Eur J Pediatr (2009) 168:897–905
DOI 10.1007/s00431-009-0967-3

REVIEW

Environmental tobacco smoke (ETS) and respiratory health in children

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Received: 25 November 2008 / Accepted: 26 February 2009 / Published online: 20 March 2009

Abstract Environmental tobacco smoke (ETS) is a major risk factor for poor lung health in children. Although parental smoking is the commonest source of ETS exposure to children, they are also exposed to ETS in schools, restaurants, public places and public transport vehicles. Apart from containing thousands of chemicals, the particle size in the ETS is much smaller than the main stream smoke, and therefore has a greater penetrability in the airways of children. Exposure to ETS has been shown to be associated with increased prevalence of upper respiratory tract infections, wheeze, asthma and lower respiratory tract infections. Even developing fetuses are exposed to ETS via the umbilical cord blood if the mother is exposed to tobacco smoke. The placenta also does not offer any barrier to the penetration of ETS into the fetus. The immune system in these babies is more deviated toward the allergic and asthmatic inflammatory phenotype and therefore makes them more prone to develop asthma later in life. An increased awareness of the harmful effects of ETS on children's health is warranted.

Keywords Environmental tobacco smoke (ETS) · Asthma · Respiratory tract infection · Children

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Introduction

It is estimated that around 1.3 billion people smoke worldwide [109], and this number is predicted to only increase in the forthcoming years, especially since smoking continues to increase amongst the youth and mainly amongst young girls [111]. An estimated 100 million people died due to tobacco consumption during the twentieth century. If the current smoking pattern continues, an estimated one billion people will die from tobacco-related causes during the twenty-first century [15, 83].

What is more worrying is the fact, that one does not need to be a smoker to be affected by the harmful effects of tobacco smoke. Passive exposure to tobacco smoke in children contributes significantly to morbidity and mortality. Children in particular, seem to be the most susceptible population for the harmful effects of environmental tobacco smoke. Children are exposed to tobacco smoke not only in their homes [108], but also in schools, restaurants, child care settings, cars, buses and other public places. However, exposure at home during parental smoking is likely the commonest source of environmental tobacco smoke (ETS) exposure to children. Exposure to ETS amongst children at homes have been reported to vary from 27.6% in Africa, 34.3% in South East Asia, 50.6% in Western Pacific, and up to 77.8% in Europe [111]. Airborne nicotine concentrations in homes have been shown to vary from less than 1 to over 10 μg/m^3, while those in offices have been shown to range from near 0 to over 30 μg/m^3 [106]. Levels in restaurants tend to be even higher, and concentrations in confined spaces like automobiles can be higher still. Measurements of ETS-associated respirable suspended particles in homes where smoking occurs range from a few microgram per cubic metre to over 500 μg/m^3, but those in restaurants can easily exceed 1,000 μg/m^3[106] due to increased numbers of smokers and poor ventilation. A recent survey reported that the percentage of children exposed to ETS in public places is around 86.1% in Europe, 64.1% in Western Pacific, and 43.7% in Africa [111].

The greatest contributor to ETS, especially for young children, is from mothers who smoke. From reports that are available, the prevalence of maternal smoking varies from 13% in Sweden [9] and 23.8% in the USA [22] to approximately 32% in Austria [2]. In fact, children can get exposed to the harmful components of tobacco smoke even before they are born, if their mothers smoke.

At least 150 epidemiological studies on ETS and non-cancer respiratory health effects in children have been published in the last 25 years. Several reviews [95–105] have already been published, and there is a strong consensus that ETS damages children's health and increases the prevalence of asthma and dry cough during childhood. Children living in a smoke-filled environment are more susceptible to upper and lower respiratory tract infections such as the common cold, middle ear disease [1, 19, 87], infections with respiratory syncytial virus, [29, 53, 56], bronchitis [68, 101], pneumonia, and other serious bacterial infections [77, 78, 96, 101]. Sudden infant death syndrome has also been directly linked to ETS exposure by numerous studies [30, 48, 69, 114]. The literature is replete with studies on the role of ETS exposure on childhood asthma [8, 12, 39, 49, 55, 66, 74, 97, 100]. During the past decade, ETS exposure has been shown to be increasingly associated with behavioral and cognitive problems in children [16, 17, 113]. ETS exposure has been shown in some studies to adversely affect physical growth in young children [18, 70]. Although smoking and ETS exposure is a well-known risk factor for cancer in adults, there is emerging evidence that it may also be associated with childhood cancers, such as leukemia and lymphoma [7, 64, 73, 88].

