–2.96).[24] However, this effect was mediated by depression and attention difficulties at age 10.[24] The literature reviewed at this time does not support an association on overall cognitive function but there have been an association seen for adolescent outcomes, with increases in cigarette and cannabis use, and a suggestion of increased mental health symptoms and school delinquency.[21]

More research is needed to clarify the neurodevelopmental impact of marijuana on the developing fetus. In 2017 and 2018, respectively, the American College of Obstetricians and Gynecologists and the American Academy of Pediatrics issued separate committee opinion discouraging physicians from suggesting use of marijuana during preconception, pregnancy, and lactation and advising individuals who are pregnant or nursing to avoid marijuana.[25, 26]

CONCLUSIONS

The meta-analyses and high-quality studies referenced provide invaluable data regarding the risks of prenatal smoke exposure on childhood outcomes. Smoking, unlike many other factors that affect pregnancy, is a modifiable risk. Public health initiatives must prioritize resources for cessation of maternal as well as paternal smoking, if not prior to pregnancy, then as soon as possible during pregnancy.

There is also data that reduction in perinatal smoke exposure to a fetus improves other childhood outcomes, like childhood overweight.[20] A large meta-analysis of 229,158 families from 28 European birth cohorts evaluated the associations of parental smoking during pregnancy, specifically quitting or reducing smoking, and maternal as well as paternal smoking together, with outcomes of preterm birth, low birth weight, and childhood overweight. If smoking is quit in the first trimester of pregnancy, the risk of small size for gestational age is the same as seen in non-smokers. Additionally, pregnant individuals who reduced their smoking between the first and third trimesters, without quitting, reduced their risk for small for gestational age births.[20] These data provide important findings regarding the measurable impact cessation of tobacco smoke exposure has on offspring. Prioritization of resources dedicated to cessation of maternal as well as paternal smoking, if not prior to pregnancy, then as soon as possible during pregnancy could improve the health of children worldwide.

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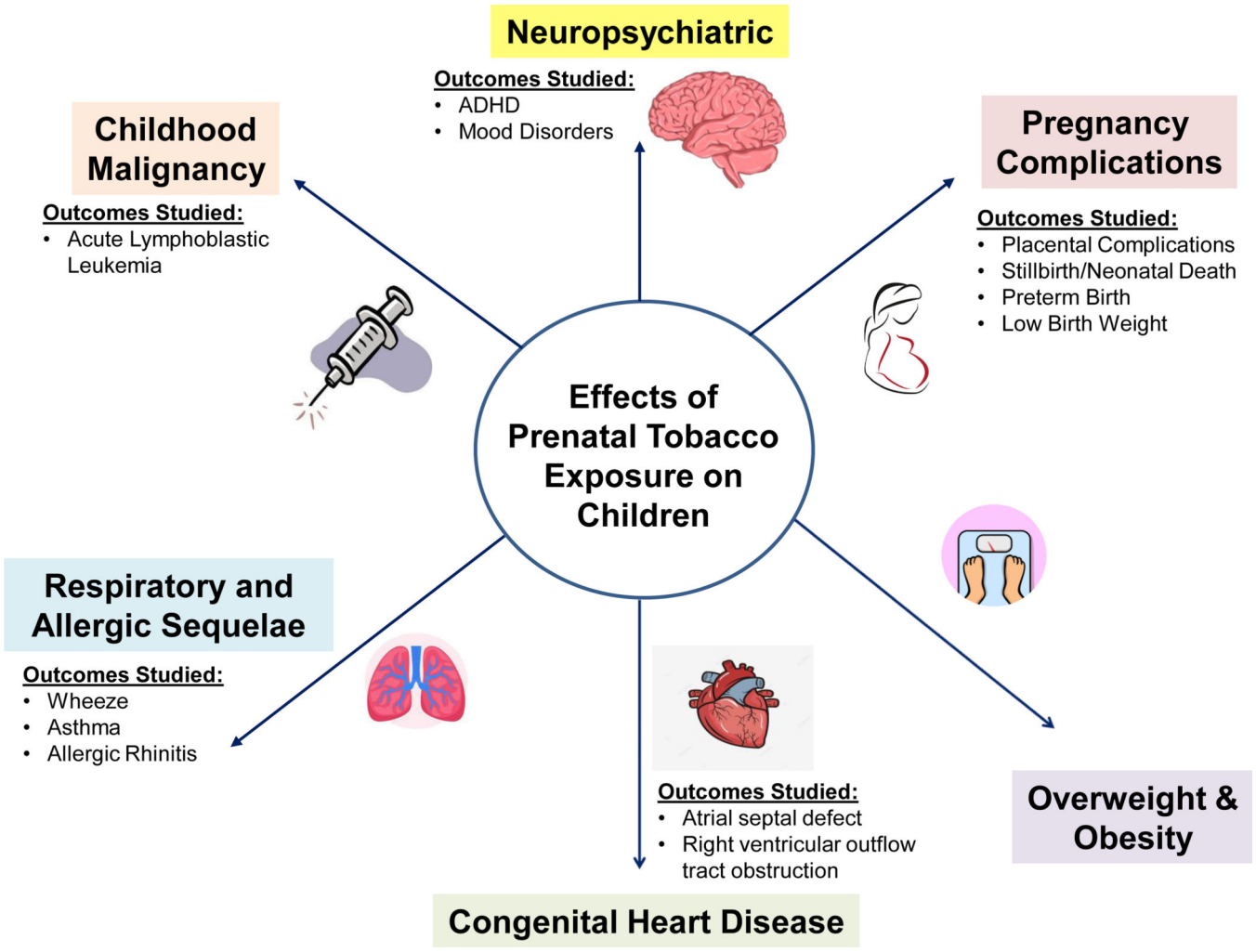

