

Decreased importance of environmental risk factors for childhood asthma from 1996 to 2006

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ABSTRACT

Background: The large increase in asthma prevalence continues in several, but not all areas. Despite the individual risk factors that have been identified, the reasons for the observed trends in prevalence are largely unknown.

Objective: This study sought to characterize what trends in risk factors accompanied trends in asthma prevalence.

Methods: Two population-based cohorts of 7-8-year-old children from the same Swedish study areas examined by expanded ISAAC questionnaires were compared 10 years apart. In 1996 3,430 (97% participation) and in 2006 2,585 (96% participation) questionnaires were completed. A subset was skin-prick tested: in 1996, 2,148 (88% participation) and in 2006, 1,700 (90% participation) children. The adjusted population attributable fraction (aPAF) was calculated using the prevalence and multivariate odds ratio of each risk factor.

Results: The prevalence of current asthma and wheeze were similar in 1996 and 2006. Allergic sensitisation however increased from 21% to 30%. The prevalence of parental asthma increased from 17% to 24% while respiratory infections and maternal smoking decreased (60% to 29% and 32% to 16%, respectively). The aPAFs of non-environmental risk factors for current asthma increased 1996-

2006: Allergic sensitization from 35% to 41%, parental asthma from 27% to 45% and male sex from 20% to 25%. Conversely, the aPAFs of environmental risk factors decreased: Respiratory infections from 36% to 32% and damp home and maternal smoking from 14% and 19% respectively to near zero in 2006.

Conclusions and Clinical Relevance: From 1996 to 2006 the non-environmental risk factors parental asthma, allergic sensitisation and male sex had an increasing or constant importance for current asthma in 7-8-year-old children. The importance of the environmental exposures damp home, respiratory infections and maternal smoking decreased. This counter-balancing in risk factors may explain the level prevalence of current asthma.

INTRODUCTION

Asthma is an often life-long disease characterised by persistent airway inflammation and variable airway obstruction. A key feature is airway hyperresponsiveness to triggering factors, with the typical symptoms of wheezy breathing, breathlessness and cough.¹ Its incidence, remission and relapse rates are highest during childhood.^{2, 3} The prevalence of asthma has increased since the 1950's,⁴ and it has been estimated that today more than 300 million people are affected worldwide.⁵ Asthma has thus become a serious public health issue with a considerable impact on health economics.^{6, 7}

Trends in disease prevalence are estimated using repeated cross-sectional studies in the same areas and age groups with identical methods. Some such studies have demonstrated a plateau in the prevalence of childhood asthma in both high-prevalence countries such as the United Kingdom and Australia^{8, 9} and in regions with more moderate prevalence such as Germany and Norway.^{10, 11} We recently demonstrated the same plateau in asthma symptoms in Swedish school children between 1996 and 2006 using general population samples.¹²

Several risk factors for childhood asthma have been identified, including allergic sensitisation, parental asthma, allergic rhinitis and maternal smoking.^{3, 13-15} However, their impact on prevalence trends over time has rarely been studied. A recent plateau in childhood asthma prevalence could in principal be explained by 1) saturation with asthma in children susceptible to the disease, or 2)

changes in the risk factor pattern resulting in an attenuation of a previously increasing risk in the population. Repeated cross-sectional studies of disease and risk factors can suggest how risk factor patterns affect time trends in disease. To evaluate the impact of a risk factor on the population level, both its strength of association and its prevalence must be taken into account.

We conducted two large population-based studies, in 1996^{13, 16} and 2006^{12, 17} respectively, of 7-8-year-old children with near total participation. The aim was to investigate trends in wheeze, asthma and in their associated risk factors, assessed by comprehensive and validated questionnaires and skin prick tests. A further aim was to estimate the impact of changes in the risk factor patterns for asthma and wheeze in the population.