This review highlights the effects of ETS on respiratory health in children and is based on a PubMed database search from 1990 up to October 2008. The key words used for this review were environmental tobacco smoke, second hand smoke, maternal smoking, parental smoking, smoking at home, smoking at school, tobacco smoke and children, tobacco smoking and genetic susceptibility.

Effect of environmental tobacco smoke on fetuses

The harmful effect of ETS begins even before the child is born. Circulating nicotine from the mother's blood has been shown to reach the fetus by crossing the placenta. The harmful particulate matter present in the ETS also reaches the fetus through the blood. This decreases the amount of oxygen and nutrients supplying the fetal tissues. Maternal smoking or ETS exposure to pregnant mothers has been shown to cause premature delivery, childhood malformations and low birth weight in the third trimester [61, 94]. It has been previously reported that the placenta does not offer a protection barrier for the passage of nicotine and other harmful pollutants present in ETS [51, 115]. Increased cotinine levels have been observed in the amniotic fluid of pregnant non-smokers exposed to ETS, as well as in the urine of their newborn infants on the first day of life [40], confirming that the fetus is exposed to the components of maternal ETS exposure. Circulating nicotine has been shown to affect the placental function by inducing the release of norepinephrine and epinephrine into the maternal blood, thereby causing decreased blood flow to the placenta [59]. High levels of carboxyhaemoglobin have been reported in the blood of the mother and the fetus, either from active smoking or ETS exposure. Increase carboxyhaemoglobin levels reduce blood flow and decrease the delivery of oxygen and nutrients to the fetus. This may have an effect on cell growth and development [52]. Although fetal hypoxia and ischemia are the major contributors to developmental lung defects, nicotine has also been implicated in various studies to have a direct effect on fetal development by impairing the maturation of the lungs [6].

Exposure to ETS during pregnancy therefore has deleterious effects on the growing fetus, thereby predisposing the newborns to increased respiratory morbidity after birth (Table 1).

Effect of ETS on childhood asthma

Babies born to mothers who smoked during pregnancy have been shown to have increased risk of wheezing (40%) [58, 82], increased risk of asthma (83–246%) [28, 38, 60, 62, 82] and increased prevalence of airway hyperresponsiveness [27, 42, 102, 116]. These observations have been reported from UK [82], USA [60], Australia [116], India [41] and Sweden [27].

A study conducted in 3-year-old children who were exposed both pre- and postnatal ETS reported increased prevalence of wheeze (OR 1.14; CI 1.07–1.21) and increase use of cough mixtures (OR 1.07; CI 1.01–1.14), when compared to children born to non-smoking parents [44]. Children exposed to ETS show an increased risk of development of asthma and worsening of pre-existing asthma. In a study based on the birth cohort in Finland that included almost 60,000 children, the risk of developing asthma amongst children 7 years of age increased in a dose-dependent manner with the mothers' smoking rates during pregnancy: OR 1.23 (95% CI 1.07–1.42) for <10 cigarettes/day and OR 1.35 (95% CI 1.13–1.62) for >10 cigarettes/