Figure I:
Overview of Childhood Outcomes Associated with Tobacco Smoke Exposure During Pregnancy

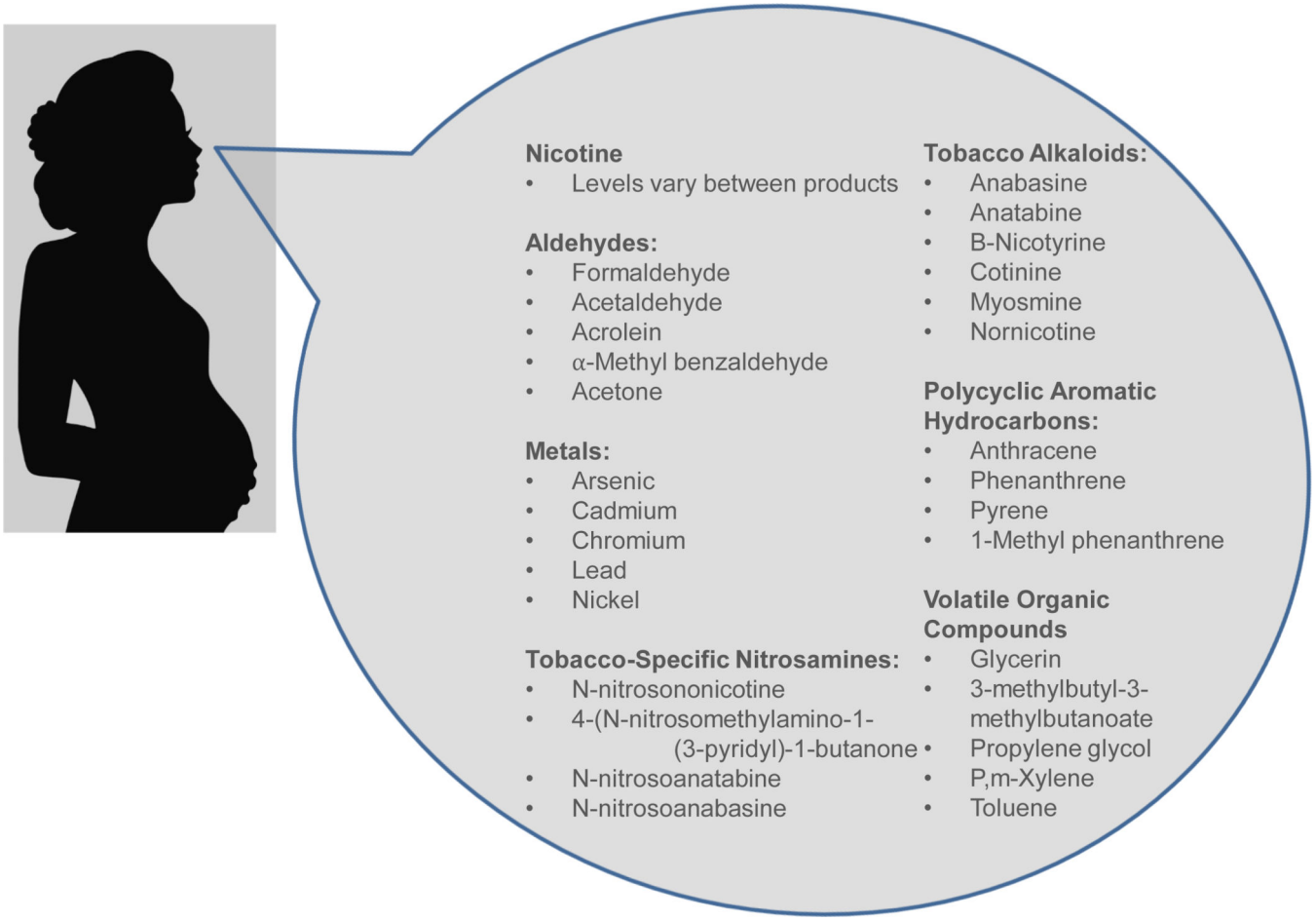

Figure II:

Chemicals reported in aerosols, refill solutions and cartridges of e-cigarettes

List of chemicals as reported in: Cheng T. Chemical evaluation of electronic cigarettes. *Tob Control*. 2014;23 Suppl 2(Suppl 2):ii11-ii17. doi:10.1136/tobaccocontrol-2013-051482