**Effects of Smoking on Asthma**

SK Jindal

**Abstract**

Tobacco smoking has several adverse associations with asthma. The odds ratios for prevalence of asthma are high for both active smoking and ETS exposures. In-utero exposure of foetus from maternal smoking, as well as its tertiary exposure from maternal passive-smoking are also known to be responsible for development of asthma in childhood. Smoking adversely affects the health and treatment-outcomes of asthma. There are increased requirements of drugs for smoker and ETS exposed asthmatics. Smoking is also an important factor in the development of airway remodelling, fixed airway obstruction and an exaggerated lung function decline.

Table 1: Different associations of atopy and asthma with smoking exposure

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<tbody>
<tr>
<td>1.</td>
<td>Higher odds ratios for prevalence of</td>
<td>4.</td>
<td>Airway inflammation, remodeling and lung function decline</td>
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<tr>
<td></td>
<td>• Allergic sensitisation</td>
<td></td>
<td>• Exaggerated lung function decline</td>
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<td></td>
<td>• Asthma</td>
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<td>• Fixed airway obstruction</td>
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<td>2.</td>
<td>Poorer asthma control</td>
<td>5.</td>
<td>Treatment effects</td>
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<td></td>
<td>• Increased Emergency Room visits</td>
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<td>• Relative resistance to inhaled corticosteroids</td>
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<td></td>
<td>• Increased hospitalisations</td>
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<td>• Increased theophylline clearance</td>
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<td></td>
<td>• Frequent acute episodes</td>
<td></td>
<td>• Requirement for add-on therapy with anti-muscarinics and monoclonal anti IgE antibodies</td>
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<td>• Increased need for maintenance pharmacotherapy</td>
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<td>• Differential treatment responses</td>
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<td>3.</td>
<td>Development of asthma due to In-utero smoking exposure</td>
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<tr>
<td></td>
<td>• Maternal smoking (Passive)</td>
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<td>• Maternal passive smoking from others (Tertiary smoking)</td>
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Table 2: Odds Ratio (OR) of smoking with asthma reported in recent studies

<table>
<thead>
<tr>
<th>Active Smoking OR (95% CI)</th>
<th>ETS Exposure OR (95% CI)</th>
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<tbody>
<tr>
<td>1. Jindal SK et al, 2012*</td>
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<tr>
<td>Cigarette</td>
<td>1.82 (1.54 – 2.15)</td>
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<td>Bidis</td>
<td>2.87 (2.58 – 3.20)</td>
</tr>
<tr>
<td>Others</td>
<td>3.15 (2.58 – 3.84)</td>
</tr>
<tr>
<td>2. Agrawal S, 2012*</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>1.35 (1.49 – 2.25)</td>
</tr>
<tr>
<td>Women</td>
<td>1.72 (1.34 – 2.21)</td>
</tr>
<tr>
<td>3. Kim O, 2012*</td>
<td></td>
</tr>
<tr>
<td>Smoking of &gt; 20 days</td>
<td>-</td>
</tr>
<tr>
<td>4. Mitchell et al, 2012*</td>
<td>Cigarettes/ dayO.R.</td>
</tr>
<tr>
<td></td>
<td>1-9: 1.27</td>
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<tr>
<td></td>
<td>10-19: 1.35</td>
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<td></td>
<td>20 +: 1.56</td>
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95% CI = 95% Confidence Intervals

smokers compared to 10.9% in the asymptomatic group.7

The epidemiological relationship of ETS-exposure with asthma in children, though variable from different countries, is significantly high in most of the recent studies.8,10 The ISAAC Phase Three programme examined the influence of parental smoking in children of 6-7 years and 13-14 years age-groups employing a study-questionnaire.8 Both maternal and paternal smoking were associated with an increased risk of asthma in children of both age groups though the odds ratios were higher for maternal smoke exposure. There was also a clear dose relationship of number of asthma symptoms with number of cigarettes smoked.8 ETS exposure was also shown to increase the risk of respiratory symptoms in 1718 never-smoker Chinese school-children.8 There was also a dose response relationship of number of cigarettes with impairment of lung function assessed by spirometry performed at baseline and at 18 month follow-up.8 Similarly, prevalence of wheeze and asthma was shown among ETS exposed Japanese children of 6 to 15 years of age.10 There was an increased prevalence of wheeze and asthma in children of 6 to 10 years of age who were exposed to heavy passive smoking of 7 or more pack years in the households.10

