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“Pulmonary Effects of Maternal Smoking on the Fetus and Child: Effects on Lung Development, Respiratory Morbidities, and Life Long Lung Health”

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Summary

Maternal smoking during pregnancy is the largest preventable cause of abnormal in-utero lung development. Despite well known risks, rates of smoking during pregnancy have only slightly decreased over the last ten years, with rates varying from 5-40% worldwide resulting in tens of millions of fetal exposures. Despite multiple approaches to smoking cessation about 50% of smokers will continue to smoke during pregnancy. Maternal genotype plays an important role in the likelihood of continued smoking during pregnancy and the degree to which maternal smoking will affect the fetus. The primary effects of maternal smoking on offspring lung function and health are decreases in forced expiratory flows, decreased passive respiratory compliance, increased hospitalization for respiratory infections, and an increased prevalence of childhood wheeze and asthma. Nicotine appears to be the responsible component of tobacco smoke that affects lung development, and some of the effects of maternal smoking on lung development can be prevented by supplemental vitamin C. Because nicotine is the key agent for affecting lung development, e-cigarette usage during pregnancy is likely to be as dangerous to fetal lung development as is maternal smoking.

Keywords

In-utero smoke; Lung development; Asthma; Wheeze; Preterm birth; Forced expiratory flows

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Introduction

Maternal smoking during pregnancy continues to be a large public health problem and can have lifelong effects on childhood respiratory health (1,2). In-utero smoke exposure has significant effects on the developing lungs with long lasting / permanent structural changes, altered pulmonary function, increased respiratory illness, and an increased risk of asthma. It is also the largest preventable cause of preterm delivery and low birth weight, which are also important determinants of childhood pulmonary function. This review will outline the current epidemiology of smoking during pregnancy with its complex underpinnings and evidence of lifelong pulmonary effects. We will then synthesize the current evidence of the important mechanisms by which in-utero smoke affects lung development including genetic / epigenetic influences of susceptibility. Finally, we will discuss emerging alternative modes of nicotine exposure and important areas of future research to protect lung development.

Prevalence of smoking during pregnancy

Internationally, the prevalence of maternal smoking during pregnancy varies widely by country and in the United States, widely by state. Among European countries, smoking during pregnancy rates range from lows of 5% in countries such as Sweden, Austria, and Switzerland to mid-levels of 15-20 % in the Netherlands, Serbia, and Croatia, and to highs of 40% in Greece (3-5). Rates are generally lower in Asia, Africa and the Middle East, though the rate approaches 15% in Turkey (6). While the rate of active smoking during pregnancy is low in China, exposure to second hand smoke while pregnant exceeds 50% (7). In England, the smoking during pregnancy rate is approximately 20% (8) and has unfortunately remained stable in recent years.

In the United States (US), despite being a focus of attention by the Surgeon General for the last 40 years, at least 12% of pregnant women smoke and more than 50% of smokers in the US who become pregnant continue to smoke (9). In the US, rates vary from 6% in states such as Massachusetts and New Jersey to very high levels of 30% in West Virginia (10). US rates of smoking during pregnancy have only decreased about 0.1% per year, with some states such as Louisiana, West Virginia and Mississippi actually showing significant increases in recent years (10). Rates of smoking during pregnancy in Canada are roughly similar to that of the US (11). While use of combustible tobacco products during pregnancy is generally more common than smokeless products, in India and Bangladesh use of smokeless tobacco during pregnancy is approaching 25% (12) partially reflecting a perception of health benefits for smokeless tobacco products as well as their low cost. The use of smokeless tobacco products during pregnancy is also common in Sweden and among Alaskan Native Americans in the US.

Smoking in pregnancy is a unique morbidity in that it is addictive, heavily advertised (13,14) and has complex societal factors. Teen pregnancy, low income and education, living with another smoker, depressive symptoms, and alcohol consumption are important factors increasing the odds of smoking during pregnancy with a gradient linking the number of risk factors to the percentage of smoking (15). The association with low income, age, and

education is surprisingly constant worldwide. In addition, certain genotypes significantly increase the likelihood of nicotine addiction / failure to quit (16,17). The number of pregnant smokers is also likely underestimated since studies have shown at least 20% of pregnant smokers falsely report the habit (18). Quit rates of smokers who become pregnant is also surprisingly consistent across cultures and countries, with about 50% of smokers quitting within the first trimester, and 50% continuing to smoke throughout pregnancy (19).

These data show that the rate of smoking during pregnancy remains high, and that some rates are only slowly decreasing while others are increasing such that tens of millions of affected infants are born every year and will continue to for years to come.

Childhood respiratory health after maternal smoking in pregnancy

Multiple studies have shown increased lower respiratory illness in infants born of mothers who smoke (20-23). Taylor and Wadsworth (22) studied 12,743 children and found significantly increased bronchitis and hospital admissions for lower respiratory illness in children from smoking mothers. Tager et al. (24) also found increased lower respiratory illness with prenatal but not with postnatal exposure. Similarly, multiple studies have shown increased wheezing and asthma in children born of mothers who smoked during pregnancy (25-29) and large trials have now demonstrated that prenatal exposure is an independent risk factor and more critical than postnatal exposure. In a 10 year longitudinal study of 6,000 children, Gilliland et al. (29) demonstrated that in-utero smoke was independently associated with physician diagnosed asthma with an OR of 1.8 (95% CI 1.1-2.9). A pooled analysis of eight birth cohorts (3) involving 21,000 children showed maternal smoking only in 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. A recent study also showed a highly significant interaction between maternal smoking during pregnancy and low birth weight on risk of offspring asthma diagnosis (risk ratio 8.8 [95% CI 2.1-38] and 1.3 [95% CI 1.0-1.8] for LBW vs. normal birth weight exposed to in-utero smoke, respectively) (27). Maternal smoking also encourages children to smoke and seems to increase the adverse effects of their offspring's personal smoking habits (30).

