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Lifetime exposure to cigarette smoking and the development of adult-onset atopic dermatitis

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Summary

Background Adult-onset atopic dermatitis (AD) has recently been recognized as a distinct disease entity, but its risk factors have not yet been clearly defined. Although gestational and perinatal exposure to tobacco smoking may be associated with the development of classic AD, the association between active/passive smoking and adult-onset AD remains controversial.

Objectives To determine if exposure to smoking, including environmental tobacco smoke (ETS), is associated with the risk of adult-onset AD.

Methods Tobacco smoking and exposure to ETS were measured in a case–control association analysis in 83 patients with physician-diagnosed adult-onset AD and 142 age- and sex-matched controls.

Results Multiple logistic regression analyses showed that, among the potential environmental risk factors, both current and ever smoking were significant risk factors for adult-onset AD [odds ratio (OR) 4·994 and 3·619, respectively], compared with never smoking. Also, packs per year was significantly associated with adult-onset AD (OR 1·058, 95% confidence interval 1·028–1·089), suggesting a lifelong cumulative risk in current smokers. Moreover, nonsmokers with adult-onset AD reported significantly more exposure to ETS.

Conclusions Early and/or current exposure to cigarette smoking may contribute cumulatively to the development of adult-onset AD. Exposure to ETS in childhood is associated with the development of adult-onset AD. Adults should be discouraged from smoking to prevent adult-onset AD in themselves and their family members.

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Conflicts of interest
None declared.

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Atopic dermatitis (AD) is characterized by chronic relapses of dermatitis in patients with a personal or family history of atopic disease. The onset of AD commonly occurs in early childhood, although symptoms can persist or begin in adulthood.[1] Depending on the age of onset, AD preferentially affects specific locations on the skin. For example, AD usually affects flexural areas with lichenification in children, while adult-onset AD preferentially affects the face and hands.[2] Taking into consideration the familial tendency towards specific antigen sensitization to AD, a complex interplay of genetic and environmental factors may play an important role in the pathogenesis of AD.[3] Several important environmental factors are considered risks for AD, including food allergens, aeroallergens and infectious agents such as *Staphylococcus aureus*;[4,5] this study focuses on tobacco smoking and its possible contribution to AD. Although the development of AD was thought to occur in very early childhood, recently several groups from Japan,[6] Australia[2] and the U.S.A.[7] have described adult-onset AD. Both classical AD and adult-onset AD cases present with intensive itching. However, adult-onset AD differs from classical AD by preferentially affecting the face, hands and nonflexural areas[7,8] and a prurigo-like pattern occurs more frequently in adult-onset AD.[9] Except for a study in Italy demonstrating the outcome of patch tests in patients,[8] no risk factors have been defined for adult-onset AD.

Although there is an increased risk of asthma from gestational and perinatal exposure to smoking,[10,11] studies investigating the influence of such exposure on the development of AD show mixed results.[10–14] Wang *et al.*[12] reported that exposure to smoke during pregnancy might increase the risk of childhood AD, but results from other reports are inconsistent with these findings.[13,14] A molecular investigation found blood IgE to be elevated in infants born to mothers who smoked,[15] and there are reports that active smoking might increase IgE in asthmatic patients.[16,17] Evidence that exposure to environmental tobacco smoke (ETS) during early childhood predisposes the child to later AD has been documented,[12,13] but the association between current smoking and the development of AD remains unclear. Using mail-in questionnaires from a study population of 40 888 subjects, Bo *et al.*[18] reported an association between active smoking and the development of AD in Norway [odds ratio (OR) 1·31], but the association did not reach significance. In the U.K., self-reported mail-in questionnaires from 150 patients with AD also suggested a similar but insignificant association with smoking (OR 1·1).[19] In France, an analysis of 14 578 subjects reported a significant association between active smoking and AD in adolescents (OR 1·8).[20] Although the approaches varied considerably, from very large surveys with no clinical data to smaller clinical studies, these studies consistently indicate an association of active smoking with AD. The studies, however, did not specifically address the association of active smoking and adult-onset AD, probably because they were studying cases of classical AD in which the age of onset precedes the onset of smoking behaviour. Moreover, self-reported questionnaire surveys are subject to inaccurate diagnosis for AD and a low response rate, and they lack a physician diagnosis. Smoking more than 10 cigarettes per day is reported to increase the risk of hand eczema, also suggesting a potential link between smoking and adult-onset AD.[21] Thus, the current evidence consistently suggests a link between tobacco smoking and AD, but a more thorough investigation is required to support the link. Moreover, how adult-onset AD is associated with smoking has never been addressed. In this hospital-based, case–control study we investigated whether exposure to tobacco smoke, including current smoking, ever smoking and ETS, is associated with the risk of adult-onset AD. It represents the first study to investigate directly the possible association between ETS exposure and adult-onset AD.