METHODS

Study populations

The establishing of the Obstructive Lung Disease in Northern Sweden (OLIN) paediatric study has been described in detail.¹⁶ Briefly, in 1996 all schoolchildren in first and second grade (age 7-8 years with few exceptions) in three municipalities in Sweden were invited to a questionnaire survey and 3,430 (97% of the invited, 49% girls) children participated. This cohort has been followed annually until age 19 years.^{13, 18} In 2006 a new cohort was identified using identical methods: first and second grade schoolchildren in the same areas were invited and 2,585 (96%, 48% girls) participated, the lower number of participants due to lower birth rates.^{12, 17}

Procedures

The questionnaire included the International Study of Asthma and Allergy in Childhood (ISAAC)¹⁹ core questions and added questions regarding symptoms, disease diagnoses, medications and potential risk factors including lifestyle factors.^{13, 20} Questionnaire reports of physician-diagnosed asthma were clinically validated, finding a very high specificity and high sensitivity.¹⁶ In 2006 the same questionnaire was used, which has been published in full.^{12, 17} The ethical review board at Umeå University approved the studies.

In both 1996 and 2006, the children in two of the three municipalities were invited to skin prick testing for allergic sensitisation. In 1996, 2,148 (88%, 50% girls) of the invited children participated.^{13, 20} In 2006, 1,700 (90%, 50% girls) children participated.¹⁷ Ten standard inhalant allergens were used: birch, timothy, mugwort, cat, dog, horse, *Dermatophagoides pteronyssinus*, *D. farinae*, *Cladosporium* and *Alternaria*, with histamine 10 mg/ml as positive control and glycerol as negative control (Soluprick, ALK, Hørsholm, Denmark). Allergic sensitisation was defined as at least one positive (≥ 3 mm) wheal after 15 minutes. Serum samples from a subset of the children showed excellent correlation between a positive wheal and IgE >0.35 I.U./ml both in 1996² and 2006.¹⁷

Definitions

Current wheeze: Wheezing or whistling in the chest in the last twelve months. *Current asthma*: Physician-diagnosed asthma and either wheeze or use of asthma medications in the last twelve months. *Damp home*: Indoor moisture damage or moulds. *Respiratory infections*: A history of pertussis, croup, pneumonia or other severe respiratory infection. *Maternal smoking*: Mother currently smoking. *Low birth weight*: Birth weight $<2,500$ gram. Risk factors were categorised as primarily environmental: e.g. breastfeeding <3 months; early city living; respiratory infections; no siblings (indicating lower infectious load); damp home and maternal smoking, or non-environmental: e.g. male sex; parental asthma and allergic sensitisation.

Statistical analyses

The ISAAC recommendations¹⁹ for analysing questionnaire data were followed. Analyses which included data on allergic sensitisation were limited to the skin tested children. We used the Statistical Package for Social Science (SPSS) software, version 11.5 (SPSS Inc, Chicago, IL, USA). Prevalence comparisons used the two-sided χ^2 test or Fisher's Exact Test when appropriate, with a $p < 0.05$ significance level. The importance of each risk factor was studied as its strength of association with wheeze/asthma, the prevalence of the risk factor, and as adjusted population attributable fraction (below). Strength of association was expressed as univariate risk ratios (RR) and multivariate odds ratios (OR) including their 95% confidence intervals (95% CI). The multivariate associations were stable also when the five weakest risk factors were excluded stepwise.

The population attributable fraction (PAF) is an estimate of the proportion (percentage) of disease in the population that can be attributed to an exposure. Asthma is a multifactorial disease and thus, adjusted population attributable fractions (aPAF) with 95% CI were back-calculated from the multivariate odds ratios. Data on aPAF are presented for the six most important risk factors for current asthma and wheeze in 1996 and/or 2006 identified through multivariate analyses. The method described by Eide *et al.*²¹ was followed, using the *aflogit* procedure in STATA 9.1 (STATA Corp, Texas, USA) to adjust for covariance between risk factors. The 95% CIs of aPAFs are inherently wide due to their being based on 95% CI estimates both for the prevalence of risk factors and the associations in the multivariate analysis. Owing to the mathematical method no 95% CIs were calculated for negative aPAF values.²¹

RESULTS

Prevalence

From 1996 to 2006 there were no statistically significant changes in the prevalence of current wheeze and current asthma (from 11.7% to 13.0%, $p=0.13$ and from 5.3% to 6.1%, $p=0.18$, respectively) (Table 1). These data have previously been published in detail.¹²

There were however substantial changes in the prevalence of risk factors. Generally, the prevalence of known environmental risk factors decreased, while non-environmental factors increased or were stable. The prevalence of respiratory infections decreased by half from 59.9% to 28.6% ($p<0.01$), as did maternal smoking, from 31.5% to 15.8% ($p<0.01$), and also the prevalence of breastfeeding <3 months and damp home decreased. Conversely, the prevalence of non-environmental risk factors was unchanged or increased: Allergic sensitisation increased from 20.6% to 29.9% ($p<0.01$)¹⁷ and parental asthma increased from 17.2% to 24.4% ($p<0.01$).