In addition to the above direct effects of in-utero smoke on offspring lung development, maternal smoking during pregnancy is the largest preventable cause of low birth weight and prematurity (31) which are also important risk factors for altered lung development (2). A meta-analysis of 20 prospective studies (32) of over 100,000 women found that smoking in pregnancy increased preterm births by about 25%. Although not the focus of this review, this statistic illustrates the dynamic impact that in-utero smoke exposure can have on offspring pulmonary function.

Childhood pulmonary function testing

Infants born after in-utero smoke exposure are reported to have altered pulmonary function tests soon after delivery and prior to any significant postnatal smoke exposure, supporting the impact of in-utero smoke exposure on fetal lung development. These changes include

altered tidal breathing patterns, decreased passive respiratory compliance, and decreased forced expiratory flows (33-35). Such changes in pulmonary function test (PFT) measurements were also seen in preterm infants (mean gestation 32 weeks) tested at 36 weeks of postmenstrual age showing that the effect on fetal lung development is not limited to the end of gestation (34).

Longitudinal PFT data from prospective birth cohorts have demonstrated persistent deficits in pulmonary function, again supporting developmental alterations and the impact of lifelong pulmonary function trajectories. Cunningham et al., (36) performed tests on 8800 nonsmoking school children aged 8-12 and found reduced forced expiratory flows in children whose mothers smoked during pregnancy that were not explained by postnatal smoke exposure. A recent prospective study with a 21 year follow up has now demonstrated that the decreases in FEV₁ (forced expiratory volume in 1 second) and FEF₂₅₋₇₅ (forced expiratory flows between 25% and 75% of FVC, MMEF) persist at 21 years of age in males (1).

Genetic and epigenetic factors

Not all children born after in-utero smoke exposure have decreased PFTs and increased respiratory morbidity. This variability in manifestation may, in part, be due to differences in maternal and fetal genetic susceptibility and / or epigenetic factors. The role of genotype relative to the development of asthma, sensitivity to maternal smoking, and difficulty in quitting smoking have been demonstrated in recent studies (37-39).

CYP1A1 and GSTT1 are enzymes involved in the metabolism and detoxification of toxic metabolites from tobacco smoke. Common deletions or structural polymorphisms in the glutathione transferase gene increase both the risk of asthma and sensitivity of the fetus to maternal smoking (37,39). Studies (38) have shown that a grandmother's smoking can affect the grandchild's lung development even if the mother did not smoke, likely via effects on methylation pathways. This emphasizes the importance of intergenerational smoking cessation, although the impact of this benefit will be delayed. In addition, the lung is developing in utero, from the embryonic through the pseudoglandular, canalicular, saccular, and to the beginning of the alveolar stage, and there are multiple steps involving different molecular mediators within each of these stages (40). Therefore it is likely, though not yet well demonstrated, that the effect of in-utero smoke exposure will be dependent on the timing, duration, and extent of exposure within the context of lung development.

Lessons from animal models: the role of in-utero nicotine in affecting lung development

As outlined above, there is robust data that in-utero smoke exposure leads to reduced pulmonary function in the offspring. There are many potential mechanisms through which in-utero smoke exposure may impact lung development including the thousands of chemicals found in tobacco smoke, hypoxemia due to carbon monoxide, alterations in placental structure, and toxins among many other factors. Tobacco smoke contains thousands of compounds such that identifying whether one or more plays a key role in the

pathogenesis of smoking related lung disease is difficult. Although there are probably several chemicals involved, nicotine is of particular interest in prenatal exposure as it can easily cross the placental barrier. Levels of nicotine and cotinine are measurable in the fetus and closely mimic maternal levels. Levels in the umbilical vein are similar to the maternal vein nicotine. Tissue distribution studies showed levels of nicotine in fetal lung similar to levels in fetal blood; therefore lungs in fetuses of smokers can be exposed to concentrations of nicotine similar to that seen in the blood of smokers. As outlined in next several paragraphs, experimental data suggests that nicotine appears to be one of the primary mediators of the altered pulmonary function caused by in-utero smoke exposure.

