

Review article

Linkage between smoking and asthma

Smoking is one of the most important preventable public health problems. Prevalence of smoking is decreasing in the Western world but lot of work is left. We reviewed the most important papers related to smoking and asthma. Despite of decreasing smoking figures in Finland, about 15–20 per cent of pregnant women smokes. Children's exposure to harmful effects of environmental tobacco smoke (ETS) still continues. Exposure to tobacco smoke during pregnancy and in early childhood both deteriorates permanently children's lungs and increases their asthma risk. The exposure of adults to ETS also increases their asthma risk. Both passive exposure to ETS and active smoking worsen asthma. In addition, smoking asthmatics run a higher risk of developing COPD compared to non-smokers. Smoking prevalence among the population can be regulated through legislation, but the health care personnel have a central role in encouraging smoking cessation among smoking patients.

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It's easy to understand that tobacco smoke, which contains several chemicals, is harmful to asthmatics. Maternal smoking during pregnancy and exposure to tobacco smoke in the home deteriorate child's lung function and increase his or her life-long risk of asthma. It has been much more unclear, how exposure to environmental tobacco smoke influences adult health, but both passive and active smoking is always harmful to asthmatics. During the last years, a lot of studies have been made in this field. We reviewed the most important papers from the last decade to get the newest knowledge and to know how to tackle the problem. This review is associated with Finnish Allergy Programme (1) and GARD (Global Alliance against Respiratory Diseases) project (2).

Smoking among Finns

Smoking prevalence among Finnish adults has been decreasing, albeit slowly. According to a study by the Finnish National Public Health Institute 26% of men and 17% of women in working age smoked daily in 2007 (3). Follow-up studies among pupils show that smoking among adolescents has also started to diminish: 22% of boys and 23% girls between the age of 14 and 18 smoked in 2005 (4).

Exposure to environmental tobacco smoke has been reduced through legislation (5). The Finnish authorities

have aimed at preventing people's exposure to tobacco smoke by enacting restricting laws (Table 1). According to a study by Lund et al. (6) only 7% of Finnish parents said to smoke indoors, although 23% of the families, which were involved in this study, had at least one smoking adult member. In the United States as much as 40–60% of children continue to be exposed to tobacco smoke at home (7).

Male smoking has decreased in comparison with the situation in the 1980s, but female smoking has remained at a stable level. About 15–20% of women smoke during pregnancy. While smoking prevalence decreases among the general population, among women it is more

Table 1. Development of the Finnish Tobacco Act

The Finnish Act on Measures to Restrict Tobacco Smoking and its amendments	Entry into force	Main measures
13.8.1976/693	1.3.1977	Ban on advertising
19.8.1994/765	1.3.1995	Ban on smoking in workplaces and on indoor public premises. Prohibition to sell tobacco products to persons under 18.
9.4.1999/487	1.3.2000–1.7.2003	Restrictions on smoking in restaurants and bars
21.7.2006/700	1.6.2007	Ban on smoking in restaurants and bars

common among the less educated. Over 30% of fertile Finnish women smoke in the less educated groups (3). These factors contribute to the risks of children as a result of the harmful effects of environmental tobacco smoke. According to our previously unpublished observation 42% of pre-school children, who had contracted asthma, had parents, who said to smoke outdoors. Among adult asthmatics smoking prevalence is at least at the same level as among the general population (8) (Fig. 1).

Tobacco smoke

Tobacco smoke contains over 4,000 chemical compounds, of which over 100 have been found harmful to human health. They include about 50–60 carcinogens, several mutagens and many irritating or toxic substances, like a small amount of lethal polonium-210 isotope. It has been counted that one puff of cigarette smoke contains 10^{16} oxygen radicals. Tobacco smoke may cause toxic cell damage directly, and the chemical compounds therein begin several reactions in cells. Cigarette smoke and its oxygen radicals activate inflammatory cells, which contribute to the activation of growth factors and matrix metalloproteinases. These are causing protease-antiprotease imbalance and advancing tissue destruction (9).

