Review Article
Indian J Med Res 120, November 2004, pp 443-453

The relationship between tobacco smoke & bronchial asthma

S.K. Jindal & Dheeraj Gupta

Department of Pulmonary Medicine,Postgraduate Institute of Medical Education & Research Chandigarh, India

Received May 12, 2004

Bronchial asthma is a common disease and an important cause of morbidity among both children and adults. Tobacco smoking, both active and passive *i.e.*, exposure to environmental tobacco smoke (ETS) has got important effects on asthma. Smoking by adults causes bronchial irritation and precipitates acute episodes. It also increases bronchial responsiveness and causes airway sensitization to several occupational allergens. Smoking may also increase the disease severity. Continued smoking by adult asthmatics is the likely cause of irreversibility of airway obstruction and development of chronic obstructive pulmonary disease. ETS exposure affects asthma in a similar fashion. Parental smoking is commonly associated with increased asthma symptoms, respiratory infections, acute episodes and frequent hospitalization of children. Bronchial responsiveness and airway sensitization may also increase. Childhood exposure to smoking is also considered as a risk factor for the development of asthma. Similarly, *in utero* exposure to maternal smoking may be independently responsible for early onset asthma. ETS exposure in adult asthmatics from smoking by spouses, siblings or colleagues is equally troublesome. There is increased morbidity and poorer asthma control. Asthmatic symptoms sharply decline after the ETS exposure is reduced.

Key words Bronchial asthma - bronchial hyper-responsiveness - chronic obstructive pulmonary disease - environmental tobacco smoke - tobacco smoking

Bronchial asthma is a common disorder which affects about 4 per cent of adult male and about 1.3 per cent of adult female population in north India[1]. Prevalence of asthma in adults is reported to be generally similar from Mumbai *i.e.*, 3 per cent physician-diagnosed asthma[2]. In children, however, the prevalence figures are markedly variable from about 1.8 to 12.4 per cent in different reports[3-5].

Tobacco smoking and exposure to environment tobacco smoke (ETS) are some of the several important variables which are likely to affect the incidence, recognition and clinical presentation of asthma. Smoking adds to the morbidity besides influencing the prevalence and natural history of asthma.

Role of smoking in asthmatic and atopic individuals has drawn a greater interest in the recent times because of its presumptive role in the pathogenesis of chronic obstructive pulmonary disease (COPD). There is at least some evidence available now which suggests a possible link between atopy, asthma, smoking and COPD. Almost half a century ago, the Dutch investigators had proposed that COPD developed in smokers from an exaggerated damage to the airways in patients with an underlying atopic diathesis, what was popularly known as the Dutch hypothesis[6]. To some extent, the Dutch hypothesis is revisiting the airway disorders scenario[7]. It is therefore, important to dwell upon the issue of asthma-smoking association.

Table I. Role of active smoking in asthma in adults

1.	Increased bronchial responsiveness
2.	Frequent bronchial irritation symptoms
3.	Increased sensitization to occupational agents
4.	Aggravation of acute episodes
5.	Association with asthma severity
6.	Risk factor for asthma ?
7.	Exaggerated decline in lung functions
8.	Role in development of fixed airway obstruction and COPD ?

Table II. Environmental tobacco smoke exposure and asthma

1.	Aggravation and occurrence of increased prevalence of respiratory symptoms
2.	Bronchial hyper-responsiveness in adults
3.	Aggravation of asthma symptoms
4.	Precipitation of acute episodes
5.	Risk factor for development of asthma (both children and adults)

EFFECTS OF ACTIVE TOBACCO SMOKING ON AIRWAYS (TABLE I)

Relationship with COPD

The deleterious effects of smoking on airways are well established. Tobacco smoking induces airway inflammation with influx of a variety of inflammatory cells such as the neutrophils, lymphocytes, eosinophils, mast cells and macrophages. Various inflammatory mediators are released which include lipids, chemokines, cytokines and growth factor[8]. The cytokines along with different proteolytic enzymes cause inflammatory damage which is further augmented by oxidative stress. The resultant airway injury is responsible for COPD which, unlike asthma is an irreversible and progressive cause of airway obstruction[8-10]. There are studies which support a partial reversibility of airway obstruction in patients with predominant eosinophilic inflammation[11,12]. It has been shown that those COPD patients who demonstrate eosinophilia in sputum or broncho-alveolar lavage (BAL) fluid show significant clinical response to bronchodilatory and anti-inflammatory therapy[12,13]. This group of COPD patients have greater nonspecific bronchial hyper-reactivity (BHR) to inhaled histamine or methacholine and a higher serum IgE levels[14-16]. Higher airway eosinophilia is also associated with expression of interleukin-5 proteins in asthma and in exacerbation of COPD[17].