Table 1 Effects of environmental tobacco smoke (ETS) in children

Study	Design/population	Sample size	Source of cohort or controls	Outcome
Vahidnia et al. [107]	Survey of pregnant women from the USA	10,108	Pregnant women enrolled in the child health and development studies	Childhood malformations
Johansson et al. [43]	Cohort study in children from Sweden	8,850	1—children with non-smoking mother during pregnancy, 2—fetal exposure, 3—postnatal exposed, 4—pre- and postnatal exposed	Wheezing and rhinitis by 3 years of age
Keskinoglu et al. [46, 47]	Case control in children from Turkey	300	150 of children with LRTIs and 150 healthy children	Increase incidence of lower respiratory tract infections (LRTIs)
Hugg et al. [33]	Cross sectional in children from Finland and Russia	512 Finnish and 581 Russian	Children aged 7–16 years from neighbouring towns across the border of Imatra in Finland and Svetogorsk in Russia	Increase risk of asthma
Pattenden et al. [82]	Cross sectional in children from Austria	53,879	Children with mothers who smoked during pregnancy, parental smoking in the first 2 years, current parental smoking	Increase wheeze, asthma, bronchitis and nocturnal cough
Zlotkwaska and Zedja [118]	Cross sectional in children from Poland	1,561	School children aged 9–11 years	Increase risk of bronchitis, wheeze and attacks of dyspnoea
Jaakkola and Gissler [37]	Cohort study in children from UK	58,841	Children singleton births were followed for 7 years using nationwide registries	Increase the risk of asthma during the first 7 years of life
Blizzard et al. [5]	Cohort study in infant from Australia	4,486	Infants from birth to 12 months of age for hospitalisation with respiratory infection	Increase risk of infant hospitalisation
Lee and Galant [57]	Cross sectional in children from the USA	5,762	Children from the 4th, 7th and 10th grades in southern California	Increase prevalence of asthma
Gold et al. [28]	Birth cohort in children from the USA	499	Children of asthmatic/allergic parents	Wheeze episodes in the first year of life, lower respiratory illness in the first year of life, low birth weight
Jedrychowski and Flak [40]	Cohort study in children from Poland	1,129	Children 9 years old exposed congenitally and postnatally to ETS	Increase risk of respiratory illnesses
Chen et al. [11]	Cross sectional in children from Canada	892	Children 6–7 years old living in Humboldt, Saskatchewan	Increase risk of asthma in allergic children
Lewis et al. [58]	Prospective study in children from the UK	15,712	Children born in Britain during 1 week of April 1970	Wheezing by 5 years of age
Martinez et al. [65]	Cross sectional in infants from the USA	1,200	Infants enrolled at birth between 2980 and 1984	Increase incidence of wheezing lower respiratory tract illnesses during the first year of life
Tager et al. [104]	Cross sectional in infants from the USA	97	Infants before 6 months of age	Lower levels of VFRC were associated with an increased frequency of lower respiratory illness LRI, especially in female infants
Young et al. [116]	Cross sectional in infants from Australia	63	Infants at a mean age of 4 1/2 weeks	Present airway responsiveness in infants

day [37]. A California study [57] that investigated 5,762 children who were studying between the fourth and tenth grades found a significant association between in utero and maternal smoking without subsequent postnatal, exposure environmental tobacco smoking and emergency room visits during the first year of life, OR 3.4 (95% CI 1.4–7.8). In contrast, current exposure to ETS was associated with 1.9-fold (95% CI 1.2–3) increased odds of emergency room visits.

A cohort study of 9-year-old children from Poland found strong evidence that children exposed to ETS in their homes were more susceptible to acute respiratory tract illnesses when compared to unexposed children. The observation of a dose–response relationship between ETS exposure and respiratory illness [for lower ETS exposure (odd ratio OR=1.32, 95% CI 0.83–2.1), for higher ETS exposure (OR=1.74, 95% CI 1.06–2.87)] supports a causal explanation for the association observed. Moreover, increased exposure to ETS and a history of associated allergy more than tripled the risk of acute respiratory tract illness (OR=3.39, 95% CI 1.93–5.93) [40]. Similar observations have been reported from another study in Poland [118] and in Turkey [46].

In a study of 3,909 school children in India, parental smoking was found to be associated with childhood asthma with an adjusted odds ratio of 1.57 (95% CI 1.09–2.31; Cheraghi M, abstract submitted to ERS conference, 2009). The risk of development of respiratory symptoms has been reported when either the father or mother [11] smoked in the house. Moreover, a large body of epidemiological studies indicates that early exposure to passive smoking, especially from smoking mothers increases the risk of developing asthma in childhood [26, 33, 35, 36, 79, 82, 110] (Table 1).

Effect of ETS on risk of respiratory tract infections in children

Apart from its effects on development of asthma, maternal and ETS exposure has been shown to be associated with impaired lung function and increase in respiratory symptoms in infants and young children [96]. Several studies have also shown that parental smoking is associated with an increased incidence of both upper and lower respiratory tract infections [29, 47, 50, 65, 101].