Materials and methods

Patient recruitment

We conducted a hospital-based, cross-sectional, case–control study. Patients with AD were recruited from a dermatological clinic at our medical centre from 1 January to 15 December 2008. It was probable that the patients with AD in this tertiary centre were not newly defined cases because many of them had visited local clinics before they sought advice at our medical centre. A diagnosis of AD was based on the criteria proposed by Hanifin and Rajka.[22] These include four major criteria, pruritus, chronic or relapsing dermatitis, dermatitis affecting flexural surfaces in adults, and a personal or family history of cutaneous or respiratory atopy, and 23 minor criteria, including hypopigmented patch, infraorbital darkening, cheilitis, hyperlinearized palm and elevated IgE, etc. To be included in the study, the patients had to meet three major criteria plus at least one minor criterion or two major criteria plus at least three minor criteria.[22] Any patient who was aged > 20 years when AD symptoms first appeared was considered to have adult-onset AD. We took a medical history and performed physical examinations and blood biochemistry examinations to exclude other diseases causing pruritus, such as contact dermatitis, asteatotic dermatitis and metabolic diseases. Suspected cases were also biopsied to exclude other mimicking cutaneous diseases, including cutaneous T-cell lymphoma. Patients were excluded if they had received any topical treatments for at least 2 weeks or systemic treatment for 2 months prior to the study, or if they had active skin diseases other than AD, including human immunodeficiency virus (HIV) infection and cancers of any origin. In total, we enrolled 83 patients with AD (27 men and 56 women, age 58·14 ± 18·69 years). Patients visiting the same hospital in the Department of Preventive Medicine for medical diseases other than atopic diseases were referred to the Department of Dermatology as hospital-based controls. They were excluded if they had active skin disease, a past history of AD, allergic asthma, allergic rhinitis, allergic conjunctivitis, cancers of any origin or HIV infection, or were taking oral corticosteroids. A total of 142 similar aged, normal hospital-based controls (52 men and 90 women, age 57·15 ± 15·66 years) were included. A board-certified dermatologist took a medical history, examined the whole surface the body, and assigned a Scoring Atopic Dermatitis (SCORAD) severity index score for each subject. Venous peripheral blood was drawn and the serum was stored at −70 °C until assayed. IgE levels from patients with AD were measured in a College of American Pathologists-accredited laboratory at the same hospital. The study was approved by the institutional review board of the hospital. All clinical assessments and specimen collections were conducted according to Declaration of Helsinki principles. Each participant signed an informed written consent form before entering the study. Patients or controls who did not sign the inform consent were excluded (15 and 20, respectively), leaving us with enrolment rates of 0·85 (83/98) and 0·88 (142/162), respectively.

Questionnaire

Patients with dermatologist-confirmed adult-onset AD and non-AD controls were interviewed by a well-trained staff member using a questionnaire modified from the Nordic Occupational Skin Questionnaire (NOSQ-2002).[23] Our modified questionnaire contained more detailed questions about smoking behaviour. Smoking pack years, packs per day and age of exposure to ETS were all recorded. Smoking pack year

was defined as the multiplication of 'packs smoked per day' by 'years as a smoker'. This 'smoking pack year' is an exposure indicator for cumulative smoking dose and, although it is an approximate rate, it was the best method available to us for evaluating current smoking levels. It cannot be used to estimate the ETS dosage. Occupation was categorized as office worker, industrial worker, house worker, farmer and fisherman, student or none of the above.

MAST®-CLA® assay

The MAST®-CLA® allergen-specific IgE assay (MAST Immunosystem Inc., Mountain View, CA, U.S.A.) is an *in vitro* test for the semiquantitative determination of circulating allergen-specific IgE concentrations in human sera. Sensitized allergens were determined following the manufacturer's instructions. The intensity of the result was determined by a densitometer, scored semiquantitatively from 0 to 4+. A score of about two was assumed to be positive.

