

Editorial

Exposure to environmental tobacco smoke and adult asthma

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The relationship between the respiratory system and the environment involves a complex, dynamic interaction of genetic susceptibility, host defense, and toxicity. The problems of tobacco addiction have evolved over centuries. The possible relationship between smoking and oral cancer was recognized as early as the 19th century. The use of tobacco results in an estimated 4 million deaths each year worldwide. Approximately 3000 adolescents start smoking every day; 4.5 million children and adolescents smoke cigarettes; 1 million use smokeless tobacco (1).

“Environmental tobacco smoke” (ETS) is a term widely used to refer to the mixture of side-stream smoke and exhaled mainstream smoke that pollutes air in locations where tobacco smoking takes place (2). ETS contaminates the indoor air in homes and workplaces. The adverse effects of ETS on the respiratory tract have been extensively characterized (3, 4). Among children, ETS causes lower respiratory infections, middle-ear disease, sudden infant death syndrome, and asthma (5). Half of the world's children may be exposed to ETS, exacerbating symptoms in 20% of children with asthma. Recent reports have reinforced previous conclusions that exposure to ETS causes the onset of childhood asthma and exacerbation of symptoms throughout life (6–10). However, the effects of ETS exposure on adult asthma have not yet been investigated extensively, and the available data are limited (11).

Specific questions which have to be answered to understand the effects of ETS in asthma in adults include

- 1) whether there are data supporting ETS as a cause of asthma in adults
- 2) whether there are data indicating that exposure to ETS is associated with exacerbations of asthma in adults
- 3) whether there are differences between exposure to ETS in the home and at the workplace (11, 12)
- 4) whether ETS in childhood may lead to persistent airway abnormalities and, in some asthmatics, to the development of irreversible airflow obstruction.

Does exposure to ETS cause asthma in adults?

A few studies have examined the role of exposure to ETS as a potential causative factor for asthma in adults.

Greer et al. (13) attempted to determine the association between occupational and air-pollutant exposure with the development of adult asthma through the analysis of a standardized respiratory questionnaire administered to a cohort of 3914 nonsmoking adults in 1977 and again in 1987. Ambient air-pollution concentrations were estimated over a 20-year period with monthly interpolations from fixed-site monitoring

stations applied to ZIP code locations by month of residence and work site. Second-hand smoke exposure was significantly associated with the development of asthma (related risk [RR]=1.45; confidence interval [CI]=1.21 to 1.75).

The association between passive exposure to tobacco smoke and respiratory symptoms was examined in a sample of 4197 never-smoking adults of the Swiss Study on Air Pollution and Lung Diseases in Adults (SAPALDIA) (14). They constituted the never-smoking subsample of a random sample of 9651 adults (aged 18–60 years) in eight areas in Switzerland. Information on exposure to passive smoking and standardized questions on respiratory symptoms were obtained via a questionnaire administered by trained examiners. After controlling for age, sex, body mass index (BMI), study area, atopy, and parental and sibling history, ETS was associated with an elevated risk of wheezing apart from colds (odds ratio [OR] 1.94, 95% CI 1.39–2.70), an elevated risk of bronchitis symptoms (OR 1.59, 95% CI 1.17–2.15), an elevated risk of symptoms of chronic bronchitis (OR 1.65, 95% CI 1.28–2.16), an elevated risk of dyspnea (OR 1.45, 95% CI 1.20–1.76), and an elevated risk of physician-diagnosed asthma (OR 1.39, 95% CI 1.04–1.86). It was not associated with an increased risk of allergic rhinitis, including hay fever. In this study, the association of ETS with dyspnea, wheeze, and asthma showed evidence of a dose-dependent increase with hours per day of exposure, whereas association with symptoms of bronchitis was stronger with years of exposure.

Inconsistencies across studies on the association of ETS and pulmonary function may be clarified by addressing potentially susceptible subgroups. Kunzli et al. (15) determined the association of exposure to ETS at work with FVC, FEV₁, and FEF_{25–75%} in life-time never smokers ($n=3534$) of the SAPALDIA random population sample (age 18–60 years). The multivariate regression models were adjusted for height, age, education, dust/aerosol exposure, region, and ETS at home. Overall, ETS was not significantly associated with FVC (0.7%; 95% CI: –0.4 to +1.8), FEV₁ (–0.1%; –1.3 to +1.1), or FEF_{25–75%} (–1.9%; –4.2 to +0.5). Effects were observed among asthmatics ($n=325$), FEV₁ (–4.8%; 0 to –9.2); FEF_{25–75%} (–12.4%; –3.7 to –20.4); FVC: (–1.7%; +2.1 to –5.5), particularly in asthmatic women ($n=183$): FVC –4.4% (–9.6 to +1.1); FEV₁: –8.7% (–14.5 to –2.5); FEF_{25–75%}: –20.8% (–32 to –7.6), where duration of exposure to ETS at work was associated with lung function (FEV₁ –6% per hour of ETS exposure at work ($P=0.01$); FEF_{25–75%}: –3.4%/h ($P<0.05$). In nonasthmatic women ($n=1963$) and in men, no significant effect was observed.

Flodin et al. compared 79 asthma patients, diagnosed

between the ages of 20 and 65 years, with 304 randomly drawn population controls of similar age from the same catchment area as the patients (16). The comparison involved questionnaire information on smoking habits, occupational exposure, dwelling conditions, various suspect allergenic exposure, and atopy. Those who had smoked for 3 years or more, present or past, were at increased risk of bronchial asthma (OR 1.9; 95% CI 1.1–3.3). Adjustment by multiple logistic regression for age and sex as well as atopy and air pollution at work, did not change the relative risk estimate. ETS at work involved a slightly greater risk.