Tobacco smoke permeates the ambient air through the so-called sidestream smoke, when the smoker is not inhaling smoke to his or her lungs, and through the so-called mainstream smoke, when the smoker exhales smoke. As regard to environmental tobacco smoke the share of sidestream smoke is 50–90% and the share of mainstream smoke is 10–50% (10). Sidestream smoke is especially hazardous to health, because it contains more harmful compounds than the mainstream smoke, its temperature is lower and the airflow course is different. When the particles mix with indoor air, they become

smaller in size, and consequently in sidestream smoke most of the particles belong to the so-called inhalable fraction.

Effects of exposure to environmental tobacco smoke

As regard to children, tobacco smoke is one of the most harmful elements in the environment. When a woman smokes during her pregnancy, harmful elements are transferred to the fetus via the placenta. The fetus can have same levels of cotinine as a smoker in such a situation (11). Maternal smoking is the most important source of exposure during childhood and causes considerable damage to health. It is, however, difficult to distinguish between the damages caused by exposure in the womb and during early childhood. About 30–40% of women are able to quit smoking during pregnancy, but as much as 60% resume their habit after childbirth. Up to 90% of the women, who smoke during pregnancy, continue to do so after 5 years (11). The low education level of the parents (OR 2.42) and single parenthood (OR 2.17) increase child's risk to be exposed to environmental tobacco smoke, and child's atopy decreases it (OR 0.61) (12). Infant exposure to tobacco smoke impairs permanently lung function and increases the number of lower tract respiratory infections, the risk to contract asthma and asthma exacerbations (13).

Influence of children's lung function

Studies have found that infant exposure to environmental tobacco smoke impairs lung function during childhood by 0.5–7% according to measurable spirometry values (13). A meta-analysis of 21 studies discovered a reduction by 1.4% in the forced expiratory volume in 1 s (FEV₁) and a reduction by 5% in the mid-expiratory flow (MEF₅₀) without identifying the effect of the time of exposure (14).

Studies have found that prenatal exposure to maternal smoking impairs child's lung function immediately after birth (15), during infancy (16, 17), later during childhood (18), and during adult life (19). It has been suggested that smoking during pregnancy affects lung function more heavily than postnatal exposure. A recent multicenter study of more than 20 000 school-aged children concluded that maternal smoking during pregnancy reduced FEV₁-value by –1% and MEF₂₅-value by –6%. Parental smoking during the study period caused reductions by –0.5% and –2%, respectively (18).

It seems that the adverse effect of parental smoking on children's lung function continues even during adolescence. A fresh study by Rizzi et al. (20) discovered that children, whose parents smoke, had significantly lower flow rates in small airways compared with children of non-smoking parents. Maternal prenatal smoking was associated with considerable adverse effects. Environ-

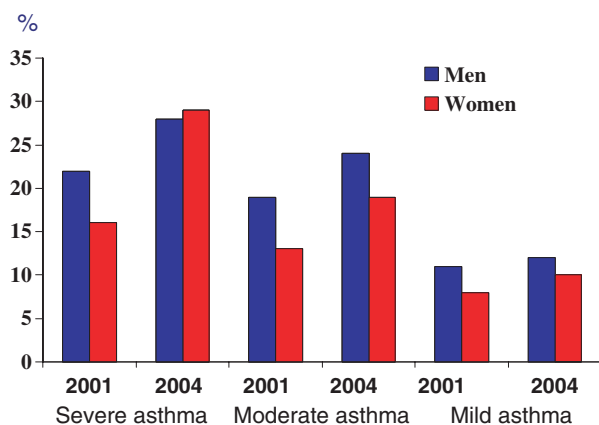


Figure 1. Smoking (%) among asthma patients in Finland according to the asthma category (8).

mental tobacco smoke obstructs children's small bronchi (21). This has been explained by the observation that the airway wall gets thicker as the smooth muscle increases and the development of lung alveoli is disturbed as a result of exposure to tobacco smoke (22). It has been suggested that genetic polymorphism is linked with the stage of pulmonary dysfunction among children, who have been exposed to tobacco smoke (23).