Statistical analysis

This was a case–control, cross-sectional study investigating the association between exposure to tobacco smoke and risk of adult-onset AD. Most cases were not new, as they had visited many local clinics before visiting our medical centre. A one-sample Student's *t*-test was used to determine the differences in continuous variables, such as age, height and weight between cases of AD and controls. For categorical and proportional data, such as sex and presence of allergen-specific IgE, a χ^2 test or Fisher's exact test was used. The 2 : 1 frequency matching was used as an initial step based on age and sex. Age matching was applied at a range of ± 3 years. Controls were recruited from visitors to the hospital's Department of Preventive Medicine. We could not easily match extremely old patients; thus, the best-matched control was taken from the visitors to the Department of Preventive Medicine within a 3-day time frame. Multiple unconditional logistic regressions were used to analyse the OR for developing adult-onset AD (SPSS v.14.0; SPSS, Chicago, IL, U.S.A.). $P < 0{\cdot}05$ was considered significant.

Results

Demographic characteristics of patients with adult-onset atopic dermatitis and controls

In total, we enrolled 83 patients with physician-diagnosed adult-onset AD and 142 age- and sex-matched controls (Table 1). There were no significant differences in height and weight between the patients with adult-onset AD and the controls. The age of onset of AD in the patients ranged from 22 to 64 years (mean 47). Blood IgE levels were higher than standard normal values in the patients with adult-onset AD (729·22 ± 1990·63 vs. < 100 IU mL^{-1}). The patients with AD had a SCORAD severity index score of 44·96 ± 21·16 and all had intense generalized itching; eight of the 83 patients with AD had asthma. The patients with AD had a significantly higher rate of smoking (53%, 44 current and ever smokers) than the controls (18·3%, 26 current and ever smokers). There was no significant difference in the ages that they started smoking (23·66 ± 13·87 vs. 22·88 ± 4·73 years, respectively). We found that a significantly higher proportion of nonsmokers with adult-onset AD had past exposure to ETS (33%) compared with controls (12%). Most cases and controls were industrial workers, and there was no significant occupational difference between the two groups.

Both current smoking and exposure to environmental tobacco smoke are associated with adult-onset atopic dermatitis

We ran a multiple logistic regression analysis to determine the risk factors for adult-onset AD. Adjusting for sex and age, we found that both current and ever smokers had a significantly higher OR for developing AD compared with nonsmokers [4·994, 95% confidence interval (CI) ~1·66–15·37 and 3·619, 95% CI ~1·30–10·03, respectively] (Table 2).

Cumulative risk for adult-onset atopic dermatitis from smoking

To investigate further the effect of dosage, we used a multiple logistic regression analysis to determine the cumulative risk for adult-onset AD from current smoking. As seen in Table 3, after adjusting for sex and age, we found smoking pack year to be significantly associated with adult-onset AD (OR 1·058, 95% CI 1·02–1·08). Ordinal classification of smoking pack years is also shown in Table 3. Pearson's correlation did not show a significant association between smoking pack years and the SCORAD severity index in the patients with AD (OR 1·007, 95% CI 0·95–1·05).

Nonsmokers among patients with adult-onset atopic dermatitis reported more exposure to environmental tobacco smoke

We also performed another multiple logistic regression to analyse the effects of timing and location of exposure to ETS and the development of adult-onset AD in nonsmokers (Table 4). After adjusting for sex and age, we found that more nonsmokers with adult-onset AD reported ETS exposure regardless of timing (exposure in childhood vs. in adulthood) and location (exposure at home vs. at work), although those exposed to ETS early in life reached significance (OR 2·916, 95% CI 1·11–7·70). For ever smokers, however, the effect of ETS exposure seemed to be masked as shown by similar ORs for different exposure timings and locations. These data suggest that early exposure to ETS predisposes people toward the future development of adult-onset AD.