Some of the initial studies examining the effect of in-utero smoke exposure demonstrated that prenatal cigarette smoke caused decreased lung volume, decreased number of saccules and septal crests, and decreased elastin fibers in a fetal rat model (41). Maritz et al. (42) subsequently showed nicotine exposure *alone* caused similar changes in rat pup lung, supporting the important role of nicotine. Sekhon et al. (43) demonstrated that nicotinic acetylcholine receptors (nAChR) are extensively expressed in the fetal non-human primate lung. In one study, pregnant rhesus monkeys were infused subcutaneously with nicotine at 1.5 mg/kg/day or saline from day 26 to 160 of gestation (term is 165 days). Cesarean sections were done at 160 days and pulmonary function measured at 24 hours of age. This study demonstrated that nicotine crossed the placenta of the pregnant monkey and upregulated $\alpha 7$ nAChR in the airway epithelial cells and fibroblasts in the fetal monkey lung (Figure 1), which translated into increases in collagen in a similar distribution (44). Pulmonary function testing in these offspring showed changes similar to those seen in human offspring after in-utero smoke exposure including significant decreases in mean mid forced expiratory flow (45). Overall, experimental studies of the effects of nicotine on lung development in mice, rats, sheep, and monkeys have shown thicker alveolar walls, increased airway smooth muscle and collagen deposition, and airway hyper-responsiveness with airflow restriction (46-48). The increased collagen and decreased elastin caused by prenatal nicotine exposure likely underlies the changes in pulmonary function with decreased passive respiratory compliance and forced expiratory flows caused by maternal smoking in pregnancy.

Studies in mice have suggested that an additional potential mechanism by which prenatal nicotine exposure leads to decreases in expiratory flows is by affecting airway growth. Nicotine stimulated lung branching and dysanaptic lung growth in a dose dependent fashion in embryonic murine lung explants (49). This was further studied in vivo in a murine model in which pregnant mice were treated with nicotine from gestation day 7 to postnatal day 14. Similar to changes seen in humans and non-human primates, this combination of pre- and postnatal nicotine exposure caused significant decreases in forced expiratory flows in the offspring (47). A primary mediator of this effect appeared to be the $\alpha 7$ nAChR as the effect of nicotine was lost in $\alpha 7$ nAChR knockout mice (47). Further studies in this model demonstrated that the critical period for perinatal nicotine exposure to alter forced expiratory flows was exposure that corresponded to the end of the pseudoglandular period through the canalicular and saccular periods, but before most of alveolarization (47), suggesting a primary effect of nicotine on airway growth. This was confirmed by stereologic analysis of airway size and diameter, which showed an increased number of airways of small diameter

with nicotine treatment (Figure 2). These data suggest that prenatal nicotine exposure leads to decreased forced expiratory flows by stimulating epithelial cell growth and potentially lung branching to result in longer and more tortuous airways.

Potential approaches for primary prevention

A recent Cochrane review (50) concluded that smoking cessation programs reduce the proportion of women who smoke and reduce the rate of preterm birth. This review concluded that the effect was larger when counseling was combined with other strategies such as providing feedback with biochemical measures. It also found incentive based interventions to be effective, but these randomized controlled trials were underpowered to assess the effect on preterm births. A recent meta-analysis (51) involving 1.3 million women demonstrated that the introduction of antismoking legislation reduced preterm birth rates by 10%. This was likely due to cessation in the smoking mother, but also in those around her with subsequent decreased exposure to passive smoke. Cnattingius et al. (52) studied 250,000 women who delivered consecutive singletons examining women who either began smoking or stopped smoking in between the two deliveries. The risk of preterm birth was either increased or decreased respectively in a dose dependent fashion, indicating that effective smoking cessation efforts should reduce preterm birth.

Nicotine replacement therapies have also been studied as a means of smoking cessation. However, based on the data above, it is likely that nicotine itself will continue to have significant adverse effects on lung development. Also, randomized controlled trials have not demonstrated that nicotine replacement is effective or safe in promoting smoking cessation during pregnancy. Another recent Cochrane Review (53) examined the safety and efficacy of six trials of nicotine-replacement therapy (NRT) in 1745 pregnant smokers, and no significant differences for smoking cessation or other important birth related outcomes were demonstrated between randomized groups.

Evidence from studies in non-human primates (54) and from a recent randomized clinical trial (33) of vitamin C supplementation (500mg/day) to pregnant smokers unable to quit smoking, suggest that vitamin C may prevent some of the effects of in-utero smoke exposure on offspring respiratory health. The newborns whose mothers had been randomized to vitamin C had significantly improved newborn pulmonary function tests with significant increases in passive respiratory compliance and significantly improved tidal breathing measurements compared to newborns whose mothers were randomized to placebo. Ninety-two percent of these infants were followed to one year of age, and there was also a significant decrease in the incidence of wheeze among offspring born to mothers randomized to vitamin C versus placebo (21% versus 40%; RR 0.53 [95% CI from 0.32 to 0.90]). The effect of maternal smoking on newborn lung function was also associated with the maternal genotype for the $\alpha 5$ nAChR receptor gene (rs16969968) ($p < 0.001$ for interaction), which is the $\alpha 5$ nAChR structural polymorphism that has the strongest link to lung disease (55) (Figure 3). This study was not powered to examine preterm births between the randomized groups, but a large trial (56) of vitamin C (1000 mg) and vitamin E (400 IU) supplementation during pregnancy found a reduction in preterm birth (RR 0.76; 95% CI 0.58-0.99) and placental abruption in the treated versus untreated smokers.