The cumulative prevalence of having 0-4 of the environmental (damp home; no siblings; maternal smoking and respiratory infections) and non-environmental (male sex; parental asthma; low birth weight and allergic sensitisation) in 1996 and 2006 are displayed in Figure 1. The prevalence of having one or more environmental risk factor for current asthma decreased from 75.9% to 48.0% ($p<0.01$), and from 31.2% to 11.3% ($p<0.01$) for having two or more environmental risk factors. In contrast, the prevalence of having one or more non-environmental risk factors increased from 66.8%

to 72.1% ($p<0.01$), and the group having three or four non-environmental risk factors nearly doubled from 3.2% to 6.1% ($p<0.01$).

Risk factor analyses

Out of a large screening for potential risk factors, the most relevant univariate relationships are listed in Table 2. The statistically significant risk factors for current asthma and current wheeze by univariate analysis were stepwise entered into a multivariate model (Table 3). In general, the risk factor relationships were similar for current asthma and current wheeze.

For current asthma in 1996 and 2006 the most important risk factors were allergic sensitisation (odds ratio, OR 4.34 and 3.70) and parental asthma (OR 3.13 and 4.73) (Table 3). Respiratory infections was the strongest environmental risk factor in both years, OR 2.08 and 2.88. Respiratory infections was even more strongly associated with current wheeze. For current asthma and current wheeze, damp home and maternal smoking lost their statistically significant associations from 1996 to 2006. The associations of male sex with current wheeze increased from 1996 to 2006.

Population attributable fraction

The importance on the population level of each risk factor was estimated using adjusted population attributable fractions (aPAF) which takes into account both the prevalence and the strength of association by multivariate analysis. For current asthma in 1996 the most important risk factors were respiratory infections, aPAF 36% (95% CI 10%-54%); allergic sensitisation, aPAF 35% (22%-46%) and parental asthma, aPAF 27% (15%-38%) (Figure 2). Damp house, maternal smoking and male sex all had aPAF:s between 14% and 20%.

In 2006 the aPAFs of parental asthma and allergic sensitisation had increased to 45% (29%-58%) and 41% (24%-54%). As the aPAF of male sex had also increased, the three major non-environmental risk factors had increased their aPAFs substantially. Conversely, the aPAFs of the major environmental risk factors decreased: respiratory infections decreased to aPAF 32% (15%-45%), and the aPAF of damp house and maternal smoking decreased to near zero.

Also for current wheeze a general pattern of decreased importance of environmental risk factors and increased importance of non-environmental factors from 1996 to 2006 was seen. The aPAFs of non-environmental risk factors increased or were stable: Male sex from 8% to 25%, allergic sensitisation from 24% to 34% and parental asthma from 14% to 15%. The aPAFs of current wheeze for all three environmental risk factors decreased: Respiratory infections from 51% to 41%, damp home from 13% to 2% and maternal smoking from 10% to 2%.

DISCUSSION

We have shown trends in asthma and wheeze from 1996 to 2006 and the parallel changes in risk factor patterns. The prevalence of current wheeze and asthma did not increase significantly despite substantial increases in allergic sensitisation and parental asthma, both important risk factors for asthma in the first^{2, 13, 16, 20, 22} as well as in the second cohort.^{12, 17} We also observed parallel decreases mainly in the studied environmental risk factors maternal smoking, respiratory infections and living in a damp home.