Exposure to ETS increases the risk of hospitalisation for respiratory disease amongst infants. In a large cohort study involving 4,486 infants, Blizzard et al. reported that infants whose mothers smoked in the same room had a 56% increased odds of being hospitalised, while in those infants whose mother smoked while holding the infant was 73% higher and if the mother smoked while feeding the infant, the odds increased to 95% or higher [5]. These observations clearly highlight the risk of increased hospitalisation for infants if their mothers smoke.

There were increased risks for bronchitis and hospitalisations amongst children whose mothers smoked. The harmful effects of ETS seem to be more prevalent during exposures in the fetal period than in the early neonatal period, since the effect seems to be more pronounced amongst babies whose mothers smoked during pregnancy as compared to babies whose mothers smoked after the babies were born. These findings indicate that the crucial exposure period for the harmful effects of ETS seems to be in the prenatal period, when lung growth seems to be highest [67, 104] (Table 1).

Effect of ETS on lung function in children

Several studies have reported that prenatal (maternal smoking) and/or postnatal exposure to ETS adversely affects the lung function of children [13, 23, 71, 92, 98]. Hanrahan et al. studied the impact of maternal smoking on lung function changes (functional residual capacity) in new born infants using helium dilution measurement and reported that maternal smoking during pregnancy was associated with significant reductions in forced expiratory flow rates, thereby indicating that maternal smoking impairs in utero lung development [31]. In a follow-up study, Tager [104] showed that the decreased ventilation at functional residual capacity seen with prenatal smoke exposure correlated directly with increased lower respiratory illnesses in the first year of life.

In a large international study from nine countries in Europe and North America involving more than 20,000 children aged between 6 and 12 years, Moshammer et al. [71] reported that smoking during pregnancy was associated with significant decreases in lung function parameters such as FEV_1 and MEF_{25}. A 4% lower maximal mid expiratory flow (MMEF) corresponded to a 40% increase in the risk of poor lung function (MMEF 75% of expected). Associations with current passive smoking were weaker though still measurable, with effects ranging from 0.5% (FEV_1) to 2% maximal expiratory flow (MEF50). This large epidemiological study confirms the long-lasting effects of smoking during pregnancy on the decline in lung function of children, an effect which was greater than current or past ETS exposure. Poor lung function in childhood has lasting effects because it predicts a worse prognosis of asthma in adulthood.

In a large study involving 5,933 school children born to mothers who smoked during pregnancy, Gilliland et al. [24] reported that in utero exposure to tobacco smoke was associated with a significant decrease in lung function during childhood, and that this effect was further augmented in children who had asthma. This in utero effect was stronger than subsequent ETS exposure after birth. Similar observations have been reported in a study involving 8,800 children 8–12 years old in the USA [14]. These observations suggest that the effect of prenatal exposure to tobacco smoke can last at least up to adolescence. Exposure to ETS after birth also has a significant impact on lung health.

A study conducted in Finland found that exposure to ETS was associated with a decline in peak expiratory flow rate and increase in respiratory symptoms among asthmatic children [89]. Mannino and colleagues in the USA also found a strong association between higher serum cotinine levels and worse lung function among children aged 8 to 16 years [63].

Considering the high number of children exposed to maternal smoking in utero and the even higher number exposed to passive smoking after birth, this risk factor for reduced lung function growth remains a serious paediatric and public health issue.

Why is ETS more harmful than mainstream cigarette smoke?

ETS is one the commonest and harmful forms of indoor air pollutants. ETS is composed of midstream smoke (SS), emitted from the shouldering tobacco between puffs and exhaled mainstream smoke (MS) from the smoker. When a cigarette is smoked, roughly half of the smoke generated is SS and the other half MS. ETS, SS, and MS are complex mixtures of over 4,000 chemicals, at least 50 of which are known to cause cancer, ischemic heart disease and respiratory diseases like asthma and COPD in humans [106].

A major quantitative difference is that ETS is a diluted mixture of SS and exhaled MS. In addition, because SS is produced at lower temperatures and under more reducing conditions than MS, many carcinogens and other toxicants are generated in greater amounts in SS than in MS. Therefore, SS contains more potent carcinogens than MS per unit of tobacco smoked [4]. There are also differences between MS and ETS in the physical state of various constituents. For example, nicotine is present primarily in the particulate phase in MS and in the vapour phase in ETS. Also, as ETS ‘ages’ over time, the constituents of the particle phase shift to the vapour phase [4, 90, 99]. Furthermore, particle sizes are smaller in ETS (0.01–1.0 µm) than in MS (0.1–1.0 µm), and are therefore more likely to penetrate deeper into the airways. Overall, SS and ETS smoke therefore seems to be more harmful than the MS smoke [43].