Risks of e-cigarette use during pregnancy

Given that nicotine appears to be the primary ingredient in tobacco smoke that affects lung development, use of electronic nicotine delivery devices (referred to as e-cigarettes from here on) during pregnancy is an area of major concern (57). In the last few years, use of e-cigarettes has increased almost exponentially especially among younger people (58). This increase in use is coupled with a perception of safety of e-cigarettes that has yet to be proven. While e-cigarettes are potentially safer than conventional cigarettes, there are significant areas of concern about e-cigarette safety. First, surveys suggest that increasing numbers of people are using just e-cigarettes alone (58-60). Thus, in considering the safety of e-cigarettes, they must be compared to use of no tobacco-derived products at all, not to use of conventional cigarettes.

Second, the combination of the addictive nature of nicotine coupled with the perception of relative safety suggests that e-cigarette use during pregnancy will likely increase (61). While nicotine replacement therapy has been used during pregnancy (62,63) on the basis that nicotine alone will be safer than conventional cigarette use, the potential continued use of e-cigarettes by e-cigarette-only users during pregnancy raises heightened safety concerns. The fact that about half of conventional cigarette users continue to smoke while pregnant (9,64) suggests that significant numbers of e-cigarette users will also continue e-cigarette use during pregnancy, thus exposing the fetus to nicotine. Remarkably, a recent survey of pregnant women showed nearly 40% did not realize e-cigarettes contained nicotine or could be addictive, and 40% felt them to be less harmful than traditional cigarettes (61).

Third, it is likely that the amount of nicotine delivered by e-cigarettes will increase in the future. Critical elements in considering the health effects of the type of e-cigarette used are potential dose of nicotine delivered, potential contaminants, constituents, flavorings, and heat-generated by products. Recent studies by Talih et al (65) demonstrates that nicotine delivery by e-cigarettes can be modeled primarily as a ratio of nicotine-concentration in the e-juice, temperature of the vaporizer, and volume of the puff. In practical terms this means that depending on the puff volume and nicotine concentration, e-cigarettes deliver as high or higher amounts of nicotine as do conventional combustion cigarettes (65,66). As e-cigarette users become more experienced, they tend to take higher volume puffs and obtain higher levels of nicotine equaling the nicotine levels achieved by smokers of conventional cigarettes (65,66). In addition, the technology used in e-cigarettes is rapidly evolving such that levels of nicotine delivered are sure to increase.

Together this makes the potential use of electronic nicotine delivery devices during pregnancy likely to be a major concern in the future, and it is imperative that physicians work to educate their patients of the dangers of such devices. Finally, it is important to note that the U.S. Food and Drug Administration recently announced that it is extending its regulatory authority over all Electronic Nicotine Delivery Systems which provides some hope for increased regulation.

Conclusions

The developing fetal lung is very sensitive to the effects of in-utero tobacco products with altered lung function demonstrated at birth that is long lasting and likely affects subsequent lung trajectory and lung health. These deficits are consistently demonstrated as decreases in forced expiratory flows, among others, and are likely mediated by nicotine crossing the placenta to interact with nicotinic acetylcholine receptors that are expressed in fetal lung. Since in-utero smoke / nicotine exposure may prohibit the individual from attaining their maximum lung growth, they are more predisposed to premature pulmonary aging and the development of chronic obstructive pulmonary disease. This makes continued focus on cessation of all tobacco products prior to and during pregnancy of vital importance. Given the difficulty of fighting nicotine addiction and the continued use of tobacco products by millions during pregnancy, it is also critical to identify primary prevention approaches to block the effects of in-utero nicotine on lung development.

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References

1. Hayatbakhsh MR, Sadasivam S, Mamun AA, Najman JM, O'callaghan MJ. Maternal smoking during and after pregnancy and lung function in early adulthood: A prospective study. *Thorax*. 2009; 64:810–814. PM:19525264. [PubMed: 19525264]
2. Stocks J, Hislop A, Sonnappa S. Early lung development: lifelong effect on respiratory health and disease. *Lancet Respir Med*. 2013; 1:728–742. PM:24429276. [PubMed: 24429276]
3. Neuman A, Hohmann C, Orsini N, et al. Maternal smoking in pregnancy and asthma in preschool children: a pooled analysis of eight birth cohorts. *Am J Respir Crit Care Med*. 2012; 186:1037–1043. PM:22952297. [PubMed: 22952297]
4. Vivilaki VG, Diamanti A, Tzeli M, Patelarou E, Bick D, Papadakis S, Lykeridou K, Katsaounou P. Exposure to active and passive smoking among Greek pregnant women. *Tob Induc Dis*. 2016; 14:12. PM:27051356. [PubMed: 27051356]
5. Smedberg J, Lupattelli A, Mardby AC, Nordeng H. Characteristics of women who continue smoking during pregnancy: a cross-sectional study of pregnant women and new mothers in 15 European countries. *BMC Pregnancy Childbirth*. 2014; 14:213. PM:24964728. [PubMed: 24964728]
6. Caleyachetty R, Tait CA, Kengne AP, Corvalan C, Uauy R, Echouffo-Tcheugui JB. Tobacco use in pregnant women: analysis of data from Demographic and Health Surveys from 54 low-income and middle-income countries. *Lancet Glob Health*. 2014; 2:e513–e520. PM:25304418. [PubMed: 25304418]
7. Zhang L, Hsia J, Tu X, Xia Y, Zhang L, Bi Z, Liu H, Li X, Stanton B. Exposure to secondhand tobacco smoke and interventions among pregnant women in China: a systematic review. *Prev Chronic Dis*. 2015; 12:E35. PM:25789496. [PubMed: 25789496]
8. Dhalwani NN, Tata LJ, Coleman T, Fiaschi L, Szatkowski L. A comparison of UK primary care data with other national data sources for monitoring the prevalence of smoking during pregnancy. *J Public Health (Oxf)*. 2015; 37:547–554. PM:25336275. [PubMed: 25336275]
9. Fillion KB, Abenhaim HA, Mottillo S, et al. The effect of smoking cessation counselling in pregnant women: a meta-analysis of randomised controlled trials. *BJOG*. 2011; 118:1422–1428. PM: 21880109. [PubMed: 21880109]