This was a study of two large cohorts of children of the same age and residence with excellent participation using identical and validated methods. Unlike some previous well-designed risk factor studies²³⁻²⁶ the invited cohorts were based on the general population, i.e. all children in three areas, and not selected from high-risk populations. Limitations to our study were lack of objective tests for asthma, such as pulmonary function or bronchial challenge tests, and objective assessments of risk factors. However, the diagnosis of childhood asthma has been validated in the 1996 cohort with very high specificity and positive predictive value, and good sensitivity.¹⁶ The outcome “current wheeze” is widely used and, unlike physician-diagnosed asthma, not prone to diagnostic differences between geographical regions.^{27, 28}

Globally the prevalence of asthma and allergic conditions has increased parallel to major environmental and lifestyle changes and numerous publications have addressed strength of associations (risk/odds/hazard ratios).^{3, 23, 26, 29, 30} At the population level, however, a strong but rare risk factor has limited importance. Thus, a measure taking into account both the strength of association and the prevalence of a risk factor, such as the population attributable fraction, is of greater value. The population attributable fraction should not be interpreted as “the proportion of

disease caused by a risk factor” when the etiologic relationship has not been elucidated.³¹ This holds especially true for unmodifiable risk factors. We thus instead used adjusted population attributable fractions to illustrate the combined effects of changes in exposure prevalence and strength of association (risk). Expressed as aPAFs, the risk factor models accounted for $\geq 85\%$ of current asthma and 78% of current wheeze both in 1996 and 2006. To our knowledge this is the first study using this method in estimating the effect of trends in risk factors on the prevalence of asthma.

Allergic sensitisation¹⁷ and parental asthma both increased in prevalence. Accordingly, their corresponding aPAFs of asthma and wheeze tended to increase. Less than half (35% in 1996, 41% in 2006) of current asthma was attributable to allergic sensitisation, similar to the 38% in a recent meta-analysis.³² The meta-analysis however concluded that the proportion of asthma attributable to sensitisation is much dependent on how sensitisation is defined. In our study the importance of allergic sensitisation was even lower for current wheeze, indicating that the attributable fraction of sensitisation seems to increase with increasing severity of symptoms.³³ These findings support the idea that childhood asthma should not be regarded as a single allergic disease entity, but rather as being comprised of several phenotypes.^{34, 35} The prevalence of the allergic asthma phenotype increased in the present study. Unfortunately, the cross-sectional nature of the study precluded analyses of time patterns in wheeze, which has previously been used to further phenotype asthma in childhood.

The high incidence of asthma in children^{2, 36} and adolescents,^{37, 38} which may to some part reflect also increased awareness, probably explains the rise in prevalence of parental asthma between 1996 and 2006. The prevalence of parental asthma susceptibility genes, however, is unlikely to have changed during the ten-year period. Also the strength of association of current asthma with parental asthma and, accordingly, the aPAF, seemingly increased although there was an overlap in confidence intervals. This could be explained by non-genetic parental factors (shared environment or lifestyle in the family) not adjusted for by the multivariate risk factor model. Another possibility is that the environment of the latter cohort triggered previously “silent” susceptibility genes shared by both parents and children.

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Severe respiratory infections caused by rhinovirus and respiratory syncytial virus (RSV) is a known risk factor for asthma.³⁹⁻⁴¹ From 1996 to 2006 we observed a 50% decrease in the prevalence of respiratory infections (RSV, pertussis, croup and pneumonia), and its attributable fractions of wheeze and asthma also decreased. The Swedish community-based vaccination programme against *Bordetella pertussis* was halted between 1979 and 1995, and hence the 2006 but not the 1996 cohort was vaccinated. Correspondingly, the prevalence of having had pertussis decreased from 48% to 3%, $p < 0.001$. The aPAF of current asthma and wheeze for respiratory infections tended to decrease. The present study was not designed to target specifically the effect of pertussis vaccination on asthma, and previous studies of vaccinations and atopic disease present conflicting results.^{42, 43} Although the link between vaccinations in general and sensitisation is not clear, vaccination against pertussis may be beneficial regarding the development of wheeze.

The prevalence of maternal smoking decreased by 50% between 1996 and 2006, in line with recent findings in Swedish adults.^{44, 45} In 1996 maternal smoking was an important and statistically significant risk factor for both current asthma and wheeze. The importance of maternal smoking for current asthma and wheeze decreased to near zero in 2006. This promising finding is in line with a recent prospective study of Swedish school children.⁴⁶ It underlines the negative effect of environmental tobacco smoke,^{16, 47} and clearly suggests that decreasing this exposure has beneficial effects on children's health. A group especially susceptible to asthma are low birth weight children of smoking mothers, owing to a synergistic interaction.⁴⁸ Decreased prevalence of maternal smoking may thus explain why low birth weight was no longer a significant risk factor for current asthma in 2006 in contrast to 1996 in this material.