It can be assumed that the COPD patients who demonstrate eosinophilic airway inflammation had either an atopic diathesis or were asthmatics before they started smoking. Smoking in the presence of atopy (or asthma) causes an exaggerated decline in lung function and fixed airway obstruction leading to the development of COPD. There are other investigators however who dispute the role of eosinophils in COPD. According to this belief, the presence of eosinophils in COPD may only suggest the presence of concurrent asthma[11,12].

Role of smoking on bronchial responsiveness and asthma

Bronchial hyper-responsiveness is the hallmark of asthma although it is also demonstrable in conditions other than asthma. There is enough evidence to show an increased bronchial responsiveness in smokers in a number of population surveys[18]. It has been also demonstrated in clinical studies including from our Centre in both symptomatic and asymptomatic subjects[19-21]. But the relationship between smoking and BHR remains debatable. It is unclear whether tobacco smoking is causally related or it only unmasks and aggravates the pre-existing bronchial responsiveness. Smoking causes a lot of annoyance and bronchial irritation to most smokers and may also increase bronchial responsiveness. Smoking may also cause or increase sensitization to several occupational allergens although not to common inhalational allergens[22]. It has been also shown to increase the incidence of asthma on exposure to some occupational agents[23]. Available data suggest that sensitization to common allergens is in fact reduced in smokers or that smokers are less likely to develop new sensitization[24,25]. On the other hand, these observations could be attributed to the reluctance of atopic or asthmatic patients to continue or start smoking because of an apparent increase in respiratory symptoms on exposure to smoking[26].

Smoking as a risk factor for asthma has remained debatable. The true asthmatics are generally believed to be nonsmokers and in epidemiological studies smoking is considered almost as an exclusion criterion for diagnosis of asthma[27]. Evidence of an association between smoking with asthma is unequivocal[28,29]. Smoking may perhaps play the role of a trigger and act as an aggravating factor of asthma[30]. Its role as a potential risk factor, selection factor (healthy smoker effect) and modifying factor (severity) of asthma was studied in the

epidemiological study on the genetics and environment of asthma (EGEA)[31]. Active smoking was associated with asthma severity but no clear relationship of smoking habits with asthma were observed in first degree relatives[31]. Further, asthmatic subjects who smoke have been reported to be resistant to inhaled corticosteroid therapy[32]. There was no change in other lung functions, or eosinophil markers even with high dose inhaled budesonide in asthmatic patients who smoked[32].

INVOLUNTARY SMOKING AND ASTHMA (TABLE II)

Children

Respiratory symptoms: Ample data are available on the role of involuntary smoking on asthma more than that available on active smoking by patients. Smoking is an active trigger of asthma and therefore not many asthma patients would venture to start or continue with smoking. Further, an association between current smoking and asthma is masked by the self-selection bias either in favour of starting or quitting smoking[33].

Involuntary smoking generally refers to the exposure of non-smoker individuals to environmental tobacco smoke (ETS) caused by smoking of parents, sibs, spouses, friends and others living, working or staying in close company. Such an exposure has been associated with aggravation and occurrence of increased prevalence of respiratory symptoms, acute respiratory infections, bronchial hyper-responsiveness and asthma, especially in children[34-36]. In addition, there is decreased lung function and a small reduction in the rate of lung growth and development in children of smoking parents.

Annoying and irritation symptoms of the eyes, nose, throat and airways in nonsmokers on exposure to ETS in the indoor environment such as the households and airline flights are common[37-39]. Increased prevalence of cough, phlegm, wheeze, asthma and chest colds on ETS exposure were reported in cross-sectional studies in children from several cities of the United States[40-42]. Maternal smoking was shown to have a 20-35 per cent increase in the rate of respiratory illnesses and symptoms in children while the paternal smoking was associated with a smaller, but substantial on successive annual examinations[43].

Bronchial asthma: Most of the earlier studies related ETS exposure with bronchospasm in asthma. Majority of parents of asthmatic children reported that cigarette smoking aggravated asthma of their children and that elimination of smoking generally led to improvement of symptoms[44] . On the other hand, no significant relationship of respiratory symptoms of nonsmoker adults with the smoking status of family members was observed in other studies[45-47]. A weak association for wheeze and dyspnoea with ETS exposure from spouses were observed among smoking women from US and France[48].