Asthma and related factors were assessed by mailed questionnaires among 2041 young adult participants in a smoking prevention project in California in 1993 (17). After adjusting for sex, race, and educational level, family history of asthma was strongly associated with subjects' asthma (OR 3.1, 95% CI: 2.4–4.3 for physician-reported asthma; OR 3.3, 95% CI: 2.4–4.5 for current asthma). Exposure to parental smoking (both parents smoked more than half a pack of cigarettes a day) during childhood (reported when participants were in grade 7) was significantly associated with physician-reported asthma (OR 2.9, 95% CI: 1.6–5.6) and current asthma (OR 3.3, 95% CI: 1.7–6.4).

These studies have a different methodology but provide some indication that ETS may induce asthma in adults. In the April issue of *Allergy*, another epidemiologic study is presented (18). Due to the small number of epidemiologic studies assessing the causal role of ETS in adult-onset asthma, this study is of importance. In a case-control study of 15 813 subjects living in western Sweden, the authors examined self-reported ETS as well as other factors. Increased OD for asthma was associated with exposure to molds (OR 2.2, 95% CI 1.4–3.5), a known cause or trigger of asthma (17, 19–21) and to ETS in never-smokers (OR 2.4, 95% CI 1.2–2.5). The study was carefully carried out, but, as in previous studies, it was based on a questionnaire, so that the magnitude of exposure to ETS could not be recorded, and exposure to ETS at work was not assessed, although this can be a significant confounding factor. Although case-controlled studies may be subject to some biases, these have been ruled out as far as possible in the present study.

In the study published in the April issue of *Allergy* (18), never-smoking men were more susceptible to ETS than never-smoking women. This result is rather surprising and needs to be confirmed, since studies have indicated that women are more vulnerable to the respiratory effect of tobacco smoking (active smoking) than men (22). This vulnerability is not clearly understood, because a case-control study of the effects of airway caliber and smoking showed that women's greater susceptibility to asthma in early adulthood was, at least partly, explained by their smaller airway caliber (23).

What can be concluded from these studies?

Taken together, these epidemiologic studies appear to extend the adverse effects of ETS and strongly suggest that exposure to ETS not only causes lung cancer (24, 25) and ischemic lung diseases (26) but probably also causes asthma in children and in adults.

However, there are only five studies examining exposure to ETS and adult onset asthma (13, 14, 16–18): two longitudinal studies, two case-control studies, and one cross-sectional study. In these studies, some methodological barriers mostly inherent in the study design limited the available data and the evaluation of the adequacy of the data for risk assessment (11). Thus, more epidemiologic studies are needed to confirm the causative role of ETS in asthma.

The study of Kunzli et al. (15) is of great importance since it studied lung function in different groups of subjects exposed to ETS. The size of the observed effect among susceptible subgroups (asthmatic patients in general and asthmatic women) has to be considered clinically relevant. However, due to the inherent limitations of this cross-sectional analysis, selection or information biases may not be fully controlled. For example, asthmatic women reported higher exposure to ETS at work than asthmatic men. Given the public health importance of identifying susceptible subgroups, these results ought to be replicated.

Moreover, patients can be exposed to ETS at home or at the workplace, and epidemiologic studies will need to address possible differences or additive effects, as has been done for lung cancer. Thus, new epidemiologic studies are needed and should incorporate better evaluation of exposure to ETS.

How does exposure to ETS cause asthma in adults?

Epidemiologic studies are important, but mechanistic studies will need to explain the links between ETS and persistent airway inflammation in asthma.

The relationship of ETS to total IgE in adults was examined in the Epidemiological Study of the Genetics and Environment of Asthma, Bronchial Hyper-responsiveness, and Atopy (EGEA) (27). The results show that an increase in total IgE in relation to active smoking may be evidenced even in asthmatics

despite the healthy smoker effect. In susceptible subjects, such as women who are first-degree relatives of asthmatics, total IgE may increase in relation to passive smoking.

The relationships between smoking and allergy are complex (28, 29). Smoking has been shown to be associated with the development of occupational asthma to some proteins, suggesting that smoking may be a risk factor for allergy to crab fumes or laboratory animals (30–32). The association of ETS and allergy has also been studied, but conflicting results have been observed. Risk factors associated with asthma and rhinoconjunctivitis were examined among Swedish farmers. Exposure to ETS did not appear to affect the risk of allergen sensitization or respiratory symptoms (33). During the first 3 years of life, both prenatal and postnatal exposure to ETS appears to have an adjuvant effect on allergic sensitization (34–38). Thus, it is possible that ETS may increase allergy, but probably only in predisposed subjects.

Although it has long been believed that cigarette smoke is injurious to the lower respiratory tract, the exact early mechanisms and early events responsible for this injury remain unclear (39). Smoking is known to increase the inflammatory burden of the lower respiratory tract through a number of related but separate mechanisms. These include the recruitment of increased numbers of inflammatory cells, alteration in cell subtypes, enhancement of some cellular functions, and proinflammatory mediator release (40). In addition, cigarette smoking *in vitro* and in animal models appears to promote neurogenic inflammation, increase oxidative stress, and lead to the elevation of cysteinyl leukotrienes, all of which could potentially lead to an amplification of the airway inflammation already present in asthmatics.

If long-term exposure to ETS can lead to airway inflammation that may become persistent over time, there are also epigenetic phenomena which may occur (41, 42). These are heritable, alternative states of gene activity that are not explained by mutation, changes in gene sequence, or normal developmental regulation. Exposure to ETS might act on some corepressors or coactivators and induce permanent gene expression or silencing, leading to persistent airway inflammation.

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