10. Tong VT, Dietz PM, Morrow B, D'Angelo DV, Farr SL, Rockhill KM, England LJ. Trends in smoking before, during, and after pregnancy--Pregnancy Risk Assessment Monitoring System, United States, 40 sites, 2000-2010. *MMWR Surveill Summ.* 2013; 62:1-19. PM:24196750.
11. Gilbert NL, Bartholomew S, Raynault MF, Kramer MS. Temporal trends in social disparities in maternal smoking and breastfeeding in Canada, 1992-2008. *Matern Child Health J.* 2014; 18:1905-1911. PM:24474592. [PubMed: 24474592]
12. Hossain MS, Kypri K, Rahman B, Arslan I, Akter S, Milton AH. Prevalence and correlates of smokeless tobacco consumption among married women in rural Bangladesh. *PLoS ONE.* 2014; 9:e84470. PM:24416234. [PubMed: 24416234]
13. Anderson SJ, Glantz SA, Ling PM. Emotions for sale: cigarette advertising and women's psychosocial needs. *Tob Control.* 2005; 14:127-135. PM:15791023. [PubMed: 15791023]
14. DiFranza JR, Wellman RJ, Sargent JD, Weitzman M, Hipple BJ, Winickoff JP. Tobacco promotion and the initiation of tobacco use: assessing the evidence for causality. *Pediatrics.* 2006; 117:e1237-e1248. PM:16740823. [PubMed: 16740823]
15. Kahn RS, Certain L, Whitaker RC. A reexamination of smoking before, during, and after pregnancy. *Am J Public Health.* 2002; 92:1801-1808. PM:12406812. [PubMed: 12406812]
16. Sarginson JE, Killen JD, Lazzeroni LC, Fortmann SP, Ryan HS, Schatzberg AF, Murphy GM Jr. Markers in the 15q24 nicotinic receptor subunit gene cluster (CHRNA5-A3-B4) predict severity of nicotine addiction and response to smoking cessation therapy. *Am J Med Genet B Neuropsychiatr Genet.* 2011 PM:21268243.
17. Liu JZ, Tozzi F, Waterworth DM, et al. Meta-analysis and imputation refines the association of 15q25 with smoking quantity. *Nat Genet.* 2010; 42:436-440. PM:20418889. [PubMed: 20418889]
18. Shipton D, Tappin DM, Vadiveloo T, Crossley JA, Aitken DA, Chalmers J. Reliability of self reported smoking status by pregnant women for estimating smoking prevalence: a retrospective, cross sectional study. *BMJ.* 2009; 339:b4347. PM:19875845. [PubMed: 19875845]
19. Alshaarawy O, Anthony JC. Month-wise estimates of tobacco smoking during pregnancy for the United States, 2002-2009. *Matern Child Health J.* 2015; 19:1010-1015. PM:25112459. [PubMed: 25112459]
20. Rantakallio P. Relationship of maternal smoking to morbidity and mortality of the child up to the age of five. *Acta Paediatr Scand.* 1978; 67:621-631. PM:750195. [PubMed: 696308]
21. Fergusson DM, Horwood LJ, Shannon FT. Parental smoking and respiratory illness in infancy. *Arch Dis Child.* 1980; 55:358-361. PM:7436471. [PubMed: 7436471]
22. Taylor B, Wadsworth J. Maternal smoking during pregnancy and lower respiratory tract illness in early life. *Archives of Disease in Childhood.* 1987; 62:786-791. PM:3662581. [PubMed: 3662581]
23. Margolis PA, Keyes LL, Greenberg RA, Bauman KE, LaVange LM. Urinary cotinine and parent history (questionnaire) as indicators of passive smoking and predictors of lower respiratory illness in infants. *Pediatr Pulmonol.* 1997; 23:417-423. PM:9220523. [PubMed: 9220523]
24. Tager IB, Hanrahan JP, Tosteson TD, Castile RG, Brown RW, Weiss ST, Speizer FE. Lung function, pre- and post-natal smoke exposure, and wheezing in the first year of life. *Am Rev Respir Dis.* 1993; 147:811-817. PM:8466114. [PubMed: 8466114]
25. Zlotkowska R, Zejda JE. Fetal and postnatal exposure to tobacco smoke and respiratory health in children. *Eur J Epidemiol.* 2005; 20:719-727. PM:16151886. [PubMed: 16151886]
26. Lannero E, Pershagen G, Wickman M, Nordvall L. Maternal smoking during pregnancy increases the risk of recurrent wheezing during the first years of life (BAMSE). *Respir Res.* 2006; 7:3. PM: 16396689. [PubMed: 16396689]
27. Bjerg A, Hedman L, Perzanowski M, Lundback B, Ronmark E. A strong synergism of low birth weight and prenatal smoking on asthma in schoolchildren. *Pediatrics.* 2011; 127:e905-e912. PM: 21422092. [PubMed: 21422092]
28. Pattenden S, Antova T, Neuberger M, et al. Parental smoking and children's respiratory health: independent effects of prenatal and postnatal exposure. *Tob Control.* 2006; 15:294-301. PM: 16885578. [PubMed: 16885578]