Environmental tobacco smoke and children's asthma

Children, whose parents smoke, run a higher risk of contracting asthma (OR 1.21–1.37). Pre-school children, who are exposed to environmental tobacco smoke, have a higher risk of asthma than school-aged children (OR 1.44 vs 1.26), and mother's smoking during pregnancy even increases the asthma risk compared with exposure only after birth (13). Moreover, the length of exposure has an influence. According to a meta-analysis of five birth cohorts, 10-year exposure (OR 1.42) to tobacco smoke increased the asthma risk more than 5-year exposure (1, 22) (13). The effects reach far into adulthood. Prenatal exposure to tobacco smoke increases the adult (15–70 years) asthma risk more (OR 3.5) than mere postnatal exposure because of mother's smoking (OR 1.9) (Skorge et al. 2005). In addition, those smoking adolescents, whose mothers have smoked during pregnancy, have a higher asthma risk in comparison with adolescents, whose mothers have not smoked during pregnancy (OR 8.8 vs 3.9) (24).

The increasing asthma risk is probably a result of several factors. The described impairment of lung function in childhood is an asthma risk factor itself. Postnatal exposure to tobacco smoke increases the number of lower respiratory tract infections, which are known risk factors for asthma (OR 1.26–2.13) (13). The risk is the highest in small children (OR 1.71 at the age of 0–2 years and 1.25 at the age of 3–6 years). A small child with smoking parents has twofold risk to be hospitalized as a result of a lower respiratory tract infection compared with children of nonsmoking parents (25). The hospitalization risk seems to be even higher in children, whose parents smoke during pregnancy and who are atopic (OR 3.31 vs 1.74).

The link between exposure to tobacco smoke and airway responsiveness is ambiguous. Young et al. (26) observed increased airway responsiveness in 1-month-old healthy infants with smoking parents compared with infants, whose parents were nonsmokers. A meta-analysis by Cook et al. (27) found out that exposure to environmental tobacco smoke has only a minor increasing effect on airway responsiveness among school-aged children (OR 1.29).

Neither has the increasing or decreasing effect of environmental tobacco smoke on allergic sensitivity been showed reliably (28, 29). There is preliminary evidence that maternal prenatal smoking has an adverse effect on the development of infant's native immune response (30)

and it increases baby's oxidative stress (31). It seems that the magnitude of the damages induced by the exposure to environmental tobacco smoke in early age is dependant on genetic polymorphism. A study of 2950 US children (aged between 10 and 16) concluded that polymorphism of glutathione *S*-transferase gene has an influence on asthma and wheezing risk in children, who have been exposed to tobacco-related toxins during pregnancy (32).

Exposure to environmental tobacco smoke increases the number of asthma exacerbations, their degree of difficulty, and the use of asthma medication, emergency hospital visits, and school absenteeism (13). According to observations asthma becomes milder, when exposure to tobacco smoke diminishes.

Influence of environmental tobacco smoke on asthma in adults

Researchers have been looking for a long time for evidence of the connections between the adult exposure to environmental tobacco smoke and the asthma risk. The published studies have been analyzed in two Finnish studies (33), which came to the conclusion that asthma risk increases as a consequence of environmental tobacco smoke (OR 1.15–3.30). A population-based case-control study in the Pirkanmaa district in South Finland (521 patients, 932 control subjects) showed that both the continuous lifelong and the recent exposure to environmental tobacco smoke increase asthma risk. Home exposure (OR 4.77) seems to increase more the risk than exposure at workplace (OR 2.16) (34). Moreover, a Swedish study showed increased asthma risk as a result of exposure to environmental tobacco smoke, when the daily time of exposure was more than 5 h (OR 1.79) (35). On the basis of these studies, it is clear that exposure to environmental tobacco smoke and asthma risk in adults is strongly linked. On the other hand, decreasing exposure seems to diminish the risk.

Researchers have tried to explain the mechanism, why tobacco smoke increases asthma. Animal studies suggest that it is partly induced by oxidative stress, which leads to an increase in cysteinyl leukotriene levels (36). On the other hand, the increased asthma and atopy risk may be caused by the tobacco smoke-related toxic damage of bronchial mucosa leading to bigger allergen penetration.