Several investigators had reported a relationship of parental smoking with subsequent development of asthma in their children[49-52]. Children of mothers with 12 or fewer years of education and who smoked ten cigarettes or more per day, were 2.5 times more likely to develop asthma than those of non-smoking mothers[49]. It was reported that the prevalence of parent-reported asthma increased from 5 to 7.7 per cent and of the functionally impaired asthma from 1.1 to 2.2 per cent in children if their mothers were smokers[51].

Maternal smoking of above half a pack of cigarettes per day was identified as an independent risk factor for childhood asthma developing in first year of life[52]. Similar observations were reported in other studies where asthma symptoms and their severity in children were related with the maternal smoking[53-55].

Studies on the effects of parental smoking on childhood asthma include the longitudinal studies on incidence of asthma as well as the case control studies[56]. A birth cohort of 762 infants was followed in the US through the first three years of life and also at the age six[57]. The incidence of wheezing was looked at in the three subsets: (*i*) those who had wheezing before the age 3 (transient wheezing); (*ii*) those who developed wheezing after the age 3 (late onset wheezing); and (*iii*) those who had wheezing both before and after the age 3 *i.e.*, persistent wheezing. The incidences of early onset, transient wheezing were significantly associated with maternal smoking (>10 cig/day). The persistent wheeze subgroup was also at a higher risk with maternal smoking but the confidence limits did not exclude occurrence by chance. These associations were independent of sex and ethnicity or presence of eczema, non-infective rhinitis and maternal asthma[57].

The cumulative incidence of wheezing among children of smoking mothers was increased in a study based on the parental recall at the age of five years in the nationwide, British 1970 birth cohort[58]. Another study from the same cohort, excluded wheezing in the first year of life and included information from follow up studies at 5 and 10 yr of life, wheezing was separated as wheezy bronchitis and wheeze associated with asthma [59]. Maternal smoking was associated with only wheezy bronchitis and not asthma. There was little relationship between parental smoking and incidence of asthma in a smaller longitudinal study on the follow up of 722 children over a mean period of nine years[60].

In a meta-analysis of longitudinal studies on early and late incidence of asthma and wheezing, maternal smoking had a stronger and significant association in the first 5-7 yr of life than for incidence in school years or the entire childhood excluding the first year[56]. In studies where effects of maternal and paternal smoking were compared, there was a consistent association with mother's smoking, but not with smoking by fathers[56]. Several studies that appeared subsequent to this meta-analysis had also shown similar results[61-64].

We had conducted a survey for prevalence of asthma among adolescent school children at Chandigarh[3]. Using a previously standardized questionnaire, data from 9090 students in the 9 to 20 yr age range were analyzed[1,3]. More students with asthma (41%) had parents or other family members smoking at home compared to non-asthmatics[3]. Another study was undertaken in the neighboring state of Haryana, on 2000 school children in rural setting using a questionnaire of the ISAAC[5,65]. Multivariate analyses showed passive smoking as an important risk factor associated with asthma in children, the others were pets at home and the absence of windows in the living room[5,65]. A smaller hospital based study in the children failed to show any significant risk of developing asthma with passive smoking[66].

There is significant evidence in favour of ETS exposure as a risk factor of asthma[67-69]. Childhood cigarette smoking and ETS exposure, even at low levels of exposure were independently associated with asthmatic symptoms[67]. It has been suggested that ETS exposure in early life combines with the hereditary factors to produce an early onset of persistent wheeze and its absence might delay, but not prevent the onset of wheezing in children with atopic heredity[70]. Genetically, predisposed children were at higher risk of developing sensitization against home dust mites when exposed to ETS[71].

The critical period of ETS exposure whether during pregnancy or later and risk of developing asthma has also remained a matter of debate. The prevalence of respiratory symptoms in school children was related more closely to the current maternal smoking than to the past smoking by the mother [56]. Other studies on this issue have shown conflicting results. In a study of 1129 Polish children, both upper and lower respiratory infection were found to relate to current maternal smoking than to smoking by the mother during pregnancy[72]. In another study in 705 students of fifth grade, it was the maternal smoking during pregnancy rather than the current smoking by mother which was associated with asthma[73]. Interestingly, wheezing was inversely associated with current maternal smoking[73]. A large Scandinavian Study on 15, 962 children of 6-12 yr age group had also showed similar results in which asthma attacks, dry cough and asthma treatment were positively associated with ETS exposure during the first two years of life and inversely related to current smoking[74]. *In utero* exposure to ETS as the cause of impaired lung function, bronchial hyper-reactivity and early onset asthma have been supported in several other studies[75,76].