A pattern emerges where respiratory infections, home dampness and maternal smoking, all environmental exposures associated with asthma in numerous studies^{12, 13, 15, 16, 29, 47, 49} decreased in importance between 1996 and 2006. It seems that a larger proportion of asthma and wheeze was attributable to the non-environmental risk factors parental asthma and allergic sensitisation in 2006 compared to 1996. Both these factors have shown independent associations with persistence of childhood wheeze and asthma.^{3, 15, 50} In addition to an increase in the allergic asthma phenotype, this suggests that wheeze in the latter OLIN paediatric cohort may be more likely to persist. The decreased importance of environmental risk factors is probably related both to decreased prevalence of these risk factors, and also an effect of the larger proportions of children in 2006 with parental asthma and/or allergic sensitisation.

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In conclusion, despite a substantial increase in the prevalence of allergic sensitisation in school children in this area between 1996 and 2006, the prevalence of asthma and wheeze was level. This was seemingly explained by decreased impact of the environmental exposures respiratory infections, damp home and maternal smoking. These risk factor trends and the increase of the allergic asthma phenotype may seriously affect the future remission probability of asthma in this region. The findings further illustrate the changing risk factor patterns for conditions with complex aetiologies. A level prevalence may in fact reflect counteracting trends in risk factors, which argues that risk factors should be monitored closely also in other areas.

ETHICAL APPROVAL

Approval for the study was acquired from the ethical committee at the University Hospital of Northern Sweden in Umeå.

CONFLICT OF INTEREST

None of the authors has any conflict of interest.

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LEGENDS TO FIGURES

Figure 1. Prevalence of environmental and non-environmental risk factors. Prevalence of environmental (damp home, no siblings, maternal smoking and respiratory infections) and non-environmental (male sex, parental asthma, low birth weight and allergic sensitisation) risk factors in the children tested for allergic sensitisation, grouped by cumulative number of risk factors.

Figure 2. Current asthma – aPAF. Adjusted population attributable fractions of risk factors for current asthma in 1996 (black circles) and 2006 (white circles) by multivariate analysis. The 95% confidence intervals (CIs) are included, note that CIs are not computed for negative aPAFs.

Figure 3. Current wheeze – aPAF. Adjusted population attributable fractions of risk factors for current wheeze in 1996 (black circles) and 2006 (white circles) by multivariate analysis. The 95% confidence intervals (CIs) are included, note that CIs are not computed for negative aPAFs.

Table 1. Prevalence of asthma symptoms in the last twelve months, environmental and non-environmental risk factors, in 1996 and 2006 respectively.

	Prevalence, % (n)		2006 vs. 1996 p-value
	1996 (n=3,430)	2006 (n=2,585)	
Symptom			
Current wheeze	11.7 (400)	13.0 (335)	0.128
Speech-limiting wheeze	1.3 (44)	1.2 (32)	0.877
Exercise-induced wheeze	6.2 (213)	7.4 (190)	0.080
Wheezing without a cold	5.8 (200)	6.5 (167)	0.313
Dry cough at night	12.4 (426)	13.0 (335)	0.533
Current asthma	5.3 (181)	6.1 (157)	0.184
Environmental risk factors			
Breast-fed <3 months	16.4 (544)	10.5 (261)	<0.001
City living first year	66.1 (2,152)	66.2 (1,610)	0.950
Respiratory infections	59.9 (1,958)	28.6 (708)	<0.001
No siblings	5.5 (186)	7.3 (187)	0.004
Damp home	17.5 (586)	12.3 (309)	<0.001
Maternal smoking	31.5 (1,050)	15.8 (401)	<0.001
Ever cat at home	30.8 (1,047)	28.9 (742)	0.116
Non-environmental risk factors			
Male sex	51.0 (1,749)	51.6 (1,333)	0.658
Parental asthma	17.2 (589)	24.4 (630)	<0.001

Birth weight <2,500 g	4.2 (139)	4.0 (94)	0.412
Allergic sensitisation*	20.6 (443)	29.9 (506)	<0.001

* measured only in the skin prick tested children, n=2,148 in 1996 and n=1,700 in 2006.