Influence of environmental tobacco smoke on asthma control

Passive exposure to tobacco smoke worsens the balance of asthma. A US study followed the condition of 349 asthma patients for a period of 18 months and found out that the disease-related quality of life was worse and the use of health care services greater among exposed asthmatics, and the higher the level of exposure to environmental tobacco smoke was, the greater was the risk of emergency department visits (37). Similar results

were obtained in study, in which 189 asthmatics carried a nicotine meter for 7 days. The higher the level of nicotine was according to the meter, the greater was the risk to be hospitalized because of asthma (38). Moreover, high nicotine levels, which had been accumulated during a longer period of time and were measured from hair samples, were associated with greater needs of hospital admission.

How smoking affects the asthma risk and diagnosed asthma

For a long time researchers have tried to find out, whether smoking induces asthma in adults. Results of several studies have been contradictory, but some of them have clearly supported the hypothesis, according to which smoking increases the asthma risk. A recent Finnish study (39) analyzed thoroughly previous and current smoking habits and exposure to environmental tobacco smoke of 521 adult asthmatics and 932 control subjects. According to the results previous smoking (OR 1.47), occasional smoking (OR 1.25) and current smoking (OR 1.31–1.46) induce asthma. Women were associated with a greater risk than men in this data.

Effect of tobacco smoke on bronchial inflammation in asthma

Smoking asthmatics have different kind of bronchial inflammation than in general asthma. In addition to the normal eosinophil inflammation also neutrophils are activated (40–41). Induced-sputum samples have shown increased levels and activation of neutrophils and negative relationship between inflammation and lung function measurements. Increasing neutrophil inflammation may partly explain, why therapeutic response to inhaled and oral corticosteroids is weaker among smokers (42). Smoking asthma patients may have in the pathophysiology of their disease similar features to those of COPD, like development of emphysema and lower lung diffusion capacity (43).

Effect of smoking on lung function

Smoking accelerates the natural process of lung volume reduction, which is linked with aging. In adults FEV₁ diminishes after the age of 30 by approximately 30 ml/year; in smokers the rate is on average 40–45 ml/year (44). Predisposition to a rapid deterioration of lung function and consequently to the development of COPD is genetically determined and still poorly understood. The lung function of smoking asthma patients falls more rapidly compared with nonsmoking asthmatics (45). A Danish prospective follow-up study found out that FEV₁ decreases in nonsmoking male asthma patients by 30 ml and in females by 29 ml/year. The analogous figures for smoking asthmatics were 55 and 40 ml/year, respectively (45).

Effect of smoking on the clinical picture of asthma

Smoking asthma patients have more symptoms and exacerbations than nonsmokers (46). Smoking increases the risk of hospitalization as a result of exacerbations (47), the occurrence of asthma-related deaths (48), and also the mortality caused by other reasons among asthmatics (49). Smoking worsens the quality of life in asthma, and it increases the need of symptomatic medication and visits to the doctor (50). The motivation of smoking asthma patients to self-management can be lower than that of nonsmokers. As was said earlier, smoking reduces the effect of corticosteroids in asthma, and the treatment of smoking patients requires higher doses of medication (42). The metabolism of theophylline accelerates, and higher doses of medication are thus needed (51). Smoking increases also the frequency of upper respiratory tract symptoms and predisposes to respiratory inflammations, which may shake good asthma balance. It has been shown that smoking cessation reduces the neutrophil inflammation in the airways of asthma patients, improves the response to steroids and slows down the deterioration of lung function (52).

Conclusions

Smoking is among the most important preventable public health problems. Exposure to tobacco smoke causes several health hazards including higher risk for asthma and the effects are the greatest when exposure occurs during pregnancy and in early childhood. Small children are the most vulnerable to the harmful effects of environmental tobacco smoke, and they are exposed to tobacco smoke in the home, where mother, father or others smoke. Even adult population has a higher risk for asthma because of passive and active smoking.