The large body of evidence supporting an adverse effect of ETS exposure in children from smoking parents underlies the great importance to improve tobacco control practices among paediatricians and family physicians[77-79]. Control of ETS exposure in children has been also shown to improve the benefits of available asthma medication and health outcomes[80].

The data on BHR on ETS exposure in children are contradictory[81-83]. It was demonstrated in sedated neonates that the concentration of histamine causing 40 per cent fall in lung function indices was higher in the group of neonates who did not have family history of asthma and had non smoking parents compared to the other groups where family history of asthma and/or smoking parents were present[81]. In a meta-analysis of fifteen studies on effect of ETS exposure on BHR in school children, there was no obvious relationship between the provocation used for eliciting the BHR[82].

It can be concluded that the current evidence on effect of ETS on BHR may suggest only a small but real increase in risk and this may be only one of the possible mechanisms involved in this causality.

Allergic sensitization: It was earlier believed that ETS exposure could lead to allergic sensitization in non atopic individuals. The conclusions were based on the reported incidence of asthma/wheezing on exposure to ETS. But ETS exposure may lead to asthma/wheezing by mechanisms other than allergy. In a review of 36 studies on IgE, skin prick positivity, hay fever or eczema separately from studies on asthma in order to study the association of ETS exposure and allergy more directly, the balance of evidence did not support a positive association of atopy with parental smoking either before or after birth[84]. Other studies have shown a slightly reduced risk of eczema among the children of smokers[85,86]. Similarly, an inverse relationship with maternal smoking was seen in a study on skin prick test among infants of atopic parents[87].

Acute asthma: There is a strong association between passive smoking and emergency room visits, the presence of one smoker in the household increased the mean annual frequency of child's emergency room visits[88]. But passive smoking was not associated with hospitalization, abnormalities of pulmonary function or frequency of days with asthma. In another study, exposure to ETS was assessed by a questionnaire and urinary cotinine level; exacerbations of asthma increased with exposure to ETS whether such exposure was reported by a parent or identified on the basis of urinary cotinine level[89].

ETS exposure in adults

Clinical asthma: The effects of ETS exposure in adult asthma patients are less well understood despite the fact that many patients regard ETS as a major exacerbating factor. Precipitation and/or aggravation of nasal and respiratory allergy symptoms on ETS exposure has been reported in some studies[90,91]. We compared the indices of morbidity and control of asthma in adult asthma patients exposed versus not exposed to ETS from spouses or colleagues[92]. There was an increased morbidity in ETS exposed individuals as assessed by the number of visits to the emergency room, acute episodes, requirement of parenteral drugs and of oral corticosteroids[92].

Relation of asthma with ETS exposure in adults has earlier been assessed in inhalation challenge studies. Shortness of breath, wheezing or tightness of the chest were experienced after 2 h of ETS exposure by 5 of 14 asthmatic patients, whose baseline pulmonary function demonstrated only slight airflow obstruction previously[93]. No significant changes of dynamic lung volumes were observed between sham and smoke exposure periods[93]. In another study, ten each of asthmatic patients and control subjects were exposed to ETS for an hour, the control subjects showed no change in pulmonary function, whereas the asthmatic group demonstrated a significant linear decrease during ETS exposure[94].

In the Swiss Study on Air Pollution and Lung Diseases in Adults (SAPALDIA), incident asthma was found to be associated with self-reported ETS exposure in the previous 12 months[95]. A dose response relationship was also demonstrated. In another study, a significant association of self-reported ETS exposure and obstructive lung diseases, which included asthma, chronic bronchitis and emphysema was reported[96]. Similarly, in a study involving over 47,000 adult non smoking individuals attending a health care facility, any exposure to ETS, as well as a heavy exposure to ETS (> 40 h/wk) was significantly associated with development of asthma or hay fever[97].

There is some evidence to show the association of childhood ETS exposure with respiratory disease in adults. In a population based Swedish study, the prevalence of asthma was more in adults who were exposed to ETS during childhood compared to those who were not similarly exposed[98]. Interestingly in this study, when the population was stratified according to the family history of asthma, adults without any family history had a greater risk of asthma. This finding could be attributed to the higher rates of smoking cessation among asthmatic parents responsible for lesser exposure of children in families with asthma. But this observation could also point to the true causative role of ETS exposure in development of asthma, even in the non-atopic individuals. Maternal smoking exposure during childhood may also impair lung volume irrespective of personal smoking and appears to add to the effect of personal smoking to increase airflow limitation and COPD in adults[99].