Table 1 Demographic data, smoking status, occurrence of allergen-specific IgE and occupation among patients with adult-onset atopic dermatitis (AD) and controls

	Adult-onset AD (n = 83)	Controls (n = 142)	P-value
Age (years)	58·14 ± 18·69	57·15 ± 15·66	0·686
Height (cm)			
Male	166·73 ± 5·62	167·29 ± 8·50	0·664
Female	156·58 ± 5·80	156·87 ± 6·14	0·843
Weight (kg)			
Male	67·24 ± 10·40	68·36 ± 10·70	0·537
Female	59·42 ± 11·20	55·84 ± 8·20	0·112
Sex, male : female (%)	32·5 : 67·5	36·6 : 63·4	0·245
Age of onset (years)	47·2 ± 14·5	–	
IgE (IU mL^{-1})	729·22 ± 1990·63	–	–
SCORAD index	44·96 ± 21·16	–	–
Asthma, n	8	0	
Smoking status			
Smoker, current and ever, n (%)	44 (53)	26 (18·3)	< 0·01
Age of starting smoking in smokers (years)	23·66 ± 13·87	22·88 ± 4·73	0·743
Nonsmoker, n (%)	39 (47)	116 (81·7)	< 0·01
Nonsmoker with ETS exposure, n (%)	13 (33)	14 (12·1)	< 0·01
Allergen-specific IgE, n (%)			
House dust mite	23/51 (45)	N/A	
Cat	3/51 (5·8)	N/A	
Dog	4/51 (7·8)	N/A	
Feather	1/51 (1·9)	N/A	
Family history of atopy, n (%)	18 (19·2)	14 (9·8)	0·01
Occupation, n (%)			
House workers	6 (7·2)	12 (8·5)	0·686
Farmers and fishermen	6 (7·2)	16 (11·3)	
Industrial workers	35 (42·2)	47 (33·1)	
Office workers	15 (18·1)	32 (22·5)	
Healthcare givers	11 (13·2)	13 (9·2)	
Students	7 (8·4)	15 (10·6)	
None of the above	3 (3·6)	7 (4·9)	

Vales are mean ± SD unless otherwise indicated. ETS, environmental tobacco smoke.

Table 2 Risk of smoking in adult-onset atopic dermatitis by multiple logistic regression. Sex, age and smoking status were included in the multiple regression analysis

	Odds ratio	95% CI	P-value
Sex (male vs. female)	1·67	~0·75–3·75	0·205
Age	1·022	~0·99–1·04	0·097
Smoking/ETS exposure status (never smokers with low ETS as baseline)			
Nonsmokers with high ETS	2·215	~1·01–4·84	0·056
Former smokers	3·619*	~1·30–10·03	0·013
Current smokers	4·994*	~1·66–15·37	0·005

CI, confidence interval; ETS, environmental tobacco smoke. *Significant.

Table 3 Multiple logistic regressions for smoking pack per day in adult-onset atopic dermatitis. Sex, age and smoking pack years were included in the multiple regression analysis

	Odds ratio	95% CI	P-value
Sex (male vs. female)	1·536	~0·74–3·17	0·246
Age	1·009	0·98–1·03	0·375
Smoking pack years	1·058	1·02–1·08	< 0·001
< 5	1·155	0·24–5·57	0·144
5–15	1·781	1·09–2·91	0·032
15–25	3·129	2·75–3·56	0·013
25–35	5·449	2·85–10·6	0·002
> 35	9·243	7·42–11·41	< 0·001

CI, confidence interval.

Discussion

We found a significant association between current smoking and the development of adult-onset AD as well as an association between exposure to ETS and adult-onset AD in nonsmokers. This study not only confirms the association between current smoking and AD but it also provides more evidence showing the association between current smoking, ever smoking and ETS exposure with adult-onset AD.

Table 4 Nonsmokers exposed to environmental tobacco smoke (ETS) are associated with adult-onset atopic dermatitis. Sex, age, exposure to ETS and smoking status were included in the multiple regression analysis with nonsmokers with low ETS exposure as the baseline