It is possible to regulate the exposure of adults to tobacco smoke through legislation, but it is difficult to intervene in the domestic exposure of children by enacting new laws. Health care personnel should by all means try to promote smoking cessation among adults and adolescents and to reduce the exposure of children and adults to

Table 2. Conclusions and recommendation for future antismoking work to diminish asthma incidence

The smoke spreading directly from cigarettes is especially hazardous to health
Exposure to tobacco smoke especially during pregnancy and in early childhood deteriorates permanently children's lung function and increases their asthma risk
Smoking and exposure to environmental tobacco smoke increase the number of asthma exacerbations
Although legislation has reduced the exposure to environmental tobacco smoke, it is necessary to continue promoting nonsmoking in families and among asthma patients.
It is important to influence the attitude of young girls to smoking to prevent harmful effects upon the fetus during pregnancy

environmental tobacco smoke. It is highly important to support and advice parents, who are facing social problems. Final conclusions and recommendation are presented in Table 2.

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References

1. Haahtela T, vonHerzen L, Mäkelä M, and Allergy Programme Working Group. Finnish Allergy Programme 2008-2018 - time to act and change the course. *Allergy* 2008;**63**:634–645.
2. Bousquet J, Dahl R, Khaltaev N. Global alliance against chronic respiratory diseases. Global Alliance against Respiratory Diseases (GARD). *Allergy* 2007;**62**:216–223.
3. Helakorpi S, Prättälä R, Uutela A. Health Behaviour and Health among the Finnish Adult Population, Spring 2007. Publications of the National Public Health Institute, 2008: http://www.ktl.fi/attachments/suomi/julkaisut/julkaisusarja_b/2008/2008b06.pdf.
4. Pennanen M, Patja K, Joronen K. Tupakkakertomus 2006. (Tobacco report 2006) Publications of the National Public Health Institute, 2006: http://www.ktl.fi/attachments/suomi/julkaisut/julkaisusarja_b/2006/2006b3.pdf (In Finnish).
5. Jaakkola MS, Jaakkola JJK. Impact of smoke-free workplace legislation on exposures and health: possibilities for prevention. *Eur Respir J* 2006;**28**:397–408.
6. Lund KE, Skrandal A, Vertio H, Helgason AR. Children's residential exposure to environmental tobacco smoke varies greatly between Nordic countries. *Scand J Soc Med* 1998;**26**: 115–120.
7. Ruston L. Health Impact of Environmental Tobacco Smoke in the Home. *Rev Environ Health* 2004;**19**: 291–304.
8. Klaukka T, Hirvonen A, Karhula K, Peura S. Hyviä ja huonoja uutisia astmasta. *Astmabarometrin* 2004 keskeiset tulokset. *Suom Lääkäril* 2004;**42**:4002–4004. (In Finnish)
9. Ryttilä P, Kinnula V. Keuhkohtaumataudin varhaisdiagnostiikka: keuhkofunktiotutkimuksista inflammatio diagnostiikkaan. *Duodecim* 2005;**121**:2421–2430. (katsaus) (In Finnish)
10. The Ministry of Social Affairs and Health. A scientific review on the health effects of environmental tobacco smoke. The Ministry of Social Affairs and Health, 2000:11. ISBN 952-00-0881-0, ISSN 1236-2115. (In Finnish).
11. Stocks J, Dezauteaux C. The effect of parental smoking on lung function and development during infancy. *Respirology* 2003;**8**:266–285.
12. Jaakkola N, Ruotsalainen R, Jaakkola JJK. What are the determinants of children's exposure to environmental tobacco smoke? *Scan J Soc Med* 1994;**21**:107–112.