Some case-control studies, have failed to show a convincing association of ETS exposure with asthma in adults[100-102]. In the European Community Respiratory Health Survey, compared to "no ETS exposure", " any ETS exposure" was not associated with a greater risk of self-reported asthma[101]. After stratification, it was found that workplace ETS exposure had a significant association with asthma, while domestic ETS exposure had no impact[92]. Similarly, there was no significant association of asthma with ETS exposure at workplace or home in semi-urban Sweden[28].

Significant associations of physician diagnosed 'ever asthma' and 'current asthma' were noted with both maternal and paternal smoking in 1469 young adults, seven years after they had initially participated in a school-based smoking prevention programme[102]. In a long-term cohort study ETS exposure from working with a smoker was found to be significantly associated with incident asthma at 10 yr follow up and only among women at 15 yr. Living with a smoker was not associated with any higher risk[103].

One of the factors responsible for the conflicting results observed in various studies is lack of an agreement on or of a gold standard for epidemiological definition of asthma. Self-reported asthma, the commonly employed tool in most surveys, might underestimate the true prevalence[104]. Several studies therefore report on the new onset wheezing, which is a more sensitive indicator of asthma in adults[105]. This is substantiated by the results of other studies where ETS exposure was associated with a greater risk of wheezing than that of asthma[95].

A dose related exposure-response relationship has been observed in some studies on quantification of ETS exposure. There was a sharp decline in respiratory symptoms in bartenders after the ban on smoking in restaurants[106]. Majority of the bartenders who reported wheezing initially noted complete resolution after workplace smoking was prohibited. A 5 h reduction of workplace ETS exposure was associated with a lower risk of respiratory symptoms on follow up examinations, after controlling for upper respiratory tract infections and reduced personal smoking[106]. The dose-response relationships have been demonstrated with total daily duration of ETS exposure, number of smokers in the environment, duration of working with a smoker, a cumulative exposure index, or a biomarker of exposure (nicotine level).

Bronchial hyper-responsiveness: Airway hyper-responsiveness is shown to increase in asthma patients at the end of ETS exposure. Re-challenge studies on historically ETS sensitive subjects have confirmed the previous observations and suggested that ETS sensitivity remained unchanged for relatively long (at least 2 yr) periods of time in most smoke-sensitive subjects with asthma[107,108]. Relationship between bronchial responsiveness and maternal smoking of borderline significance was shown in asthmatic children and young adults [101]. There was no demonstrable effect of parental smoking on bronchial responsiveness among similar aged non-asthmatic subjects, despite the occurrence of significantly lower levels of airflow in association with maternal smoking[109]. It has been also observed that maternal smoking can increase the variability of peak expiratory flow (PEF) in children which might contribute to the development of asthma[110].

Suggestion can induce an attack of asthma[111]. In most of the earlier studies, it was not possible to exclude the possibility that the asthmatic symptoms on exposure to cigarette smoke were attributable to psychological factors. To test this hypothesis, 24 adult non-asthmatic non smokers and 16 asthmatic non smokers were exposed in a chamber for 1 h to a high ETS concentration (heavy smoke), a lower concentration (moderate smoke), or none. Cigarette smoke was generated by a smoking machine, located outside the exposure chamber, but visible to the subject. During control exposure, the cigarettes were smoked but the smoke was diverted from exposure chamber. Asthma patients showed significant dose response relationship for lung function supporting a physiological rather than psychological explanation of the findings[111].

We had studied BHR by methacholine broncho-provocation test, in three groups of non smoking housewives with or without history of exposure to ETS or biomass *i.e.*, solid fuel combustion[112]. The number of hyper-responders and the BHR were significantly more among the exposed than among the unexposed group. The occurrence of BHR was more evident among the ETS exposed group than among the biomass fuel combustion group[112].

In conclusion, both active smoking and passive exposure to environmental tobacco smoke have multifaceted effects on bronchial asthma and bronchial responsiveness. There is an urgent need to adopt tobacco cessation and control programmes. While asthmatic patients who smoke need to quit smoking themselves, it is rather important that they positively avoid any exposure to smoking of others.

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Reprint requests: Dr S.K. Jindal, Professor & Head, Department of Pulmonary Medicine, Postgraduate Institute of Medical Education & Research, Chandigarh, India
e-mail: skjindal@indiachest.in