	Odds ratio	95% CI	P-value
Sex (male vs. female)	1·361	~0·58–3·16	0·474
Age	0·993	~0·97–1·02	0·566
Did anybody at HOME smoke when you were younger than 20 years? (Y/N)			
Nonsmokers	2·916*	~1·11–7·69	0·031
Ever smokers	3·546*	~1·21–10·39	0·024
Current smokers	3·954*	~1·51–10·35	0·012
Did anybody at HOME smoke when you were older than 20 years? (Y/N)			
Nonsmokers	1·971	~0·77–5·06	0·159
Ever smokers	2·675*	~1·03–6·95	0·035
Current smokers	3·134*	~1·32–7·44	0·006
Did anybody at WORK smoke when you were younger than 20 years? (Y/N)			
Nonsmokers	2·866	~0·69–11·90	0·147
Ever smokers	2·854	~0·99–8·23	0·065
Current smokers	3·548*	~1·28–9·83	0·009
Did anybody at WORK smoke when you were older than 20 years? (Y/N)			
Nonsmokers	2·220	~0·92–5·35	0·076
Ever smokers	3·165	~0·98–10·22	0·075
Current smokers	3·843*	~1·21–12·21	0·021

CI, confidence interval. *Significant.

There are several ways to determine causalities in biology, including strength, consistency, specificity, temporality, biological gradient, plausibility, coherence, experimental evidence and analogy.[24] This study approached causality from these standpoints: strength (OR 3·6–4·9), temporality (mean age of starting smoking 23·66 years and the onset of AD 47·2 years), biological gradient (smoking pack year vs. AD), experimental evidence (smoking increases IgE) and analogy (smoking induces other atopic diseases such as asthma and allergic rhinitis). Therefore, smoking is probably one cause of AD.

Smoking might act as a disease risk factor, making smokers more susceptible to atopic diathesis. Various studies, for example, have suggested that current smoking is a risk factor for asthma among adolescents,[25,26] although there is a lack of prospective longitudinal studies to confirm this.[20] As in asthma, smoking might also act as a disease modifier aggravating the severity of AD in patients.[27,28] However, we did not find an association between smoking status and severity of AD, so this possibility was less likely according to our study.

Cigarette smoking may affect immunological processes; aberrant regulation of immune responses plays an important role in the pathogenesis of AD.[29] Newborns of mothers who smoke have been reported to have diminished innate immune responses.[30,31] Moreover, early exposure to ETS increases the risk of IgE sensitization to indoor inhalants and food allergens,[32] which contribute to atopy and airway hyper-responsiveness.[33] Smoking augments the production of proinflammatory cytokines such as tumour necrosis factor-α and interleukin (IL)-1 while decreases the levels of anti-inflammatory cytokines such as IL-10.[29] Tobacco smoke, containing a mixture of tens of thousands of chemical compounds, is quite different from the common defined aeroallergens, such as house dust mites. Taking all these factors together, smoking might affect the immune system, rendering people susceptible to atopic diathesis, leading to development of adult-onset AD. However, the pathogenesis might be complicated and may differ in younger children, older children and adults.

Smoking remains a major problem in Taiwan. The prevalence of smoking in 1994 was 23% in adults in Kaohsiung,[34,35] a large harbour city in southern Taiwan. A similar rate was also found around the whole island in the 2001 National Health Interview Survey.[36] Because we found that the more cigarettes smoked over time, the greater the risk of developing adult-onset AD, we strongly recommend cessation as one important means of preventing this disease. Although smoking seems to have little effect on the severity of symptoms in patients with adult-onset AD, quitting smoking theoretically would alleviate the harmful effects of smoking on the immune system.

A strength of this study is that the age at which people start smoking in Taiwan is older than in western nations. For example, the starting age for smoking in this study (about 22 years) is higher than that reported in Germany (15–21 years)[37] and in the U.S.A. (17–18 years).[38] This makes Taiwan a potentially favourable context for studying the association between adult-onset smoking and adult-onset disease. This unique setting may enable interesting scientific comparisons, and may also explain the reason that the findings of this study differ from studies carried out in different settings.[8,12,18,19]

This study had several limitations. Firstly, it was a small case–control, cross-sectional study. A larger scale, prospective longitudinal study with new incident cases would help assess the risk ratio of smoking. Secondly, there is the possibility of recall bias. Smokers tend to under-report the number of packs they smoke and a similar recall bias might occur when the subjects are asked how much ETS they were exposed to decades ago. However, both recall biases lead to an underestimate of the ORs. Thirdly, because the patients with adult-onset AD were enrolled from an outpatient clinic in the Department of Dermatology and the controls were recruited from the Department of Preventive Medicine in the same hospital, this might result in some intrinsic differences. This could be alleviated by careful selection of age- and sex-matched controls as was done in this study. Fourthly, the presence of indoor aeroallergens might confound the analysis of smoking in adult-onset AD. Finally, the high smoking rate might have affected the assessments of ETS exposure and we did not control for ETS exposure dose in adults in our analysis.