13. Office of Environmental Health Hazard Assessment California Environmental Protection Agency. Health effects assessments for environmental tobacco smoke. Office of Environmental Health Hazard Assessment California Environmental Protection Agency, 2005.
14. Cook DG, Strachan DP. Health effects of passive smoking 7. Parental smoking, bronchial reactivity and peak flow variability in children. *Thorax* 1998;**89**:560–566.
15. Stick SM, Burton PR, Gurrin L, Sly PD, Le Soeuf PN. Effect of maternal smoking during pregnancy and a family history of asthma on respiratory function in newborn infants. *Lancet* 1996;**348**:1060–1064.
16. Tager IB, Ngo L, Hanrahan JP. Maternal smoking during pregnancy: effects on lung function during the first 18 months of life. *Am J Respir Crit Care Med* 1995;**152**:977–983.
17. Dezauteaux C, Stocks J, Wade AM, Dundas I, Fletcher MF. Airway function at one year: association with pre-morbid airway function, wheezing, and maternal smoking. *Thorax* 2001;**56**:680–686.
18. Moshhammer H, Hoek G, Luttmann-Gibson H, Neuberger MA, Antova T, Gehring U et al. Parental smoking and lung function in children, an international study. *Am J Respir Crit Care Med* 2006;**173**:1255–1263.
19. Svanes C, Omenaas E, Jarvis D, Chinn S, Gulsvik A, Burney B. Parental smoking in childhood and adult obstructive lung disease: Results from the European Community Respiratory Health Survey. *Thorax* 2004;**59**:295–302.
20. Rizzi M, Sergei M, Andreoli A, Pecis M, Bruschi C, Fanfulla F. Environmental tobacco smoke may induce early lung damage in healthy male adolescents. *Chest* 2004;**125**:1387–1393.
21. Gilliland FD, Berhane K, McConnel R, Gauderman WJ, Vora H, Rappaport EB et al. Maternal smoking during pregnancy, environmental tobacco smoke exposure and childhood lung function. *Thorax* 2000;**55**:271–276.
22. Elliot JG, Carroll NG, James AL, Robinson PJ. Airway alveolar attachment points and exposure to cigarette smoke in utero. *Am J Respir Crit Care Med* 2003;**167**:45–49.
23. Palmer CNA, Doney ASF, Lee SP, Murrie I, Ismail T, Macgregor DF et al. Glutathione S-transferase M1 and P1 genotype, passive smoking, and peak expiratory flow in asthma. *Pediatrics* 2006;**118**:710–716.
24. Gilliland FD, Islam T, Berhane K, Gauderman WJ, McConnell R, Avol F et al. Regular smoking and asthma incidence in adolescents. *Am J Respir Crit Care Med* 2006;**174**:1094–1100.
25. Li JSM, Peat JK, Xuan W, Berry G. Meta-analysis on the association between environmental tobacco smoke (ETS) exposure and the prevalence of lower respiratory tract infection in early childhood. *Pediatr Pulmonol* 1999;**27**:5–13.
26. Young S, Le Souef PN, Geelhoed GC, Stick SM, Turner KJ, Landau LI. The influence of a family history of asthma and parental smoking on airway responsiveness in early infancy. *N Engl J Med* 1991;**324**:1168–1173.
27. Cook DG, Strachan DP, Carey IM. Health effects of passive smoking. 9. Parental smoking and spirometric indices in children. *Thorax* 1998;**53**:884–893.
28. Strachan DP, Cook DG. Health effects of passive smoking 5. Parental smoking and allergic sensitization in children. *Thorax* 1998;**53**:117–123.
29. Magnusson LL, Olesen AB, Wennborg H, Olsen J. Wheezing, asthma, hay fever, and atopic eczema in childhood following exposure to tobacco smoke in fetal life. *Clin Exp Allergy* 2005;**35**:1550–1556.
30. Noakes PS, Hale J, Thomas R, Lane C, Devadason SG, Prescott SL. Maternal smoking is associated with impaired neonatal toll-like-receptor-mediated immune responses. *Eur Respir J* 2006;**28**:721–729.
31. Noakes PS, Thomas R, Lane C, Mori TA, Barden AE, Devadason SG et al.