29. Gilliland FD, Li YF, Peters JM. Effects of maternal smoking during pregnancy and environmental tobacco smoke on asthma and wheezing in children. *Am J Respir Crit Care Med*. 2001; 163:429–436. PM:11179118. [PubMed: 11179118]
30. Upton MN, Smith GD, McConnachie A, Hart CL, Watt GC. Maternal and personal cigarette smoking synergize to increase airflow limitation in adults. *Am J Respir Crit Care Med*. 2004; 169:479–487. PM:14630616. [PubMed: 14630616]
31. Salihu HM, Aliyu MH, Pierre-Louis BJ, Alexander GR. Levels of excess infant deaths attributable to maternal smoking during pregnancy in the United States. *Matern Child Health J*. 2003; 7:219–227. PM:14682499. [PubMed: 14682499]
32. Ion R, Bernal AL. Smoking and Preterm Birth. *Reprod Sci*. 2015; 22:918–926. PM:25394641. [PubMed: 25394641]
33. McEvoy CT, Schilling D, Clay N, et al. Vitamin C supplementation for pregnant smoking women and pulmonary function in their newborn infants: a randomized clinical trial. *JAMA*. 2014; 311:2074–2082. PM:24838476. [PubMed: 24838476]
34. Hoo AF, Henschen M, Dezateux C, Costeloe K, Stocks J. Respiratory function among preterm infants whose mothers smoked during pregnancy. *Am J Respir Crit Care Med*. 1998; 158:700–705. PM:9730993. [PubMed: 9730993]
35. Hanrahan JP, Tager IB, Segal MR, Tosteson TD, Castile RG, Van Vunakis H, Weiss ST, Speizer FE. The effect of maternal smoking during pregnancy on early infant lung function. *Am Rev Respir Dis*. 1992; 145:1129–1135. PM:1586058. [PubMed: 1586058]
36. Cunningham J, Dockery DW, Speizer FE. Maternal smoking during pregnancy as a predictor of lung function in children. *Am J Epidemiol*. 1994; 139:1139–1152. PM:8209873. [PubMed: 8209873]
37. Breton CV, Vora H, Salam MT, Islam T, Wenten M, Gauderman WJ, Van den Berg D, Berhane K, Peters JM, Gilliland FD. Variation in the GST mu locus and tobacco smoke exposure as determinants of childhood lung function. *Am J Respir Crit Care Med*. 2009; 179:601–607. PM:19151192. [PubMed: 19151192]
38. Li YF, Gilliland FD, Berhane K, McConnell R, Gauderman WJ, Rappaport EB, Peters JM. Effects of in utero and environmental tobacco smoke exposure on lung function in boys and girls with and without asthma. *Am J Respir Crit Care Med*. 2000; 162:2097–2104. PM:11112121. [PubMed: 11112121]
39. Wenten M, Li YF, Lin PC, Gauderman WJ, Berhane K, Avol E, Gilliland FD. In utero smoke exposure, glutathione S-transferase P1 haplotypes, and respiratory illness-related absence among schoolchildren. *Pediatrics*. 2009; 123:1344–1351. PM:19403501. [PubMed: 19403501]
40. Merkus PJ, Ten Have-Opbroek AA, Quanjer PH. Human lung growth: a review. *Pediatr Pulmonol*. 1996; 21:383–397. PM:8927465. [PubMed: 8927465]
41. Collins MH, Moessinger AC, Kleinerman J, Bassi J, Rosso P, Collins AM, James LS, Blanc WA. Fetal lung hypoplasia associated with maternal smoking: a morphometric analysis. *Pediatr Res*. 1985; 19:408–412. PM:4000765. [PubMed: 4000765]
42. Maritz GS. Maternal nicotine exposure during gestation and lactation of rats induce microscopic emphysema in the offspring. *Exp Lung Res*. 2002; 28:391–403. PM:12097232. [PubMed: 12097232]
43. Sekhon HS, Jia Y, Raab R, Kuryatov A, Pankow JF, Whitsett JA, Lindstrom J, Spindel ER. Prenatal nicotine increases pulmonary alpha7 nicotinic receptor expression and alters fetal lung development in monkeys. *J Clin Invest*. 1999; 103:637–647. PM:10074480. [PubMed: 10074480]
44. Sekhon HS, Keller JA, Proskocil BJ, Martin EL, Spindel ER. Maternal nicotine exposure upregulates collagen gene expression in fetal monkey lung. Association with alpha7 nicotinic acetylcholine receptors. *Am J Respir Cell Mol Biol*. 2002; 26:31–41. PM:11751201. [PubMed: 11751201]
45. Sekhon HS, Keller JA, Benowitz NL, Spindel ER. Prenatal nicotine exposure alters pulmonary function in newborn rhesus monkeys. *Am J Respir Crit Care Med*. 2001; 164:989–994. PM:11587984. [PubMed: 11587984]