Table 2. Risk factors for current asthma and current wheeze by univariate analysis. Risk ratios (RR) with 95% confidence intervals (CI) and prevalence of the respective risk factors among cases.

Statistically significant associations in **bold** numbers.

Risk factors	Current asthma				Current wheeze			
	RR (95% CI)		Prevalence (%)		RR (95% CI)		Prevalence (%)	
	1996	2006	1996	2006	1996	2006	1996	2006
			6	6			6	6
Environmental								
Breast-fed <3 months	1.33 (0.94-1.90)	1.52 (0.99-2.32)	20.7	15.1	1.09 (0.85-1.39)	1.24 (0.92-1.68)	17.6	12.7
No siblings	1.45 (0.86-2.45)	1.76 (1.12-2.78)	7.8	12.3	1.11 (0.76-1.63)	1.34 (0.96-1.87)	6.1	9.6
Early city living	1.32 (0.95-1.82)	1.39 (0.98-1.98)	71.9	73.2	1.09 (0.89-1.34)	1.03 (0.82-1.28)	68.1	66.8
Respiratory infections	2.67 (1.85-3.87)	3.01 (2.21-4.10)	80.0	54.7	3.20 (2.47-4.14)	3.34 (2.72-4.11)	82.7	57.3
Damp home	2.04 (1.50-2.78)	1.78 (1.22-2.61)	30.3	20.0	1.77 (1.44-2.19)	1.84 (1.44-2.35)	27.3	20.5

					2.17)	2.35)		
Maternal smoking	1.38 (1.03-1.86)	1.03 (0.68-1.55)	38. 9	16. 1	1.26 (1.04-1.53)	0.98 (0.74-1.30)	36.6	15.5
Ever cat at home	0.52 (0.36-0.76)	0.66 (0.45-0.96)	18. 9	21. 2	0.70 (0.56-0.88)	0.70 (0.55-0.90)	23.8	22.2
Non-environmental								
Male sex	1.52 (1.14-2.04)	1.79 (1.30-2.47)	61. 3	65. 6	1.25 (1.04-1.50)	1.75 (1.42-2.16)	56.5	65.1
Parental asthma	3.41 (2.57-4.53)	3.76 (2.78-5.08)	41. 4	54. 8	2.51 (2.09-3.03)	2.20 (1.81-2.68)	34.3	41.5
Birth weight <2,500 g	2.19 (1.33-3.62)	1.05 (0.48-2.32)	8.8	4.0	2.07 (1.51-2.85)	0.56 (0.28-1.16)	8.3	2.2
Allergic sensitisation*	4.23 (3.03-5.91)	4.35 (2.90-6.51)	52. 4	64. 9	2.59 (2.09-3.22)	2.75 (2.15-3.53)	40.2	54.0

* Only measured among the skin prick tested children

Table 3. Risk factors for current asthma and current wheeze by multivariate analysis, in the cohorts tested for allergic sensitisation. Odds ratios (OR) and 95% confidence intervals (CI). The models were also adjusted for early city living, breast-feeding <3 months, ever having kept a cat, birth weight <2,500 g and having no siblings, with full data for 1,935 children in 1996 and 1,495 children in 2006. Statistically significant associations in **bold** numbers.

Risk factors	Current asthma		Current wheeze	
	OR (95% CI)		OR (95% CI)	
	1996	2006	1996	2006
Environmental				
Respiratory infections	2.08 (1.27-3.43)	2.88 (1.77-4.68)	3.32 (2.30-4.81)	4.55 (3.18-6.50)
Damp home	1.89 (1.19-3.01)	0.77 (0.38-1.59)	1.89 (1.36-2.64)	1.20 (0.72-1.99)
Maternal smoking	1.93 (1.22-3.03)	0.98 (0.48-1.99)	1.46 (1.05-2.02)	1.22 (0.74-2.01)
Non-environmental				
Male sex	1.62 (1.04-2.51)	1.77 (1.07-2.92)	1.22 (0.90-1.66)	1.90 (1.32-2.74)
Parental asthma	3.13 (2.01-4.87)	4.73 (2.89-7.74)	2.11 (1.51-2.95)	1.89 (1.30-2.74)
Allergic sensitisation	4.34 (2.79-6.75)	3.70 (2.27-6.04)	3.37 (2.44-4.66)	3.55 (2.48-5.07)