- Association of maternal smoking with increased infant oxidative stress at 3 months of age. *Thorax* 2007;**62**:714–717.
32. Gilliland FD, Li YF, Dubeau L, Berhane K, Avol E, McConnel R et al. Effect of glutathione *S*-transferase M1, maternal smoking during pregnancy, and environmental tobacco smoke on asthma and wheezing in children. *A J Respir Crit Care Med* 2002;**166**:457–463.
33. Jaakkola MS, Jaakkola JJK. Effects of environmental tobacco smoke on the respiratory health of adults. *Scand J Work Environ Health* 2002;**28**(Suppl 2):52–70.
34. Jaakkola MS, Piipari R, Jaakkola N, Jaakkola JJN. Environmental tobacco smoke and adult-onset asthma: a population-based incident Case-control study. *Am J Pub Health* 2003;**12**:2055–2060.
35. Larsson ML, Loit H-M, Meren M, Polluste J, Magnusson A, Larsson K et al. Passive smoking and respiratory symptoms in FinEsS Study. *Eur Respir J* 2003;**21**:672–676.
36. Dhala A, Pinsker K, Prezant DJ. Respiratory health consequences of environmental tobacco smoke. *Clin Occup Med* 2004;**5**:139–156.
37. Eisner MD, Yelin EH, Katz PP, Blanc PD. Exposure to indoor combustion and adult asthma outcomes: environmental tobacco smoke, gas stoves and wood smoke. *Thorax* 2002;**57**:973–978.
38. Eisner MD, Klein J, Hammond SK, Koren G, Lactao G, Iribarren C. Directly measured second hand smoke exposure and asthma health outcomes. *Thorax* 2005;**60**:814–821.
39. Piipari R, Jaakkola JJK, Jaakkola N, Jaakkola MS. Smoking and asthma in adults. *Eur Respir J* 2004;**24**:734–739.
40. Chalmers GW, MacLeod KJ, Thomson L, Little SA, McSharry C, Thomson NC. Smoking and airway inflammation in patients with mild asthma. *Chest* 2001;**120**:1917–1922.
41. Chalmers GW, Macleod KJ, Little SA, Thomson LJ, McSharry CP, Thomson NC. Influence of cigarette smoking on inhaled corticosteroid treatment in mild asthma. *Thorax* 2002;**57**:226–230.
42. Chaudhuri R, Livingston E, McMahon AD, Thompson L, Borland W, Thompson NC. Cigarette smoking impairs the therapeutic response to oral corticosteroids in chronic asthma. *Am J Respir Crit Care Med* 2003;**168**:1308–1311.
43. Boulet L-P, Lemiere C, Archambault F, Carrier G, Descary MC, Deschesnes F. Smoking and asthma: clinical and radiologic features, lung function, and airway inflammation. *Chest* 2006;**129**:661–668.
44. Xu X, Dockery DW, Ware JH, Speizer FE, Ferre BG Jr. Effects of cigarette smoking on rate of loss of pulmonary function in adults: a longitudinal assessment. *Am Rev Respir Dis* 1992;**146**:1345–1348.
45. Lange P, Parner J, Vestbo J, Schnohr P, Jensen G. A 15-year follow-up study of ventilatory function in adults with asthma. *N Engl J Med* 1998;**339**:1194–1200.
46. Siroux V, Pin I, Oryszszyn MP, Le Moual N, Kauffmann F. Relationship of active smoking to asthma and asthma severity in the EGEA study. Epidemiological study of the genetics and environment of asthma. *Eur Respir J* 2000;**15**:470–477.
47. Silverman RA, Boudreaux ED, Woodruff PG, Clark S, Camargo CA Jr. Cigarette smoking among asthmatic adults presenting to 64 emergency departments. *Chest* 2003;**123**:1472–1479.
48. Marquette CH, Saulnier F, Leroy O, Wallaert B, Chopin C, Demarcq JM et al. Long-term prognosis of near fatal asthma. A 6-year follow-up study of 145 asthmatic patients who underwent mechanical ventilation for a near-fatal asthma attack. *Am Rev Respir Dis* 1992;**153**:1519–1529.
49. Toren K, Lindholm NB. Do patients with severe asthma run an increased risk for ischemic heart Ulrik CS, Lange P. Cigarette smoking and asthma. *Monaldi Arch Chest Dis* 2001;**56**:349–353.
50. Gallefoss F, Bakke PS. Does smoking affect the outcome of patient education and self-management of asthmatics? *Patient Educ couns* 2003;**49**:91–97.
51. Shein JR. Cigarette smoking and clinically significant drug interactions. *Ann Pharmacol Ther* 1995;**29**:1139–1148.
52. Chaudhuri R, Livingston E, McMahon AD, Lafferty J, Fraser I, Spears M et al. Effects of smoking cessation on lung function and airway inflammation in smokers with asthma. *Am J Respir Crit Care Med* 2006;**174**:127–133.