In summary, although there are many potential risk factors contributing to development of adult-onset AD, this study provides convincing evidence of the association between both current smoking and exposure to ETS and the development of

adult-onset AD and found a link between accumulated smoking dose and this disease. Because we also found an association with early exposure to ETS, adults should be encouraged to quit smoking to prevent the occurrence of adult-onset AD in themselves, as well as in their families in this country. Further study is needed to understand the mechanisms underlying these observations and also to increase our understanding of other risk factors for adult-onset AD.

What's already known about this topic?

- Gestational and perinatal exposure to tobacco smoking might be associated with the development of classic atopic dermatitis (AD).
- Adult-onset AD is a recently recognized disease and the prevalence keeps rising.

What does this study add?

- The early and/or current exposure to cigarette smoking may contribute cumulatively to the development of adult-onset AD.
- Exposure to environmental tobacco smoke in childhood is associated with the development of adult-onset AD.

References

1 Leung DY, Bieber T. Atopic dermatitis. *Lancet* 2003; **361**:151–60.
2 Bannister MJ, Freeman S. Adult-onset atopic dermatitis. *Australas J Dermatol* 2000; **41**:225–8.
3 Lee CH, Chuang HY, Shih CC *et al.* Correlation of serum total IgE, eosinophil granule cationic proteins, sensitized allergens and family aggregation in atopic dermatitis patients with or without rhinitis. *J Dermatol* 2004; **31**:784–93.
4 Michie CA, Davis T. Atopic dermatitis and staphylococcal superantigens. *Lancet* 1996; **347**:324.
5 Rudikoff D, Lebwohl M. Atopic dermatitis. *Lancet* 1998; **351**:1715–21.
6 Kawashima T, Kobayashi S, Miyano M *et al.* [Senile type atopic dermatitis]. *Nippon Hifuka Gakkai Zasshi* 1989; **99**:1095–103.
7 Ozkaya E. Adult-onset atopic dermatitis. *J Am Acad Dermatol* 2005; **52**:579–82.
8 Ingordo V, D'Andria G, D'Andria C. Adult-onset atopic dermatitis in a patch test population. *Dermatology* 2003; **206**:197–203.
9 Tay YK, Khoo BP, Goh CL. The epidemiology of atopic dermatitis at a tertiary referral skin center in Singapore. *Asian Pac J Allergy Immunol* 1999; **17**:137–41.
10 Keil T, Lau S, Roll S *et al.* Maternal smoking increases risk of allergic sensitization and wheezing only in children with allergic predisposition: longitudinal analysis from birth to 10 years. *Allergy* 2009; **64**:445–51.
11 Magnusson CG. Maternal smoking influences cord serum IgE and IgD levels and increases the risk for subsequent infant allergy. *J Allergy Clin Immunol* 1986; **78**:898–904.
12 Wang IJ, Hsieh WS, Wu KY *et al.* Effect of gestational smoke exposure on atopic dermatitis in the offspring. *Pediatr Allergy Immunol* 2008; **19**:580–6.
13 Schafer T, Dirschedl P, Kunz B *et al.* Maternal smoking during pregnancy and lactation increases the risk for atopic eczema in the offspring. *J Am Acad Dermatol* 1997; **36**:550–6.
14 Miyake Y, Ohya Y, Tanaka K *et al.* Home environment and suspected atopic eczema in Japanese infants: the Osaka Maternal and Child Health Study. *Pediatr Allergy Immunol* 2007; **18**:425–32.
15 Miyake Y, Miyamoto S, Ohya Y *et al.* Association of active and passive smoking with allergic disorders in pregnant Japanese women: baseline data from the Osaka Maternal and Child Health Study. *Ann Allergy Asthma Immunol* 2005; **94**:644–51.
16 Oryszczyn MP, Annesi-Maesano I, Charpin D *et al.* Relationships of active and passive smoking to total IgE in adults of the Epidemiological Study of the Genetics and Environment of Asthma, Bronchial Hyperresponsiveness, and Atopy (EGEA). *Am J Respir Crit Care Med* 2000; **161**:1241–6.