Figure 1

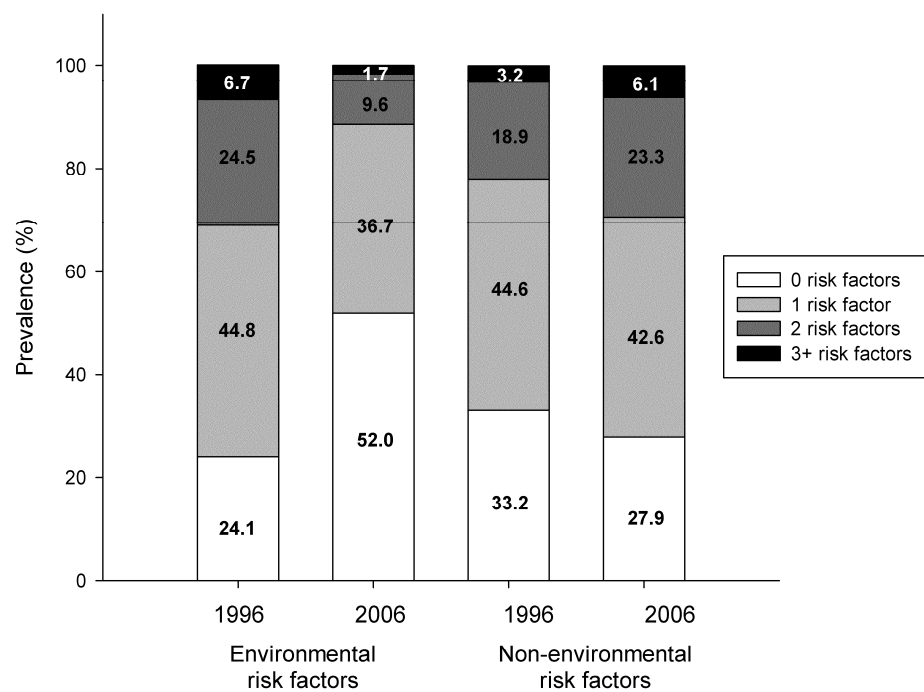


Figure 2

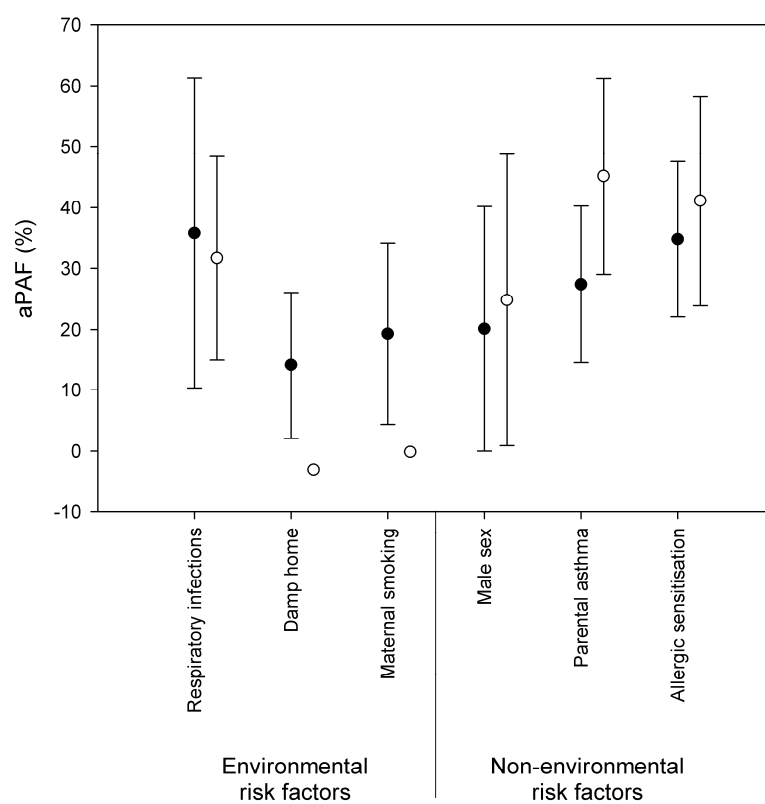


Figure 3