Why are babies in utero and children more susceptible to the harmful effect of ETS?

Children are particularly vulnerable to many environmental threats, including a contaminated and unsafe physical environment. This heightened susceptibility derives primarily from the unique biological features that characterise the various stages of development from conception to adolescence [103]. Cell growth is particularly rapid in the embryo. Lung growth occurs in the fetus with the help of interactions of various chemical processes. Exposure to toxicants which enter via the umbilical cord in mothers exposed to tobacco smoke will not only provide an opportunity to interface with the lung growth, but also increase the risk of causing cell mutations and congenital anomalies [84]. Although it was earlier believed that the placenta offers a barrier for the passage of these toxic chemicals, it is no longer true, since several studies have shown the presence of various toxic chemicals circulating in the umbilical cord [34].

Children's metabolic pathways, especially in the first months after birth, are immature and still developing. As a consequence of this biochemical immaturity, children's ability to detoxify and excrete chemicals differs from that of adults. Children are less able than adults to deal with toxic chemicals and are thus more vulnerable to them [54].

Compared to adults, children not only have higher metabolic rates, but also inhale much greater volumes of air per kilogram body weight than adults. For example, a child who is 1 year old inhales 0.53 M^3 kg/day of air as compared to an adult, who inhales 0.2 m^3/kg/day. This is roughly equivalent to the volume of air an adult would inhale if he is performing heavy aerobic exercise. The fact that children inhale greater volumes of air than adults means they inhale greater amounts of air pollutants than adults. Moreover, the size of harmful particulate matter <1 µm is just right for it to enter even up to the terminal airways and alveoli [72]. One addition factor that increases the exposure to ETS is that they often sit closer to parents, family members or care givers, and are therefore closer to the source of pollutants than other passive smokers [103].

ETS exposure and genetic susceptibility

Out of 100 people who smoke regularly, only 15–20% develop chronic obstructive pulmonary disease, indicating that genetic factors likely play an important role in determining the susceptibility to the harmful effects of tobacco smoke. On similar lines, genetic factors may also determine children’s susceptibility to the harmful effects of ETS [75, 112].

The harmful effects of ETS are mediated via the generation of reactive oxygen species, which induce oxidative stress that further leads to the generation of various inflammatory responses in the airways and lung parenchyma. Amongst the different antioxidants that dampen the oxidative stress generated by ETS, the glutathione system appears to be the most protective. A number of genes involved in xenobiotic detoxification systems, antioxidant responses, and damage repair mechanisms for tobacco smoke have been identified [21, 93]. Glutathione *S*-transferase (GST) M1 enzyme product is involved in detoxification of both reactive tobacco metabolic intermediates and reactive oxygen species and is the most important antioxidant protecting the airways from oxidative damage [32]. The amount of glutathione synthesised in the airway mucosa is under genetic control and it has been known for several years now that individuals who possess genes that impair the synthesis of glutathione have an increased susceptibility to the harmful effects of environmental air pollutants.

GSTM1 null genotype has been shown to modify the effects of fetal tobacco smoke exposure on childhood asthma and wheezing [25]. The adverse effects of in utero exposure to maternal smoking on a broad range of asthma and wheezing outcomes are largely restricted to children with GSTM1 null genotype. These findings indicate that there are important long-term effects of in utero exposure in a genetically susceptible group of children. Based on these findings, GSTM1 genotype may be an important susceptibility factor for childhood asthma after exposures during the fetal period.

Kabesch et al. genotyped a total of 3,054 school children from Germany and looked for deficiencies of the GST isoforms M1 and T1. They found that amongst children exposed to ETS, those who lacked the GSTM1 allele had a significantly increased risk for current asthma (OR 5.5, 95% CI 1.6 to 18.6) for wheeze (OR 2.8, 95% CI 1.3 to 6.0), for current wheeze (OR 4.7, 95% CI 1.8 to 12.6), and for shortness of breath (OR 8.9, 95% CI 2.1 to 38.4) as compared to GSTM1-positive individuals without ETS exposure. GSTM1 and GSTT1 deficiency and exposure to ETS therefore are significantly associated with increased adverse health effects [45].