These results are quite consistent with the findings of earlier studies which had pointed to the smoking exposure as an important risk factor of prevalence of asthma.11,12 Maternal smoking was shown to have strong and significant association as was concluded in a meta-analysis of longitudinal studies on incidence of asthma and wheezing; this relationship was particularly significant for the first 5-7 years of life than for the incidence in the school years.14

2. Effects on asthma-control

Smoking exposure is known to adversely impact the control of asthma in both children and adults. There is aggravation of respiratory symptoms, acute respiratory infections and bronchial hyper-responsiveness amongst nonsmoker individuals exposed to smoking of parents, sibs and friends.15,16 ETS exposure from parents is also related to the severity of asthma and emergency department visits of asthmatic children.17,18 In our own study on 200 never-smoker patients of asthma of 15 to 50 years of age, the control was poor and morbidity greater amongst patients exposed to ETS at home and/or at work.19,20

The poor asthma control amongst ETS exposed individuals is further supported by the findings of a recent study which demonstrated a significant reduction in episodes of poor asthma control after a decrease in ETS exposure in children.21 There were fewer hospitalisation and emergency department visits after the caregivers were provided with no-smoking cessation counselling or ETS-exposure education.21 In a similar study, smoking of caregivers was strongly associated with child exposure to ETS amongst inner-city asthmatic children in Chicago.22 Measures for smoking cessation amongst the caregivers are therefore important for adequate control of asthma. In another study among 3761 children of below 12 years of age, household ETS exposure was shown to predict asthma attacks for girls (OR: 3.11, 95% C.I. = 1.24 – 1.76).23

3. Development of asthma: In-utero exposure

Maternal smoking during pregnancy constitutes an important source of ETS-exposure for the foetus in-utero. The foetus may also be exposed to paternal smoking from the father or other family members in the company of the pregnant mother, sometimes referred to as “tertiary smoking”. The in-utero smoking exposure is shown to be associated with lung immaturity, poor lung function and development of asthma in early childhood. There was higher incidence of asthma in children of mothers who smoked.24,25

There is strong evidence in favour of foetal programming and very early life events such as ETS exposure and use of chemical domestic products in the development of asthma.26 The intrauterine insult from several such exposures could be blamed for early sensitisation and at least for some of the phenotypes of asthma.26 Similar association of foetal exposure to maternal
The interaction between maternal smoking during pregnancy and asthma outcomes has been extensively studied, with a growing body of evidence linking maternal smoking to adverse childhood asthma outcomes. Maternal smoking during pregnancy has been shown to increase the risk of wheezing, asthma, and other respiratory symptoms in children. A recent study found that in-utero exposure to maternal smoking was associated with a 1.5-fold increase in the risk of developing asthma in children.24

Besides development of asthma, maternal smoking while in utero has been shown to be associated with poor control of asthma.31 A case-control study of 2481 Latino and black subjects with asthma was done to study the clinical effect of maternal smoking and its contribution to asthma development. In this study, the odds ratio of 1.5 (95% CI 1.1 – 2.0) for recurrent wheezing was seen in children born to smoking mothers.29 In this study, the in-utero maternal smoking exposure was not shown to increase the risk of wheezing. Both maternal asthma and cigarette smoking were shown to increase the risk of preterm birth and other adverse perinatal outcomes in a retrospective analysis of 172305 singleton pregnancies in South Australia.30

The effect of smoking studied in 793 asthma patients aged 14 to 44 years clearly demonstrated an early lung function decline compared with nonsmokers.28 The authors have also shown a dose-response relationship of spirometric measures with smoking. Another population based study (Tasmanian Longitudinal Health Study) on a cohort born in 1961 reports the development of fixed airway obstruction in middle age contributed by active smoking and current clinical asthma.35 The authors of the study concluded that the association of fixed airway obstruction was equivalent to a 33 pack-year history of smoking for late onset current clinical asthma compared to 24 pack-year history for late onset clinical asthma.