46. Sekhon HS, Proskocil BJ, Clark JA, Spindel ER. Prenatal nicotine exposure increases connective tissue expression in foetal monkey pulmonary vessels. *Eur Respir J*. 2004; 23:906–915. PM: 15219006. [PubMed: 15219006]
47. Wongtrakool C, Wang N, Hyde DM, Roman J, Spindel ER. Prenatal nicotine exposure alters lung function and airway geometry through alpha7 nicotinic receptors. *AJRCMB*. 2012; 46:695–702. PM:22246862. [PubMed: 22246862]
48. Sandberg KL, Pinkerton KE, Poole SD, Minton PA, Sundell HW. Fetal nicotine exposure increases airway responsiveness and alters airway wall composition in young lambs. *Respir Physiol Neurobiol*. 2011; 176:57–67. PM:21195212. [PubMed: 21195212]
49. Wongtrakool C, Roser-Page S, Rivera HN, Roman J. Nicotine alters lung branching morphogenesis through the alpha7 nicotinic acetylcholine receptor. *Am J Physiol Lung Cell Mol Physiol*. 2007; 293:L611–L618. PM:17545491. [PubMed: 17545491]
50. Chamberlain C, O'Mara-Eves A, Oliver S, Caird JR, Perlen SM, Eades SJ, Thomas J. Psychosocial interventions for supporting women to stop smoking in pregnancy. *Cochrane Database Syst Rev*. 2013; 10:CD001055. PM:24154953.
51. Been JV, Nurmatov UB, Cox B, Nawrot TS, van Schayck CP, Sheikh A. Effect of smoke-free legislation on perinatal and child health: a systematic review and meta-analysis. *Lancet*. 2014; 383:1549–1560. PM:24680633. [PubMed: 24680633]
52. Cnattingius S, Granath F, Petersson G, Harlow BL. The influence of gestational age and smoking habits on the risk of subsequent preterm deliveries. *N Engl J Med*. 1999; 341:943–948. PM: 10498489. [PubMed: 10498489]
53. Coleman T, Chamberlain C, Davey MA, Cooper SE, Leonardi-Bee J. Pharmacological interventions for promoting smoking cessation during pregnancy. *Cochrane Database Syst Rev*. 2012; 9:CD010078. PM:22972148.
54. Proskocil BJ, Sekhon HS, Clark JA, Lupo SL, Jia Y, Hull WM, Whitsett JA, Starcher BC, Spindel ER. Vitamin C Prevents the Effects of Prenatal Nicotine on Pulmonary Function in Newborn Monkeys. *Am J Respir Crit Care Med*. 2005; 171:1032–1039. PM:15709053. [PubMed: 15709053]
55. Bierut LJ. Convergence of genetic findings for nicotine dependence and smoking related diseases with chromosome 15q24-25. *Trends Pharmacol Sci*. 2010; 31:46–51. PM:19896728. [PubMed: 19896728]
56. Abramovici A, Gandley RE, Clifton RG, et al. Prenatal vitamin C and E supplementation in smokers is associated with reduced placental abruption and preterm birth: a secondary analysis. *BJOG*. 2015; 122:1740–1747. PM:25516497. [PubMed: 25516497]
57. Spindel ER, McEvoy CT. The Role of Nicotine in the Effects of Maternal Smoking During Pregnancy on Lung Development and Childhood Respiratory Disease: Implications for Dangers of E-Cigarettes. *Am J Respir Crit Care Med*. 2016; 193:486–94. PM:26756937. [PubMed: 26756937]
58. Arrazola RA, Neff LJ, Kennedy SM, Holder-Hayes E, Jones CD. Tobacco use among middle and high school students--United States, 2013. *MMWR Morb Mortal Wkly Rep*. 2014; 63:1021–1026. PM:25393220. [PubMed: 25393220]
59. Porter L, Duke J, Hennon M, Dekevich D, Crankshaw E, Homs G, Farrelly M. Electronic Cigarette and Traditional Cigarette Use among Middle and High School Students in Florida, 2011-2014. *PLoS ONE*. 2015; 10:e0124385. PM:25969979. [PubMed: 25969979]
60. Wills TA, Knight R, Williams RJ, Pagano I, Sargent JD. Risk factors for exclusive e-cigarette use and dual e-cigarette use and tobacco use in adolescents. *Pediatrics*. 2015; 135:e43–e51. PM: 25511118. [PubMed: 25511118]
61. Mark KS, Farquhar B, Chisolm MS, Coleman-Cowger VH, Terplan M. Knowledge, Attitudes, and Practice of Electronic Cigarette Use Among Pregnant Women. *J Addict Med*. 2015; 9:266–272. PM:25974378. [PubMed: 25974378]
62. Cooper S, Lewis S, Thornton JG, et al. The SNAP trial: a randomised placebo-controlled trial of nicotine replacement therapy in pregnancy - clinical effectiveness and safety until 2 years after delivery, with economic evaluation. *Health Technol Assess*. 2014; 18:1–128. PM:25158081.