17 Tanaka K, Miyake Y, Sasaki S *et al.* Maternal smoking and environmental tobacco smoke exposure and the risk of allergic diseases in Japanese infants: the Osaka Maternal and Child Health Study. *J Asthma* 2008; **45**:833–8.
18 Bo K, Thoresen M, Dalgard F. Smokers report more psoriasis, but not atopic dermatitis or hand eczema: results from a Norwegian population survey among adults. *Dermatology* 2008; **216**:40–5.
19 Mills CM, Srivastava ED, Harvey IM *et al.* Cigarette smoking is not a risk factor in atopic dermatitis. *Int J Dermatol* 1994; **33**:33–4.
20 Annesi-Maesano I, Oryszczyn MP, Raherison C *et al.* Increased prevalence of asthma and allied diseases among active adolescent tobacco smokers after controlling for passive smoking exposure. A cause for concern? *Clin Exp Allergy* 2004; **34**:1017–23.
21 Meding B, Alderling M, Albin M *et al.* Does tobacco smoking influence the occurrence of hand eczema? *Br J Dermatol* 2009; **160**:514–18.
22 Hanifin J, Rajka G. Diagnostic features of atopic dermatitis. *Acta Dermatol Venereol* (Stockh) 1980; **92** (Suppl.):44–7.
23 Susitaival P, Flyvholm MA, Meding B *et al.* Nordic Occupational Skin Questionnaire (NOSQ-2002): a new tool for surveying occupational skin diseases and exposure. *Contact Dermatitis* 2003; **49**:70–6.
24 Lucas RM, McMichael AJ. Association or causation: evaluating links between 'environment and disease'. *Bull World Health Organ* 2005; **83**:792–5.
25 Strachan DP, Butland BK, Anderson HR. Incidence and prognosis of asthma and wheezing illness from early childhood to age 33 in a national British cohort. *BMJ* 1996; **312**:1195–9.
26 Bodner CH, Ross S, Little J *et al.* Risk factors for adult onset wheeze: a case control study. *Am J Respir Crit Care Med* 1998; **157**:35–42.
27 Reed CE. The natural history of asthma in adults: the problem of irreversibility. *J Allergy Clin Immunol* 1999; **103**:539–47.
28 Reed CE. The natural history of asthma. *J Allergy Clin Immunol* 2006; **118**:543–8.
29 Arnson Y, Shoenfeld Y, Amital H. Effects of tobacco smoke on immunity, inflammation and autoimmunity. *J Autoimmun* 2010; **34**:J258–65.
30 Noakes PS, Hale J, Thomas R *et al.* Maternal smoking is associated with impaired neonatal toll-like-receptor-mediated immune responses. *Eur Respir J* 2006; **28**:721–9.
31 Prescott SL. Effects of early cigarette smoke exposure on early immune development and respiratory disease. *Paediatr Respir Rev* 2008; **9**:3–9.
32 Lannero E, Wickman M, van HM *et al.* Exposure to environmental tobacco smoke and sensitisation in children. *Thorax* 2008; **63**:172–6.
33 Halken S. Prevention of allergic disease in childhood: clinical and epidemiological aspects of primary and secondary allergy prevention. *Pediatr Allergy Immunol* 2004; **15** (Suppl. 16):4–5.

34 Wang CS, Chou P. Characteristics and outcomes of adolescent pregnancies in Kaohsiung County, Taiwan. *J Formos Med Assoc* 1999; **98**:415–21.
35 Wang TN, Ko YC, Chao YY *et al.* Association between indoor and outdoor air pollution and adolescent asthma from 1995 to 1996 in Taiwan. *Environ Res* 1999; **81**:239–47.
36 Hsu CC, Lord AY, Tseng TS *et al.* The impact of the tobacco market opening on smoking status in Taiwan: findings from a secular smoking rates analysis. *Int Q Community Health Educ* 2005; **25**:271–81.
37 John U, Hanke M, Meyer C *et al.* Gender and age differences among current smokers in a general population survey. *BMC Public Health* 2005; **5**:57.
38 CDC. *Women and Smoking: a Report of the Surgeon General*. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention, 2001.