The BREATHE study, which was initiated in 2006 to study the risk factors for asthma involving 504 subjects between 3 and 21 years from Scotland, reported that children who are null for GSTM1 or homozygous for the GSTP1Val105 allele were more susceptible to develop asthma following exposure to ETS than those with more intact glutathione *S*-transferase status. Amongst the 13–21-year-olds, GSTM1-null status was found to interact with environmental tobacco smoke exposure and substantially reduce peak expiratory flow rate. The effects of exposure to environmental tobacco smoke in GSTM1-null children with asthma could be cumulative over time, resulting in detrimental effects on peak expiratory flow rate in 13–21-year-olds with asthma [81].

Cellular and molecular mechanisms of how ETS adversely affects respiratory health in children

ETS exposure and phagocytic function

Nicotine has been shown to inhibit the production of oxygen radicals from neutrophils and monocytes/macrophage cells and thereby suppress their phagocytic activity [76, 80, 85]. Roth et al. [85] reported that phagocytic activity of alveolar pulmonary macrophage was significantly diminished in smokers as compared to non-smokers. In vitro studies by Pabst et al. [80] have also demonstrated that nicotine inhibits the phagocytic activity of neutrophils and monocytes from the oral mucosa of those who chewed smokeless tobacco. In vivo studies by Numabe et al. [76] later confirmed these findings in human volunteers.

Exposure to particulate matter air pollution from motor vehicular exhausts has been shown to impair the phagocytic function of alveolar macrophages and neutrophils [86]. This is largely because the macrophages and neutrophils are overloaded with phagocytosing these particles and therefore do not have enough phagocyte capacity for ingesting microorganisms that enter the respiratory tract. Along the same lines, particulate matter present in ETS may hamper the phagocytosis of microorganisms and thereby increase the susceptibility to develop respiratory tract infections.

ETS exposure, T-cell function and immunoglobulin production

There has been tremendous interest in understanding the mechanisms by which environmental tobacco smoke (ETS) causes harmful effects on the fetus as well as in children. It is hoped that this understanding will likely help in developing interventional strategies to reduce the harmful effects of environmental tobacco smoke. One of the mechanisms that have been suggested is the effects of nicotine on T-lymphocyte function. The activity of T lymphocytes is primarily divided into two main types, the Th1 response, which is responsible for enhancing cell-mediated immunity and the Th2 response that is responsible for driving allergic inflammatory responses. Interestingly, nicotine has been shown to increase the production of cellular mediators that not only enhance Th2 activity [3, 20, 91, 117] but also augment the production of immunoglobulin E that amplifies the allergic immune response [10]. This may well explain the mechanisms of nicotine-induced increased allergic and asthmatic inflammatory references.

Conclusion

Exposure to environmental tobacco smoke has a significant detrimental effect on the respiratory health of children. Components of ETS are more harmful than the mean stream smoke, not only because they contain increased amounts of unburnt substances, but also because the particle sizes are much smaller and therefore enter deeper into the lung tissue.

Babies born to mothers exposed to ETS show poor lung growth and increased risk of developing asthma and respiratory tract infections. Even after birth, children are particularly most vulnerable to ETS because the lung structures and immune system are still growing and the defence mechanisms are relatively weak. There is now sufficient evidence to infer a casual relationship between parental smoking and childhood asthma and presence of symptoms such as cough, phlegm, wheeze and breathlessness. Paediatricians need to be aware about these adverse effects associated with ETS exposure in children, so that they can counsel the parents, who are the major sources of ETS for children.

Several studies have investigated the mechanisms by which ETS causes adverse health effects in children. ETS has been shown to reduce the activity of immune cells and deviate these responses to those that are normally seen in allergic responses, thereby implying that ETS enhances allergic inflammatory responses. Although these studies have shed light on possible mechanistic aspects, more research is needed to better understand these mechanisms. Not all children seem to be equally susceptible to the harmful effects of ETS. There seems to be a genetic predisposition especially with the genes associated with glutathione, an important lung antioxidant. Children, who have GSTMI null genotype, seem to show an increased susceptibility to ETS. A further understanding into these genetic factors will help detect susceptible children, so that further exposure to ETS in these children can be avoided.

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