There are also experimental data in mice to suggest that airway remodelling may occur even from in-utero exposure to maternal smoking. Offsprings of mice exposed to cigarette smoke during pregnancy had increased airway smooth muscle layer, collagen deposition and other changes seen in airway remodelling.36

Interestingly, a recent review cites the dangerous relationship of asthma with substance abuse (cocaine, marijuana, cigarette, heroin and alcohol) in causing lung function decline, increase in number of life-threatening asthma attacks and high asthma mortality.37

5. Smoking, allergic sensitisation and airway inflammation

There are a few reports on smoking relationship with different forms of atopy and asthma. Both active smoking and ETS exposure are shown to be associated with increased odds of developing aspirin-exacerbated respiratory disease.38 There were odds ratios of 1.54, 3.46 and 5.09 for active smoking, childhood ETS exposure and both childhood and adulthood ETS exposure. Foetal exposure to maternal active and passive smoking were also shown to relate to other atopic illnesses such as allergic rhinitis and eczema.8,27

The effect of ETS exposure on the development of allergic sensitisation in children was compared in children aged 2-3 years born with and without a maternal history of allergic disease.59 Using a propensity score method to control for
confounding variables, early life ETS exposure was found to be strongly associated with allergic sensitisation in children without maternal history while it reduced the sensitisation in those with positive maternal history. Increased concentrations of prostaglandin E(2) and cysteinyl leukotrienes in sputum supernatants of smoker asthma patients point towards the up-regulation of these mediators by smoking and causing worsening of airway inflammation. Smoking effect on airway inflammation has been also shown in preschool asthmatic children exposed to maternal tobacco smoking. ETS exposed children with multiple trigger wheeze had increased fractional concentrations of exhaled nitric oxide. Smoking may also affect the association of asthma with gene expression. In a study on ADAM33 gene polymorphism in Japanese women, a significant interaction was reported between some of the single nucleotide polymorphisms (SNPs) and smoking. However, there is limited information on the subject. No association of ETS exposure and the studied polymorphism was seen in another study from Mexico.

6. Effects on asthma-therapy and outcomes

There is relatively less information on the effects of smoking on pharmacotherapy of asthma. Smoking modifies the dosages and effects of drugs, especially of those administered through inhalational route. Further, the response to therapy is poor in the presence of airway remodeling. Smoking is one of the most modifiable risk factor for adverse outcomes of asthma such as increased severity, asthma related quality of life, generic mental health status and longitudinal risk of hospitalisation. Smoking cessation as well as control of ETS-exposure should therefore constitute important and essential components of asthma therapy.

Asthmatic subjects who smoke were shown to develop resistance to inhaled corticosteroid therapy with one year trial of budesonide. Even in mild asthma, the efficacy of short term ICS was shown to be significantly impaired in a placebo controlled study on 38 steroid naïve patients. The mechanism of development of ICS resistance in smokers is not exactly known. Some of the mechanisms which have been put forwards include the alterations in airway inflammatory cells, changes in glucocorticosteroid receptors and reduced histone deacetylase activity. Cigarette smoking may also necessitate changes in the requirement of bronchodilator drugs. It increases the clearance of theophylline, therefore reducing the bronchodilatory effect in patients on oral theophylline. Smoking may also increase the cholinergic tone in asthma, the additional use of anticholinergic agents such as inhaled ipratropium bromide was found to add to the bronchodilatory effect. Inhaled tiotropium has also been shown to reduce the reliever inhaler use and improve lung function in patients with clinical features of both asthma and COPD. There are however, no studies on the use of the antimuscarinic drugs in asthma alone.

Smoker asthmatics may also benefit from additional use of leukotriene receptor antagonists as was shown in the Smoking Modalities Outcomes of Glucocorticoid Therapy in Asthma (SMOG) trial. The role of monoclonal anti IgE antibody therapy with omalizumab in smoker asthmatics is not established, but requires further investigation in view of the elevated total serum IgE in the patients. Interestingly in a recent study, asthma patients with a smoking history of > 11 pack-years tended to show greater benefit with montelukast while those with smoking of < 11 pack-years benefitted more with fluticasone. In conclusion, smoking exposure is known to influence the development of allergic sensitisation and asthma as an important risk-factor. It also impacts the various asthma outcomes and treatment modalities. Smoking cessation as well as adoption of measures to avoid ETS-exposure are essential steps for the comprehensive and effective management of asthma. A probabilistic model of biological ageing of the lungs convincingly demonstrates that the combination of smoking with asthma (or COPD) is more harmful than asthma (or COPD) alone.

References