63. Coleman T, Cooper S, Thornton JG, Grainge MJ, Watts K, Britton J, Lewis S. A randomized trial of nicotine-replacement therapy patches in pregnancy. *N Engl J Med*. 2012; 366:808–818. PM: 22375972. [PubMed: 22375972]
64. Schneider S, Huy C, Schutz J, Diehl K. Smoking cessation during pregnancy: a systematic literature review. *Drug Alcohol Rev*. 2010; 29:81–90. PM:20078687. [PubMed: 20078687]
65. Talih S, Balhas Z, Eissenberg T, Salman R, Karaoghlanian N, El HA, Baalbaki R, Saliba N, Shihadeh A. Effects of user puff topography, device voltage, and liquid nicotine concentration on electronic cigarette nicotine yield: measurements and model predictions. *Nicotine Tob Res*. 2015; 17:150–157. PM:25187061. [PubMed: 25187061]
66. Farsalinos KE, Spyrou A, Stefopoulos C, Tsimopoulou K, Kourkouveli P, Tsiapras D, Kyrzopoulos S, Poulas K, Voudris V. Nicotine absorption from electronic cigarette use: comparison between experienced consumers (vapers) and naive users (smokers). *Sci Rep*. 2015; 5:11269. PM: 26082330. [PubMed: 26082330]

EDUCATIONAL AIMS

- To review the changes in pulmonary function in offspring after in-utero smoke or nicotine exposure
- To consider the key mechanisms by which in-utero smoke/nicotine affects lung development
- To outline potential interventions (both smoking cessation and therapeutic) which might protect lung development and improve lung trajectories

DIRECTIONS FOR FUTURE RESEARCH

- Development of more effective smoking cessation strategies during pregnancy
- Evaluate the effect of the maternal use of electronic nicotine delivery systems on the developing lung and develop strategies to prevent such usage
- Development of strategies such as vitamin C supplementation to reduce the risk of adverse childhood lung outcomes in the face of in-utero smoke exposure
- Better understanding of the role of epigenetics in mediating lifetime effects of in-utero tobacco exposure on offspring lung health
- Identification of genetic factors that increase the risk of and effects of maternal smoking during pregnancy on offspring lung health

Figure 1. Prenatal nicotine exposure increases $\alpha 7$ nAChR expression in fetal monkey lung (134 days gestation)

Immunohistochemical localization of nicotinic receptor subtypes in 134- day fetal monkey lung. *a* and *c* from control fetus; *b* and *d* from nicotine exposed fetus. (*a*) Anti- $\alpha 7$ (MAB 319) showing brownish-red staining in fibroblast cell layer in cartilaginous airways and vessel walls. X 100. (*b*) In nicotine-exposed fetus, greatly enhanced $\alpha 7$ staining is seen in cartilaginous airway and vessel walls. X 100. No immunostaining was seen with nonimmune serum (not shown). (*c* and *d*) Higher-power view of smaller cartilaginous airways showing relatively little $\alpha 7$ in airway wall and epithelial cell lining in control lung, but intense staining in airway wall and epithelial cells (*arrows*) from nicotine exposed lung. X 400. AEC was used as immunoperoxidase substrate, and hematoxylin was used as counterstain. A, airway lumen; V, blood vessel lumen; C, cartilage; AEC, 3-amino-9-ethylcarbazole; MAB, monoclonal antibody. (Reprinted with permission from J. Clin. Invest (43)).

Figure 2.

Adult mice exposed to prenatal nicotine have significantly greater numbers of small bronchioles compared with unexposed control animals. C57BL6/J female mice were administered either untreated water or water containing 100 $\mu\text{g}/\text{ml}$ nicotine before timed breeding and through gestation. Lungs were obtained from age-matched offspring at 8 weeks of age. Whole lungs were embedded and sectioned in an isotropic, uniform random manner to create unbiased samples for examination. Airway diameter was measured for each visible bronchus and bronchiole. Mice exposed to prenatal nicotine had significantly greater numbers of small bronchioles, with diameters between 60–90 μm ($n = 8$ per group). Error bars denote SD. * $P < 0.05$ compared with control. (Reprinted with permission of the American Thoracic Society (47) The American Journal of Respiratory Cell and Molecular Biology is an official journal of the American Thoracic Society).

Figure 3. Effect of Maternal Smoking During Pregnancy on Newborn Pulmonary Function as Modulated by Maternal $\alpha 5$ Genotype (rs16969968)

Newborns whose mothers were homozygous for the risk allele in which amino acid 398 of the $\alpha 5$ nAChR is changed from Asp to Asn showed the largest decrease in TPTEF:TE comparing placebo to vitamin C treatment. Values presented are means and 95% confidence intervals. Asp/Asp indicates mothers homozygous for non-risk allele, Asp/Asn indicates heterozygous mothers, Asn/Asn indicates mothers homozygous for risk allele. P values comparing TPTEF:TE values from newborns of mothers randomized to vitamin C versus placebo are 0.02, 0.32, 0.07 and < 0.0001 for mothers of all genotypes, Asp/Asp, Asp/Asn and Asn/Asn respectively. P values are from linear mixed models (used to allow for unequal variance) adjusting for gestational age at randomization (≤ 16 versus > 16 weeks), birthweight, and gestational age < 37 weeks, and allowing for different SD's within each genotype. (Reprinted with permission from JAMA (33)).